Chapter 1

Rational Drug Use in Clinical Practice

Drug therapy requires knowledge, judgement, skill and also sense of responsibility. The term 'rational drug use' means to prescribe drugs in appropriate dose for the appropriate period to the patient at an affordable cost. The aim is to promote better and more effective use of the drugs through consideration of efficacy, safety, convenience and cost. Recently, there has been irrational use of drugs due to number of reasons:

- There is lagging knowledge about continuing education and training in pharmacology.
- Drug regulatory authority is not well-organized and there is inappropriate supply of drugs.
- Availability of large number of drugs in the market.

Factors leading to sudden realization of rational drug use:

- New drugs have been discovered due to drug explosion.
- Drug resistance to be overcome is a challenge. There are continuing efforts to prevent development of resistance.
- Awareness about right drug use is increasing.
- Cost of treatment is an issue.
- Consumer Protection Act (CPA) sues the doctors against malpractice and negligence.

Important steps in rational drug prescribing:

- The patient's problem has to be defined.
- The therapeutic objective has to be specified.
- To choose treatment:
  1. Advice and information
  2. Treatment without drugs
  3. Treat with drugs
  4. Referral
  5. Combination of above

Start treatment and provide the patient with clear instructions and information. Monitor the treatment.

Defining the patient's problem: This is the first and most crucial step towards rational drug use. Patient makes a presenting complaint and right diagnosis is made by integrating many pieces of information like complaints of the patient, detailed history of episode, physical examination, lab investigations, etc.

Specify the therapeutic objective: Before starting the treatment, doctor should be clear what she/he wants to achieve. Having established the therapeutic objective, it will limit the treatment possibilities and will prevent lot of unnecessary drug use.

Following criteria for rational drug use should be met:

Efficacy: Efficacy is the first criterion for selection, e.g. in patients with congestive heart failure (CHF), loop diuretics are more efficacious than thiazide group of diuretics.

Safety: A rational drug use should be safe with no or minor side effects. Every drug has side effects. So, risk *versus* benefits have to be weighed. The risk is concerned with the properties of the drug, prescriber, patient, environment, e.g. benzodiazepines (BZPs) are safer than barbiturates or hypnotics for treating many conditions like anxiety, insomnia and seizures.

Convenience: It is another important factor for choosing P-drug. If this factor is not taken into account, patients may not be able to take the drug when needed, e.g. nitroglycerine (NTG) is available as tablets, as IV formulation. During the attack of angina, sublingual tablets of nitroglycerin (400 µg) are more convenient and so are P-drugs in that condition.

Cost: The prescriber's ideal choice is based on efficacy and safety, especially in the case of 'me too drugs'. The generic name should be prescribed as it is cheaper than the branded name while efficacy and safety in most of the cases are same.

Suitability: This applies to an individual patient. Before starting the treatment, it should be seen if the drug could be used in a particular patient because the patient may have certain conditions for which the P-drug may be contraindicated, e.g. β-blockers are contraindicated in bronchial asthma. To determine suitability, we need to know contraindications, alteration in pharmacodynamics/kinetics in presence of comorbidities, food drug interactions, dosage in elderly and children, etc.

A newly introduced drug is not always better and safer than the existing drug. Of the same drugs available, it is definitely more expensive. Moreover, the new drug's safety can be established after several years of use. So, choose a familiar drug whose effect is known. Choosing a patient with broad therapeutic umbrella (broad spectrum cephalosporins and chloramphenicol) is indicated in life-threatening situations for 2–3 days until a specific diagnosis is made.

Treatment with P-drugs: The market is flooded with drugs, which can be used to treat a particular condition. Reviewing all possible drugs for each and every patient can be a time consuming process. P-drug concept is used to solve the problem. P-drugs are familiar medicines prescribed regularly by doctors for a given condition.

Selection of P-drug involves the five basic steps:

1. Make the diagnosis.
2. The therapeutic objective should be targeted.
3. An inventory of effective groups of drugs should be prepared.
4. An effective group, is chosen according to criteria.
5. Out of the group, P-drug is selected.

Example: A man, 60-years old had presenting complaints of having several attacks of suffocating chest pain during exertional activity last month. The pain subsided on rest. He is non-smoker, has family history of heart attack. He is not on any medication in the past years, except occasional aspirin use. On auscultation, a murmur was found over the right carotid

artery and the right femoral artery. Physical examination revealed no other abnormalities. Blood pressure is 130/85, pulse 78 regular, and body weight is normal.

Step I: Define the diagnosis. The patient is diagnosed as a case of stable angina pectoris due to coronary occlusion.

Step II: The therapeutic objective is targeted. The aim of treatment is to abate an attack as soon as it starts. The oxygen need of the cardiac muscle is reduced and workload on heart is decreased by decreasing the preload, the contractility, the heart rate or the afterload of the cardiac muscle.

Step III: An inventory of effective groups of drugs is prepared.

There are three groups with such an effect: Nitrates, beta-blockers and calcium channel blockers. Their sites of action are summarized in Table 1.1 and their comparison in Table 1.2.

Step IV: Nitrates is the chosen group (Table 1.3).

Table 1.1: Sites of action for drug groups used in angina pectoris

Groups	*Preload*	*Contractility*	*Frequency*	*Afterload*
Nitrates	++	–	–	++
Beta-blockers	+	++	++	++
Calcium channel blockers	+	++	++	++

Table 1.2: Comparison between the three drug groups used in angina pectoris

Efficacy	*Safety*	*Suitability*
1. **Nitrates** Pharmacodynamics Peripheral vasodilation Tolerance (especialy with constant blood levels) Pharmacokinetics High first pass metabolism Varying absorption in the alimentary tract (less in mononitrates) Glyceryl trinitrate is volatile: Tablets cannot be kept for long	*Side effect* Flushing, headache, temporary tachycardia Nitrate poisoning due to long-lasting oral dosage	*Contraindictions* Cardiac failure, hypotension, raised intracranial pressure Anaemia Fast effect dosage forms: Injection, sublingual tablet, oromucosal spray.
2. **Beta-blockers** Pharmacodynamics Reduced heart contractility Reduced heart frequency Bronchoconstriction, muscle vasoconstriction, inhibited glycogenolysis Pharmacokinetics Lipophilicity increases passage through blood–brain barrier	*Side effects* Hypotension, congestive heart failure Sinus bradycardia, AV block Provocation of asthma Cold hands and feet Hypoglycaemia Drowsiness, decreased reactions, nightmares	*Contraindications* Hypotension, congestive heart failure Bradycardia, AV block, sinus syndrome Astma Raynaud's disease Diabetes Liver dysfunction Fast effect dosage forms: Injection

Contd.

Table 1.2: Comparison between the three drug groups used in angina pectoris		
Efficacy	***Safety***	***Suitability***
3. **Calcium channel blockers** Pharmacodynamics Coronary vasodilatation Peripheral vasodilatation (afterload) Reduced heart contractility Reduced heart frequency	*Side effects* Tachycardia, dizziness, flushing, hypotension Congestive heart failure sinus bradycardia, AV block	*Contraindications* Hypotension Congestive heart failure, AV block, sick sinus syndrome Fast effect dosage form: Injection

Table 1.3: Comparison between drugs with the group of nitrates				
	Efficacy	***Safety***	***Suitability***	***Cost/100 (£)****
1. **Glyceryl trinitrate** Sublingual tab 0.4–1 mg cap 1–2.5 mg Transdermal patch 16–50	NB: Volatile 0.5–30 min 0.5–7 mg 1–24 hours 1–24 hours NB: Tolerance	No difference between individual nitrates	No difference between individual nitrates	0.29–0.59 3.25–4.28 42.00–77.00
2. **Isosorbide dinitrate** Sublingual tab 5 mg Oral tab 10–20 mg Oral tab (retard) 20–40 mg	2–30 min 0.5–4 hours 0.5–10 hours NB: Tolerance			0.45–1.51 1.10–2.15 9.52–18.95
3. **Pentaerythritol tetranitrate** Oral tab 30 mg	1–5 hours			4.45
4. **Isosorbide mononitrate** Oral tab 10–40 mg Oral tab/caps (retard)	0.5–4 hours 1–10 hours NB: Tolerance			5.70–13.30 25.00–40.82

*Indicative prices only, based on prices given in the British National Formulary of March 1994.

Step V: *Choose a P-drug*: In general, three drugs are available for the treatment of an acute attack: glyceryl trinitrate (nitroglycerin), isosorbide mononitrate and isosorbide dinitrate (Table 1.3). The first two drugs in table can be given sublingually with a rapid effect. Efficacy and safety of three drugs are the same. Concerning suitability, the three drugs hardly differ in contraindications and possible interactions. So ultimate criteria is cost. As can be seen from Table 1.3, costs may vary considerably. Since tablets are cheapest in most countries, these can be the first choice. In this case, P-drug of choice for an attack of angina pectoris would be: Sublingual tablets of glyceryl trinitrate 1 mg.

Fixed drug combinations are often used as they make drug therapy simple for convenience and better patient compliance. Synergistic combinations are, e.g. cotrimoxazole and trimethoprim, carbidopa + levodopa. Also, the side effects on one drug are mitigated by the other, e.g. a thiazide and a potassium sparing diuretic. Combined treatment is also given to prevent drug resistance, e.g. multidrug therapy (MDT) in tuberculosis (TB), HIV and falciparum malaria.

CHOICE OF ANTIMICROBIAL THERAPY

Chemotherapy may not be required in certain indications like abscesses where surgical drainage is useful or in case of urinary obstruction. Broad spectrum antibiotics are given in case of unidentified pathogen and susceptibility. The parenteral route is used in case of emergency, e.g. septicemia or if the drug is not absorbed orally, e.g. gentamycin and vancomycin. After confirmation by culture and sensitivity test, narrow spectrum best antimicrobials are selected for treatment. The optimum dose and frequency must be administered. Inadequate doses cause microbial resistance. The therapy should be continued for sufficient time to prevent relapse after clinical cure, e.g. in typhoid fever, TB and infective endocarditis. Acute infections need 5–10 days treatment and prolonged therapy is avoided to prevent adverse drug reactions. In some diseases of urinary tract infection (UTI), culture report is required to show sterile sample as clinical symptoms disappear before eradication of the microorganism. When the risk of infection is high, e.g. at operative sites or when infection chances are low, but if happens can be disastrous, e.g. infection of heart valves, chemotherapy for surgical and dental procedures are given prophylactically. Some drugs need dose reduction or are contraindicated in hepatic and renal dysfunction or some genetic factors like G6PD deficiency. If a patient is already on treatment with some other drug, then the antimicrobial should be chosen avoiding any drug interactions, e.g. theophylline and erythromycin are not given together.

The misuse and irrational prescribing of antibiotics has led to emergence of resistance among antimicrobials and is a great concern nowadays. The infections with antibiotic resistant organisms have poorer prognosis. Resistance can be due to spontaneous mutation, transmission of genes from other organisms, production of enzymes that modify the drug, e.g. β-lactamases hydrolyse penicillins, efflux of drug from bacterial cell, e.g. meropenem resistance in *Pseudomonas aeruginosa*, modification of target site. Also, the antimicrobial use may lead to suppression of part of normal bacterial flora in patients which can cause multiplication of opportunistic pathogens, e.g. *Candida albicans*, *Clostridium difficile* pseudomembranous colitis caused by clindamycin. Moreover, broad spectrum antibiotics alter bacterial flora in the gut causing vitamin B complex and vitamin K deficiency as these are synthesized by intestinal bacterial flora.

Prescription writing: A prescription is the physicians' written order to the pharmacist for dispensing medication. It is a legal document for which the prescriber and the pharmacist are both responsible and subject to local regulations. It is prima facie evidence in the court of law. The salient feature of prescription is that it should be clearly state precisely what should be given. Few take words are still used but whenever possible, the language which the patient can easily understand should be used. The use of words like "take as directed" 'every 8 hourly', SOS is confusing and should be avoided and exact method and time should be mentioned. A prescription should include—name, address, age of the patient, doctor details, generic name of the drug, dosage form, total amount, label, instructions and warning, signature/initials of the prescriber (Fig. 1.1).

Superscription contains doctor and patient particulars and the symbol Rx in the name of the God of Remedies 'Jupiter'.

Inscription is the body of the prescription which contains name of the drug, dosage form and route of administration and the duration.

Patient's name: ..... Age: ..... Gender:	**SUPERSCRIPTION**	Doctor's name: ..... Qualification: ..... Reg no.: .....
Body weight: ..... Address and phone no. :		Address: ..... Contact details: .....
Diagnosis		
Rx		
Refills: Don't substitute/generic substitiution allowed	Inscription Subscription Transcription	DOC DOC stamp Sign and date

Fig. 1.1: Format of prescription

Subscription is the direction to the pharmacist regarding fulfilling the prescription.
Transcription is the instructions given to the patient by the physician.
Signature: The physician's handwritten signature will validate the prescription and allow the pharmacist to dispense the prescribed medicine.
Compliance: Long-term therapy to be successful requires patient and doctor compliance.
Patient compliance means how much the patient behaves according to the instructions given by the doctor. If the patient does not comply, it can lead to therapeutic failure in both routine practice and in scientific trial. Poor patient compliance may be due to:

1. Lack of faith in patient–doctor relationship—the doctor should inculcate trust in the patient so that he complies to his instructions. Patients should be made informed partners in treatment and encouraged to express themselves, i.e. patients should be told about the benefits and risks of treatment.
2. Unintentional non-compliance—is connecting drug intake with tasks in daily life (breakfast, bedtime) or by using calendar path.
3. Intelligent non-compliance is when a patient willfully decides not to take the drug. Reasons may be:
   - Due to side effects
   - Improvement in patient's mental condition
4. Lack of information: Most of the patients have been found unable to recollect verbal instructions. Nowadays, patient-friendly information cards are given by the doctor, pharmacists and a package insert by pharmaceutical companies.
5. Frequency and complexity of drug regimens: Patient compliance is inhibited by polypharmacy; more than 3 drugs are given.
6. Anxiety-on being newly diagnosed suffering from a disease, doctor may explain the drugs and how to take but the patient's thoughts are drifting away. The patient is often worrying about new illness and its consequences.
7. Inappropriate health benefits
8. Poverty
9. Psychiatric conditions

All these factors must be considered and modified to enhance patient's compliance.
Overcompliance: Taking more drugs than prescribed leads to overcompliance.

Doctor's compliance is the professional conduct of doctors on their part:

- They should use only drugs about which they are well-informed.
- Sufficiently approved new advances are to adopted only.
- To prescribe accurately.
- To refrain from inappropriate prescribing.
- To tell what the patients need to know.

The doctor should explain to the patient the effects of the drug, side effects, instructions about how, when the drug should be taken, warning about the drug, future consultation when to come for follow-up or earlier.

Monitor the Treatment

Was the treatment useful—Yes/No?
If disease cured, stop treatment.
No, if the disease is not cured, any side effects, yes, reconsider dosage or drug choice.

Irrational drug combinations: The national list of essential medicines published in 2022 contains 384 medicines and 23 fixed dose combinations, whereas in India, there are innumerable examples of irrational drug combinations, which are easily available and can be bought without necessarily giving a prescription.

Following needs to be done to prevent irrational prescribing:

- A rational and logical basis for bringing out a fixed dose formulation should be done.
- The misleading claims by the medical representatives and pharmaceutical industry should be taken care of.
- The practitioners should acquire the necessary knowledge and skills to prescribe rationally.
- There should be mandatory adverse drug reaction (ADR) reporting as in developed countries.
- Drugs and therapeutic review committees should be constituted in hospitals to rationalize prescribing.
- Trainings should be held for students and doctors in medical colleges to assess new drug combinations more logically.

SOURCES OF DRUG INFORMATION

To keep updated with drugs: With new drug development, a physician should know about advancements in drug therapy.

Due to lack of well-organized system for giving the latest information to physicians, pharmaceutical companies have exploited the scene. Information from pharmaceutical companies is readily available through a number of media. Medical representatives advertise at professional meetings, put advertisement in journals, or by mailing. They highlight the positive aspects of products for promotion and overlook or give little coverage to negative aspects. For analyzing the available aspects, following rules should be followed:

- More information should be acquired than from the advertisement.
- Look for authenticity of references.
- Only quality references should be taken seriously.

All the sources of the latest drug information available are:

Reference books: A reference book should be chosen based on the frequency of new editions. Reviews of books every 2–5 years can provide updated knowledge, e.g.

- Goodman and Gilman's: The Pharmacological Basis of Therapeutics
- Martindale the Extra-pharmacopoeia
- Monthly Index of Medical Specialities (commercially sponsored drugs using complete and comparative assessments.)

National list of essential drugs and standard treatment guidelines: It is a list of essential drugs chosen for each level of care of dispensary—the center, district hospital, referral hospital. Essential drugs are those that satisfy the basic healthcare needs of majority of the population. They should be available at all times in adequate amounts and in appropriate dosages.

The main priority of developing countries is the basic health care costs. The drugs occupy 40% of the healthcare budget leading to lack of funds available for other health services. The scheme of basic or essential drugs was suggested by WHO in 1945, to extend the accessibility of most necessary drugs. With advice of experts in public health, medicine, pharmacology, and pharmacy and drug management, a list of necessary drugs should be prepared up locally and periodically revised. India prepared its National Essential Drug List in 1996 that included a total of 279 drugs. Standard treatment guidelines document the preferred treatment for common health problems to promote therapeutic, effective and economically efficient prescribing.

Drug formularies and pharmacopoeias: Some information about the drugs' chemical and physical properties, methods of purification and identification and storage cannot be obtained by textbooks, reviews or journals. Such information is provided by pharmacopoeias and formulary besides clinical indications, side effects, administration and dosage recommendations. Pharmacopeia provides information of drug substances and dosage forms by a committee of physicians, e.g. British Pharmacopeia, Indian Pharmacopeia, European Pharmacopoeia. Formulary provides information about the pharmaceutical ingredients by the pharmacists committee, e.g. Pharmaceutical Codex, National Formulary of India. Pharmacopeia and drug formulary are collectively known as drug compendia, e.g. Physician's Desk Reference is published annually with supplements twice a year.

Drug bulletins are periodicals published weekly to quarterly.

Medical journals: Such as the Lancet, National England Journal of Medicine (NEJM), British Medical Journal (BMJ). They contain much information of relevance to prescribers. Good medical journals are peer reviewed, i.e. read by indigenous experts for their opinion prior to publications. Some journals are sponsored. They offer an easily digested format. They are physician's way to save time as they are reliable.

Verbal information is by consulting with specialists and gaining their practical experience or in more structured way through postgraduate (PG) training courses.

Drug information centers: Uppsala Monitoring Centre located in Uppsala, Sweden, is the World Health Organization Collaborating Center for monitoring of international drugs. It collects, assesses and communicates information from member countries, national pharmacovigilance centers in regard to the benefits, harms, effectiveness and risk of drugs. Health workers and sometimes the general public can call and get help regarding drug use, intoxication, etc.

Electronic databases: Many major reference journals such as Martindale or Meyers side effects of drugs are now directly accessible through international electronic networks. Micromedex is an extensive subscription website maintained by Truven corporation. It provides for personal digital assistant devices, online drug dosage and interaction information, and toxicological information. Databases for drug and chemical information are Medline, National Library of Medicine, PubMed and Cochrane.

BIBLIOGRAPHY

1. Bertram GK, Trevor AJ Basic and Clinical Pharmacology, 13th editon, Mc Graw Hill Education. The nature of drugs and drug development and Regulation.
2. Catalogue of drugs. Govt. of West Bengal. Calcutta, India: BG Press: 1985.
3. Impoverishing the poor: Pharmaceuticals and drug pricing in India.Vadodara, LOCOST: 2004.
4. Indian Health Report. Oxford: Oxford University Press; 2003.
5. Mike Schachter, Sir Peter Rubin. Topics in drug therapy, Editors Bennet PN, Brown MJ, Sharma Pankaj 11th edition, Elsevier publishers, pp. 5–23.
6. Satoskar RS. The expanding role of pharmacologist in the changing Indian scene. J Postgrad Med, 1986; 32:111–3.
7. Suyog Sindhu. Learning Practical Pharmacology for undergraduates 1st ed, 2014. Jaypee Brothers Medical Publishers, pp. 128–132.
8. TPGM de Vries, RH Henning, HV Hogerzeil, DA Fresle. Guide to Good Prescribing. A Practical Manual. World Health Organization. Geneva. WHO/DAP/94.11.

Chapter
2

Clinical Pharmacokinetics

The knowledge of basic pharmacokinetic concept is essential for safe and appropriate use of drugs in the clinical setting. The pharmacokinetics of a drug can be described using few pharmacokinetic parameters—absorption, volume of distribution, metabolism and elimination of a drug.

1. Absorption

Bioavailability (BA) of a drug is the rate and extent to which it reaches the systemic circulation as intact drug after administration by any route. When the drug is administered by intravenous (IV) route, BA is naturally 100%. After administration by any route, the BA depends upon the fraction of drug clearance in the liver, besides pharmaceutical factors. It can be calculated as:

Oral BA = Fraction absorbed × 1-(ER)

ER = Extraction ratio

Removal of a drug by an organ can be specified as the extraction ratio, i.e. the fraction or percentage of the drug removed from the perfusing blood during its passage through the organ.

$$\text{Hepatic clearance} = \left[\frac{FuCL_{int}}{Q + FuCL_{int}}\right] \times Q$$

where, Q—hepatic blood flow: Fu—unbound fraction of drug; CL_{int}—intrinsic hepatic clearance—it is clearance of drug from plasma devoid of influence of blood flow or protein binding

$$\text{Extraction ratio} = CL/Q$$

Extraction ratio can be classified as high (>0.7), intermediate (0.3–0.7) or low (0.3). The extraction ratio is important in predicting which factors such as intrinsic factor, protein binding, blood flow, will alter the pharmacokinetic parameters of the drug. Drugs that have high extraction ratio have a large first pass effect and the bioavailability of these drugs after oral administration is low.

Clinical significance of BA Bioavailability has vital role in the absorption of any drug and its response. Its parameter will be helpful in proper and rational use of any medicine. There are number of factors which might affect the response of a drug due to changes in bioavailability of that particular medicine.

i. Route of administration, e.g. if BA after oral administration is low, the drug cannot be given by oral route, it has to be given parenterally, e.g. lidocaine, nitroglycerine.

ii. Variability in drug response: There is greater inter-individual variability in drug concentration and response because small difference in first pass metabolism leads to large changes in BA.
iii. Relationship between oral and intravenous dose: This is determined by BA, e.g. if oral BA is 20%, then 5 times of IV dose has to be given orally to get similar plasma levels, e.g. propranolol.
iv. *Onset of action:* The time required to obtain peak plasma concentration and onset of action depends upon its rate of BA. It becomes vital when we need to select drugs with fast bioavailability in emergency condition where quick response of drug is desirable, e.g. antibiotics IV.

2. Distribution

Once drug enters the systemic circulation, the next process under pharmacokinetics is the distribution of drug to target site. So, distribution is second fundamental parameter in discussing drug disposition. Body fluid of human being is distributed into 3 main compartments—plasma, interstitial fluid and intracellular fluid (ICF). Drugs get distributed into these fluid compartments to varying extents. Extent of distribution can be determined with known amount of drug in the body.

Volume of distribution (VD): Once a drug gets access to the bloodstream, it gets distributed to other tissues depending on lipid solubility, ionization at physiological pH, extent of binding to plasma and tissue proteins, presence of tissue specific transporters (in brain and choroidal vessels), liver, kidney, GIT and differences in regional blood flow. Plasma protein binding property of drug has very important role in distribution of any drug inside the body. Interactions involving drug distribution are primarily due to displacement of one drug from its binding site on plasma proteins by another drug. Drugs highly bound to plasma proteins have a relatively small VD like oral anticoagulants, sulfonylureas. Certain nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptics are liable to displacement interactions.

Volume of distribution can be calculated as amount of drug in body/concentration in plasma.

If VD is 10–20 liters, e.g. aspirin, it indicates that a drug distributes out of plasma into the extracellular fluid (ECF), but does not enter the cells, e.g. hydrophilic drug with small molecular weight.

If VD is 22–40 liters (e.g. methyldopa), it implies that the drug reaches the ECF, but also manages to enter at least some cells, e.g. a lipophilic drug with small molecular weight.

VD > 40 liters indicates avid binding to tissues resulting in very small plasma concentration of the drug, e.g. chloroquine, digitoxin and imipramine.

Pathological states, e.g. congestive heart failure, uremia, cirrhosis of liver can alter the VD of many drugs by altering distribution of body water, permeability of membranes, binding proteins or accumulation of metabolites that displace the drug from the binding sites.

On the other hand, drugs such as digoxin, will not have much change in VD due to ascites since it itself has very large volume of distribution.

It has VD 6 L/kg because drugs sequestrated in other tissues may have VD much more than total body water or even body mass. Digoxin is concentrated in the heart, skeletal muscle, liver and kidney.

In patients with chronic liver disease and hypoalbuminemia and ascites, plasma protein binding is decreased and VD is increased.

Clinical significance of VD

1. In designing dosage regimen

- **Loading dose:** If it is desired to reach a target plasma concentration quickly after initial dose or if quick repeated doses given in the beginning, it is called loading dose.

  IV Loading dose = VD × Target concentration

  We are giving a dose sufficient to provide the desired concentration in plasma when distributed throughout the volume available to it.

  The speed at which the loading dose is given depends on the therapeutic index of the drug. For a drug with narrow therapeutic index, the loading dose is given slowly, e.g. over 30 min for theophylline and over 24 hours for digoxin. It may be given IV/orally depending upon the urgency of action. When given orally, bioavailability of drug has to be taken into account.

  Oral loading dose = VD × Target plasma concentration/BA

  where, BA—bioavailability.

2. It helps in estimating the total amount of drug at certain time in body.

Amount of drug = VD × Plasma concentration of drug at certain time

3. Hemodialysis: Another clinical application of VD is predicting usefulness of hemodialysis in cases of drug toxicity due to overdose. A small VD implies that most of the drug present in body is in plasma or blood. In overdose with such a drug, hemodialysis will be useful for quickly eliminating drug present in the body, e.g. aspirin overdose and methanol poisoning. This would not be made true if a drug is extensively bound to plasma proteins, since bound drug will not be filtered by hemodialysis, e.g. teicoplanin and ceftriaxone.

3. Biotransformation (Metabolism)

Once drug has acted upon its target after distribution, this drug needs to be eliminated from the body so that toxicity could be avoided. So, now human body will do the chemical alteration of the drug to render non-polar compounds polar to be excreted easily as they are not reabsorbed in the renal tubules. The drugs can be metabolized in the liver, kidney, intestines, lungs and plasma.

There are two types of reactions by which any drug can be metabolised in our body, i.e.

1. The non-synthetic phase I reactions are oxidation, reduction and hydrolysis–where a functional group is added or removed rendering the metabolite active or inactive.
2. The synthetic phase II reactions are conjugations—glucuronide, sulfate, glutathione, glycine conjugations, acetylation, methylation and ribonucleoside synthesis. The microsomal and non-microsomal enzymes catalyse these reactions. The microsomal enzymes are present in the liver, kidney, intestinal mucosa and lungs and catalyse phase 1 reactions and glucuronidation. The non-microsomal enzymes are present in the cytoplasm and mitochondria of hepatic cells and in other tissues including plasma. They catalyse some oxidations, reductions and all conjugations except glucuronidation.

The consequences of microsomal enzyme induction are: Inactivation of drugs by metabolism, e.g. oral contraceptives (OCPs), toxicity of drugs that are activated by metabolism, e.g. paracetamol, intermittent use of an inducer may interfere with adjustment of dose of another drug, e.g. oral anticoagulants, hypoglycemics, antihypertensives and antiepileptics.

Inhibition of drug metabolism is clinically significant if drugs utilize the same enzyme, e.g. ritonavir is CYP3A4 inhibitor and lowers the dose of other protease inhibitors given concurrently because they are metabolized by CYP3A4 isoenzyme.

Various pathophysiological mechanisms that may lead to altered disposition of the drugs due to liver disease:

- Decrease in absolute cell mass
- Alterations in hepatic blood flow
- Impaired biliary elimination
- Enterohepatic cycling may be altered leading to increase or decrease in bioavailability.
- Altered volume of distribution.
- Hepatorenal syndromes—which refers to renal impairment linked solely to liver impairment.
- Changes in plasma protein binding with indirect effects on drug clearance.
- Hepatic clearance—there are three groups of drug clearance:

A. Flow-dependent drugs: Hepatic blood flow rate is perhaps the sole criterion on which the hepatic clearance depends for the highly extracted drugs (with extraction ratio (E >0.7). The drugs with high extraction ratio undergo significant first pass elimination by the liver following oral administration. There is impairment of hepatic clearance when liver blood flow is reduced as in heart failure, in severe cirrhosis and other forms of liver failure. A small decrease in the hepatic extraction ratio may lead to a subsequent increase in bioavailability, e.g. propranolol, pethidine, pentazocine, labetalol, morphine, verapamil, etc.

B. Capacity-limited drugs: The disposition of poorly-extracted or capacity-limited drugs is more sensitive to changes in plasma protein binding and or free intrinsic clearance than to alterations in hepatic blood flow.

i. *Capacity-limited-binding-sensitive drugs:* These are the drugs which are highly bound to plasma proteins (fraction unbound <0.155). Their hepatic clearance depends on the extent of plasma binding as well as free hepatic intrinsic clearance. Patients with hepatic disease may have a low serum albumin secondary to accumulation of fluid or decreased production.

   A decrease in plasma protein binding increases hepatic clearance, resulting in decreased total drug concentration, but free drug concentration does not change if free intrinsic clearance remains unchanged, e.g. phenytoin, valproic acid, quinidine, warfarin, salicyclic acid, etc.

ii. *Capacity-limited-binding-insensitive drugs:* These are the drugs which are minimally bound to plasma proteins. In this case, hepatic clearance depends only on the free intrinsic clearance of the drug, e.g. diazepam, nitrazepam, phenobarbitone, carbamazepine, naproxen, etc.

C. Intermediate extraction ratio drugs: For drugs with intermediate extraction ratio values (0.3 < E <0.7), hepatic clearance may be altered due to alterations in hepatic blood flow, plasma protein binding and free intrinsic clearance, e.g. aspirin, codeine, quinidine

Child-Pugh score is a scoring system to measure the severity of chronic liver disease in patients with cirrhosis. It identifies patients as class A, B or C based on albumin, bilirubin concentration (S), prothrombin time, presence of ascites or encephalopathy.

Class A: (5–6 points)—well compensated liver disease—favourable prognosis

Class B: (7–9 points)—moderately advanced liver disease

Class C: (10–15 points)—decompensated cirrhosis requires liver transplantation

Drug-metabolizing capacity of liver depends on several different enzyme systems which may be compromised to a varying degree by hepatic disease, thus producing considerable interpatient variability in pharmacokinetic parameters, e.g. for diazepam, nitrazepam, carbamazepine, phenobarbital, indomethacin and caffeine.

Elimination Half-life

Half-life of elimination is the time taken for the amount of drug in the plasma concentration to fall by ½. It is determined by CL and VD.

$$\text{Half-life} = 0.693 \times \text{VD}/\text{CL}$$

Therefore, it is a secondary parameter and it is increased by increase in VD and decline in CL and *vice versa*. In disease states, e.g. renal and hepatic failure, CL and VD can change.

Clinical Significance of Half-life

- **Time for plasma concentration to fall after stopping drug:** Since half-life gives the rate of elimination at which plasma concentration of a drug decreases once dosing is stopped. After 4–5 half-lives, most of the drug is eliminated and concentration falls to negligible levels. This knowledge is particularly important in drug toxicities where measures to remove toxic drug from the body will only be useful if undertaken within 5 half-lives.
- **Time to reach steady state with chronic dosing:** When multiple doses or continuous infusion of a drug is given, the plasma concentration rises till a state is reached where rate of administration is equal to rate of elimination, is called steady state. When dosing is stopped in 4–5 half-lives, the drug reaches 94–97% of the steady state concentration. This is also true for intermittent bolus dosing, where though the plasma concentration will fluctuate during each dosing interval, average plasma concentration will remain more or less constant once steady state is reached. Understanding steady state is importent for choosing right dose and dose interval to reach a steady state concentration.
- **Loading dose:** If half-life of any drug is long, it will take a long time to reach desired plasma concentration. So, with such drug having long half-life of drug, we need higher dose to achieve steady state concentration.
- **Duration of action and dosing:** If daily dose is constant and the frequency of administration is increased, though the steady state will remain same, but there will be fluctuation in plasma concentration with peak (toxicity) and trough (loss of therapeutic effect). This is important for drugs with low therapeutic index such as digoxin or aminoglycosides. If dose rate is changed, a new average steady state concentration (CPSS) is attained over the next 4–5 half-lives.
- **Dosing frequency required to avoid too large fluctuations in plasma concentration during the dosing interval:** With multiple dosing, the extent of fluctuation is determined by half-life, dosing interval and absorption rate. If absorption is immediate and complete, fluctuation depends solely on dosing interval in relation to half-life. If a drug is given every half-life, then over one half-life, the concentration falls to half the peak concentration, i.e. the

peak concentration will double the trough concentration and the fluctuation will be 1.005. If the drug is given less frequently, then its half-life fluctuation will be small and *vice versa.*

4. Clearance

It is defined as the volume of blood cleared of drug per unit time. It describes the efficiency of irreversible elimination of a drug from the body. Elimination includes, both excretion in urine, faeces, air, etc. and metabolism into different compounds. Clearance by different organs is additive, i.e.

Clearance total = CL (renal) + CL (hepatic) + Others.

For most drugs, CL is constant over plasma concentration range used in clinical settings, i.e. elimination is not saturable and rate of elimination is directly proportional to plasma concentration, i.e. a constant fraction of drug is eliminated per unit time, e.g. phenytoin. Such drugs are said to undergo first order kinetics or linear kinetics. For drugs with zero order kinetics or non-linear kinetics, a constant amount of drug is eliminated per unit time irrespective of plasma concentration, e.g. ethyl alcohol. The elimination of some drugs approaches saturation over the therapeutic range and change over from 1st order to zero order kinetics. The plasma concentration increases disproportionately with increase in dose, e.g. phenytoin, warfarin.

Renal CL: It is the rate of excretion of drug related to its concentration in blood or plasma.

$$CL\ renal = U \times VD.$$

U = concentration of drug in urine/concentration of drug in plasma

VD = volume of distribution

Renal CL is the net result of three different processes:

1. Glomerular filtration
2. Active tubular secretion.
3. Passive tubular reabsorption.

Renal CL = Filtration + Secretion–Reabsorption.

Since only free or unbound drug can be filtered at glomerulus and filtration depends on (GFR).

$$CL_R = [(F_u \times GFR) + [Q \times F_u \times C/[Q + (F_u \times CL_i)]/[Q + (F_u \times CL_i)]] \times (1-F_r)$$

F_u = unbound fraction of the drug, CL_R renal clearance, Q is renal blood flow, CL_i is intrinsic renal CL. F_r is fraction of the drug reabsorbed from the tubule lumen.

Equation gives a fair index about the relative importance of tubular secretion and reabsorption in renal excretion of a drug. If total renal CL is >GFR, this means the drug is most likely being cleared by active secretion, if renal CL is <GFR, some of it is reabsorbed in the tubules. If Renal CL = GFR, it is neither secreted nor reabsorbed.

Clinical Significance of Clearance

CL determines the maintenance dose rate of a drug. To keep the concentration of a drug at a particular steady state concentration, it should be understanding effects of physiological and pathological variables on drug elimination, e.g. in hepatic or renal disorder.

IV maintenance dose rate = $C_{ss} \times CL$ (L/hour).