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.

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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).

C_{ss} = steady state concentration of drug in plasma

For oral route, bioavailability of drug has to be taken into consideration.

Oral maintenance dose rate = $C_{ss} \times CL/BA$

Renal disease or reduced cardiac output often reduces the clearance of drugs that depends on renal elimination. The most important renal variable in drug elimination is glomerular filtration rate and creatinine clearance is an indicator of GFR.

Dosage in patient with renal impairment = Average dosage for a normal person × patient's CL_a (patient's altered creatinine clearance/100 ml/min).

If a drug is 50% cleared by the kidney and 50% by liver and the normal dosage is 299 mg/d, the hepatic and renal elimination rates are each 100 mg/d at steady state. The corrected dosage in a patient with a creatinine clearance of 20 ml/min will be:

Dosage = 100 mg/d (liver) + 100 mg/d × 20 ml/min/100 ml/min

= 100 mg/d + 20 = 120 mg/d

If the serum creatinine clearance is S_{cr}, the altered clearance for the patient can be calculated as

$$CL_a = (140 - \text{Age}) \times \text{Body weight (kg)}/72 \times S_{cr}$$

A cause of renal failure is more likely to suffer from various non-renal ailments, like hypertension, congestive cardiac failure, nephropathy, bone disease, infection, anemia, etc. It is also likely to be subjected to different medications for various ailments. Furthermore, it is likely to respond in a different manner to these pharmacological agents. This different response may be due to abnormalities in urinary excretion, metabolism and sensitivity to drugs. In recent years, a number of nomograms have been published taking into account creatinine clearance, body weight and age of the patient, especially for drugs with a narrow therapeutic range such as gentamycin, kanamycin and digoxin. Prescribing for patients with renal disease requires knowledge of the drug biotransformation, dynamic profile, and duration of action and mode of excretion.

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Chapter
3

Posology (Dose Calculations)

It is the branch of pharmacology which deals with making calculations regarding the drug dosage.

1 ml = 15 drops (macrodrip set), 1 ml = 60 drops (microdrip set).

Dose in mg/ml = Rate (ml/min) × Concentration (mg/ml).

Problem 1: It is required to administer IV 2 mg of a drug. You have 5 ml vial containing 10 mg of the drug. How many ml are you going to draw up in a syringe?

Sol. The vial contains 10 mg in 5 ml = 2 mg /ml. So to give 2 mg, 1 ml is to be drawn in syringe.

Problem 2: Calculate concentration of drug of whose 1 g has been added to 250 ml of bag of normal saline.

Sol. Concentration = Amount of solute/Volume of solvent = 1000/250 = 4 mg/ml.

Problem 3: How many drops/min are required to infuse 1000 ml of normal saline over 24 hours using a microdrip set?

Sol. Drops/min = Volume to be infused × Drip set rate (drops/ml)/Infusion time in minutes
= 1000 × 15/2 × 60 = 125 drops/min

Problem 4: For a drug B, available in concentration of 2 g/500 ml, you are instructed by a senior consultant to administer it to a patient in dose of 3 mg/min. What rule will you set in a microdrip set?

Sol. Rate = Dose to be administered/Concentration of drug solution
= 3 × 500 × 60/2000 = 45 drops/min

Problem 5: During your bedside round, you notice that a drug is available in concentration of 1 g/500 ml, is being infused at rate of 20 ml/hr. What is the dose administered to the patient?

Sol. Dose = Rate × Concentration = 20 ml/hr × 1g/500 ml = 20 × 1000/500 = 40 mg/hr

Problem 6: A senior consultant orders to start a drug E at the rate of 10 µg/kg/min. Drug W is available as 1000 mg/500 ml. If the patient weighs 50 kg, at which rate will you infuse E in a microdrip set?

Sol. Rate = Dose to be administered/Concentration of drug solution
Drop rate = 10 × 50 × 500 × 60/1000 × 1000 = 15 drops/min

Problem 7: Your patient is receiving a drug D available as 800 mg/250 ml at a rate of 12 ml/hr. The patient weighs 40 kg. Calculate the dose in µg /kg/time.

Sol. Dose = Rate × concentration = 12 × 800 × 1000/60 × 250 × 40 = 9.14 µg/kg/min

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Chapter
4

Chronotherapeutics

All living organisms have rythms with varying frequency ranging from seconds to seasons. This rhythmicity helps all living systems survive by enabling them to adapt to the changing conditions. The circadian rhythm is the best-known chronological frequency, which approximates the earth's 24-hr rotation around the sun. Also, both disease states and drug therapy are affected by a multitude of rhythmic changes within the human body. This principle of varying circadian rhythm has been applied in the treatment of various disease states and is called chronotherapeutics. The field of chronotherapeutics is based on the delivery of medicines so that various amounts of drugs are delivered at different times in accordance with natural biorythms during a 24-hr period. Chronotherapeutics refers to:

- Drugs are given according to a person's daily, monthly, seasonal or yearly biological clock in order to optimize health benefits and minimize the adverse effects.
- Altering the biological clock: A sleep disorder can be treated by altering an individual's sleeping and waking times.

CHRONOTHERAPEUTICS

Chronotherapy is based on an interdependent relationship between the peak-to-trough rhythmic activity in symptoms of the disease and the risk factors, pharmacological sensitivity and pharmacokinetics of many drugs. The specific time, the patients take in their medication becomes more significant throughout the study so as to maintain constant drug levels throughout a 24-hour period.

There are some physiological processes which vary in circadian rhythm, e.g. morning rise in blood pressure and heart rate, decline in mid-afternoon and are minimum at midnight, gastric emptying time—rapid in morning. Many hormones like cortisol, cathecolamines, plasma rennin, aldosterone, and angiotensin are secreted in the morning. In contrast gastric acid, growth hormone, prolactin, melatonin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), adrenocorticotropic hormone peak in the evening or during sleep.

There are many diseases which show a circadian pattern. Some of the conditions benefited are—allergic rhinitis, inflammation, neoplastic—various forms of cancers, asthma, CVS disease [hypertension, angina, myocardial infarction (MI)] and peptic ulcer disease. The administration of drugs is done according to the circadian rhythm of the disease.

Table 4.1: Circadian rhythm of some diseases	
Disease	***Circadian rhythm***
Allergic rhinitis	Symptoms worse in morning
Bronchial asthma	Exacerbations most common during sleep
Osteoarthritis	Symptoms worse in middle/later part of day
Rheumatoid arthritis	Symptoms worse on awakenings
Angina, MI	Incidence higher in the morning
Stroke	Incidence higher in the morning
Peptic ulcer	Incidence higher in early morning

- **Allergic rhinitis:** Such patients suffer their worst symptoms when they wake-up in the morning. Administering an antihistamine at night provides better results in controlling this morning discomfort than the morning dose. If the drug has the peak pharmacological activity at the time of greatest distress, optimum relief may be provided to the patient.
- **Rheumatoid arthritis:** A non-steroidal anti-inflammatory drug (NSAID) such as ibuprofen effectively relieves pain if the drug is administered at least 4–6 hours before the pain reaches its peak intensity. So, NSAIDs are recommended before bedtime if patient experiences a particular high level of discomfort in the morning. Treatment with indomethacin once a day treatment scheme is more effective in controlling morning symptoms.
- **Asthma:** Asthma symptoms generally worsen at night and occur more at night than during the day. Hence, antiallergics and steroids are administered in the evening.
- **Heartburn:** The heartburn cases are worse after meals and at night. Acid secretion is greater between 10 pm and 2 am. The time of dosing of H2-blockers (antihistaminics) and proton pump inhibitors (PPIs) will determine their effectiveness. In a study conducted on a group of 18 healthy volunteers, 3 dosage regimens of omeprazole and ranitidine (Fig. 4.1) are equally effective. Patient compliance was better in single ingestion in the evening.
- **Peptic ulcer:** As the maximal acid secretion, pain and perforation of gastric and duodenal ulcers are more common at night, administration of these drugs at bedtime is more

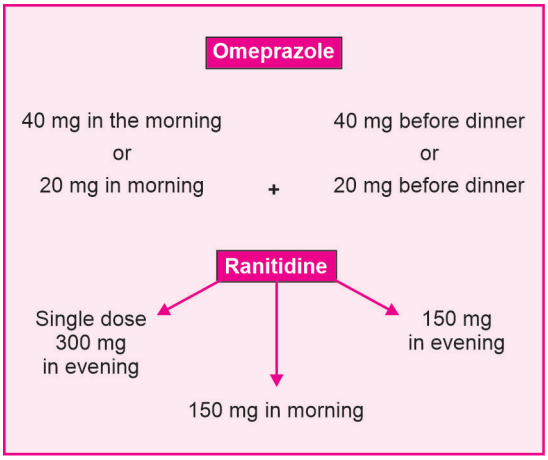

Fig. 4.1: Dose regimens in heartburn

effective. This not only decreases acid secretion more effectively but also promotes healing of ulcers and decreases their occurrence.

Hypertension: Cardiovascular (CVS) events including MI, stroke, and sudden death are more in the early morning hours, e.g. verapamil when administered at bed time, it provides optimal drug concentration between 4 am and noon. Also, propranolol and diltiazem are used as antihypertensives in chronotherapeutics.

Hypercholesterolemia: Clinical studies have shown that administration of Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors at nighttime lower serum cholesterol levels more effectively than the same dose given in the morning as HMG-CoA reductase enzyme activity is high during the night.

SKIN DISORDERS

Psoriasis: It is a chronic inflammation disease producing bumpy, flaky condition of skin due to high cell turnover which shows marked circadian variation. Inflammatory act highest at night:

- In epidermis—highest cell turnover is between 9 pm and 3 pm.
- In dermis—highest at 9 pm.

Atopic dermatitis: Treatment depends on the circadian rhythm and skin sensitivity (itching) which is highest at night.

Skin cancer: Tumor regression is greater when DNA material of skin cells is replicating. With lidocaine the pain-relieving effect is of longest duration when injected at 15:00 hrs. Nicotine penetrates skin faster at 4 am. Topical corticosteroids activity is greater when applied in the afternoon.

Use of oral contraceptives to inhibit ovulation is the application of chronobiological principles.

Chronotherapeutics is a promising but still relatively new field. It is important that physician must understand the advantage which is best-traditional treatment or chronotherapy.

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Chapter
5

Dosing in Pediatric Group

As physiological processes mature significantly in the first year of life influencing pharmacokinetic variables—absorption, distribution, metabolism, excretion. The pharmacokinetics in infants should be paid attention to while drug dosing.

Drug absorption: The factors influencing the absorption of drug are blood flow to administration site, GIT function (gastric acidity and gastric emptying time).

A. GIT absorption: In full-term infants, the gastric acid secretion begins soon after birth and increases gradually over several hours in full term infants.

The emptying of gastric contents is prolonged in the first day or so after delivery. In premature infants, the gastric emptying time is slow leading to efficient absorption in premature infants. Peristalsis in neonates is irregular and may be slow. The enzyme activity of GIT is lower in the newborn than in adults. In infants up to 4 months of age, α-amylase and other pancreatic enzymes activity in the duodenum is low. Also, in neonates there is low concentration of bile acids and lipase leading to decreased absorption of lipid soluble drugs.

B. Other routes: An appropriate formulation is used for absorption by rectal route, e.g. diazepam, theophylline are used in uncooperative infant. Digoxin or gentamycin administered by intramuscular and subcutaneous routes give variable plasma concentrations, because of low proportion of skeletal muscle and fat in children. Absorption after injection is also guided by the rate at which blood flows to the muscle or subcutaneous area injected. Hazardous drugs are cardiac glycosides, aminoglycosides and anticonvulsants, if perfusion to the muscle suddenly increases resulting in increase in drugs entering the circulation causing toxicity. Due to incomplete development of blood–brain barrier (BBB) in newborn, certain lipid-soluble drugs, such as general anesthetics, sedatives, narcotic analgesics result in increased permeability. This is the reason for neonates and infants to be sensitive to these drugs. Drugs are given by intravenous route preferably in the seriously ill newborn. Topical applied drugs applied are readily absorbed due to well hydrated skin and thin stratum corneum.

C. Drug distribution: The neonate has a higher percentage of its body weight in the form of water (70–75%) than does the adult (50–60%). Hence, the volume of distribution increases for water-soluble drugs and so loading doses are required for some drugs, e.g. aminoglycosides.

Total body fat in preterm infants (born before 37th week of gestation), is about 1% of total body weight compared with 15% in full term infants. Another factor determining drug distribution is drug binding to plasma proteins. Neonates have low protein binding capacity.

Hence, fraction of free drug increases in plasma and for some drugs—volume of distribution increases, e.g. digoxin is distributed highly in myocardium and in skeletal muscle in newborn. Also salicylates are distributed in different body systems like CNS leading to salicylism.

Drugs given in neonates with jaundice can attach to albumin by competing with bilirubin and this lipid soluble bilirubin can cross BBB to cause kernicterus, e.g. sulfonamides

Drug metabolism: Preterm and full term infants and newborns have low capacity of phase 1-hydroxylation. Also plasma esterases are in low profile activity in infants due to which succinylcholine (SCH) has longer duration of action due to poor metabolism. The drug metabolizing activities of enzymes are lower in early neonatal life than later. Glucuronide conjugation reaction reaches optimal levels between 3 and 4 years of life. As neonatal have decreased ability to metabolise drugs, they have slow clearance rates and prolonged elimination half lives of many drugs, e.g. chloramphenicol induced fatal grey baby syndrome in newborn occurs as a result of decreased metabolism of chloramphenicol by glucuronyl transferase to the inactive glucuronide metabolite. Phase 11 enzyme reactions mature between 3–6 months.

Drug excretion: Renal blood flow, the glomerular filtration rate, tubular excretion is much lower in newborn than in older infants. Also, the protein binding again affects glomerular filtration because only the free drug is filtered through the glomerulus. The glomerular filtration rate and renal plasma flow increase 50% from the first day by the end of first week. By the end of the third week, the glomerular filtration is 50–60% of the adult value. The renal excretory system matures over one year of age. Hence, the drugs eliminated by kidney like aminoglycosides, penicillins, diuretics require reduced dose in neonates. After 6 months, body weight, surface area related daily doses are the same for all ages.

Adverse reactions: There can be unexpected adverse effects in children, different from those seen in adults. Chronic therapy with phenobarbital can have significant effect on learning and behaviour in children. While children are at risk with use of corticosteroid therapy (delayed development and growth suppression). Children (<2 years) are at higher risk of hepatotoxicity from valproic acid than are adults. Long-term use of aspirin causes Reye's syndrome in patients with chicken pox. Phenothiazine use can cause extrapyramidal reactions. Use of tetracyclines can cause discoloured teeth in children. Low level function of P glycoprotein transporters at birth (extrudes its substrate from inside to outside of cells) can explain the more sensitivity of neonates to opioids than older children.

Administration of some drugs has therapeutic effect in children only. Indomethacin IV injection 0.2 mg/kg followed by two doses of 0.1 mg/kg at 12- and 24-hour intervals, causes the rapid closure of patent ductus arteriosus. Infusion of prostaglandin E1 (PGE1) causes the ductus to remain open.

PEDIATRIC DOSING BASED ON AGE, WEIGHT AND SURFACE AREA

Dose = Adult dose × Age/Age + 12
Dose = Adult dose × Weight/70
Approximate dose = Surface area of child (m^2)/1. 8 × Adult dose

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Chapter
6

Geriatric Pharmacology

Society classifies everyone >65 as elderly. The important changes in drug responses occur with increasing age in most individuals. With aging, drug kinetics and pharmacodynamic effects gradually change resulting in inter-individual differences in doses needed to produce a required effect. Alternations in the quality or quantity of drug receptors may account for altered sensitivity in the elderly. Also, there are body composition alterations and changes in function of drug eliminating organs.

A. Pharmacokinetic changes: Age-dependent alterations in pharmacokinetics result from changes in:

- **Absorption:** Rate of absorption is decreased from gastrointestinal (GIT), parenteral and pulmonary routes because of decreased blood flow. Other factors that affect absorption from GIT are:
  - Decrease in gastric acid secretion.
  - Decrease in splanchnic blood flow.
  - Decreased motility.
  - Decrease in number or absolute capacity of enterocytes.
- **Distribution:** The distribution of drugs is influenced by reduction in lean body mass, serum albumin, and total body water and increase in percentage of body fat in elderly. Also, it depends upon their lipid solubility and protein binding. The body weight is reduced so that standard doses provide a greater amount of drug/kg. The body water is less and water-soluble drugs tend to be present in high blood concentration, e.g. ethanol. The plasma albumin concentrationentration is decreased giving scope for increased free drug, e.g. phenytoin, warfarin, and meperidine.
- **Metabolism:** Liver represents the major site of drug metabolism. Liver blood flow decreases causing decreased metabolism through liver and the drug appears in high concentration in plasma for longer time.

  The phase 1 reactions undergo a greater change, i.e. those carried out by mixed function oxidases (MFOs). There is altered enzyme activity which declines in phase 1 reactions. The activity of CYT P450 enzymes is decreased.

  Also, the ability of liver to carry out conjugation phase 11 reactions undergoes much smaller changes, either due to decreased liver blood flow.

  In addition, aging changes cause decline in the ability of liver to recover from injury, e.g. caused by alcohol or viral hepatitis.

CHF is more common in the elderly and can affect hepatic function by dramatically altering the liver capacity to metabolise drugs by decreasing hepatic blood flow.

Similarly, hepatic function can be impaired by severe nutritional deficiencies that occur in old age.

- **Elimination:** Decrease in blood flow to the kidneys is 1–2%/year culminating in 50% loss.

In addition, glomerular filtration rate (GFR) undergoes concomitant decrease to 50%. The decrease in GFR has considerable impact on renal clearance of number of drugs—cardiac glycosides, antibiotics and diuretics.

Age-related decline in creatinine clearance is two-thirds of the population prolonging half-life of many drugs.

Cockcroft and Gault have defined a formula for estimating creatinine clearance from serum creatinine levels as function of patient's age.

Creatinine clearance = (140 – Patient's age) × (Patient's weight)/72 × Serum creatinine.

Aging also results in reduction of activities of renal MFOs enzymes and their inducibility.

Summing up the physiological processes of renal blood flow, glomerular filtration and tubular excretion change with aging. Though there is relatively less muscle mass in the elderly age group, serum creatinine may be in the same range as in normal young adults at creatinine clearance, even 55 ml/min. Renally eliminated drugs having a small therapeutic range, e.g. aminoglycosides, digoxin, procainamide and chlorpropamide, have risk of adverse effects. Even drugs that are normally eliminated by metabolism may pose a problem through the accumulation of water-soluble metabolites which retain pharmacological activity, e.g. hydroxylated metabolites and tricyclic antidepressants.

Pharmacodynamic changes: Changes in pharmacodynamics are important factors in the elderly. Drugs that depress CNS (sedative hypnotics) produce increased effects at any given plasma concentration. There is decreased response to β-adrenoceptor stimulants. There is increased sensitivity to unwanted effects of drugs, such as hypotension from psychotropic medications, even at adjusted dose for related pharmacokinetic changes because of receptor changes and loss of hemostatic resilience. As the vital capacity and maximum breathing capacities are lessened in the elderly, the opioid drugs are also more likely to depress respiration.

Following rules can be followed for prescribing drugs to the elderly:

- Think about necessity for drugs.
- Do not prescribe drugs having serious side effects and choose alternatives.
- Choose an appropriate drug formulation: Tablet, injection, suppository or syrup is better.
- Any new symptoms should be considered as side effects or withdrawal effects.
- Take a drug history.
- Fixed dose combination is used only to help in compliance or improve tolerance or efficacy.
- When new drug is added to the present treatment, try if other drug withdrawal is possible.
- Also, monitor patient's compliance.
- Stopping a drug is as important as starting it.

The elderly cannot tolerate neuroleptics and diuretics which cause adverse electrolyte changes. Response may alter with aging to produce a greater or lesser effect than is anticipated in younger adults.

SUMMARY

Summing up, increased incidence of multiple diseases in the aged, nutritional problems, poor compliance combined with changes in pharmacokinetics and pharmacodynamics make the elderly group vulnerable to serious adverse effects and drug interactions. The disproportionately, large number of drugs that the elderly are required to take, all contribute to this outcome.

The elderly group should be prescribed medicines only when absolutely necessary for well-defined indications and at the lowest effective dose. It is necessary to monitor well-defined endpoints, do therapeutic drug monitoring and take frequent reviews of the patent's drug history, to improve the health of the elderly population. The clinical studies with a number of drug interventions have shown that chronic diseases such as hypertension and hypercholesterolemia can be treated in the elderly as much as and often more than the young. Also, the natural history of chronic diseases of the elderly, such as osteoporosis and prostate hyperplasia can be halted or reversed by appropriate drug history.

The life span of elderly patients can be prolonged and the quality of life can be nurtured by the diligent use of drugs keeping in mind the age-related pharmacokinetic and pharmacodynamic changes.

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Chapter
7

Drug Use in Pregnancy

In pregnant women, when drugs have to be given to treat a disease, they have to be carefully prescribed. Most of the drugs administered to the pregnant women can pass through the placental barrier and expose the developing embryo and fetus to their teratogenic effects. The salient factors that affect drug passage across placenta are:

A. Lipid solubility: The drug transfer across placenta is guided by lipid solubility and degree of drug ionization, e.g. thiopental used for cesarian sections, is a lipophilic drug. It crosses placenta and produces sedation in newborn. The ionised drugs like succinylcholine cross placenta slowly.

B. Molecular size: Depending on their lipid solubility and degree of ionization, drugs with molecular weights of 250–500 dalton (Da) can cross the placenta easily. Drugs with molecular weights of 500–1000 Da move across the placenta uneasily, and those with molecular weights >1000 Da cross very poorly. Hence, heparin, a high molecular weight polar anticoagulant drug is used in pregnancy instead of warfarin as it cannot pass through placenta and affect the fetus.

C. Placental transporters: Also, the placenta has drug transporters, which transfer larger molecules to the fetus, e.g. as in Rh incompatibility, maternal antibodies cross the placenta and may cause fetal morbidity.

D. Protein binding: The extent of plasma protein binding of a drug may affect the rate and the amount of drug transferred. Though for very lipid-soluble drugs, e.g. some anesthetic gases, the drug passage across placenta depends only on placental blood flow irrespective of plasma protein binding. For poorly lipid soluble and ionized drugs, their transfer is slow and will be hampered by their binding to plasma proteins. Moreover, some drugs are greatly bound to maternal plasma proteins than in fetal plasma, e.g. sulfonamides, barbiturates, phenytoin.

E. Placental and fetal drug metabolism: The placenta is a site of metabolism for some drugs passing through it. The metabolism by placenta may create toxic metabolites. Drugs after crossing the placenta pass through the umbilical vein to enter the fetal circulation. The fetal liver receives about 40–60% of umbilical venous blood flow and the remainder bypassing the liver enters the general fetal circulation.

Physiological Changes during Pregnancy

The amount of water retained at term is 6.5 litres during the whole gestational term of pregnancy. Pregnancy is defined as hypervolemic state in which occurs active retention of sodium, potassium and water. The enlarging uterus becomes increasingly vascular with the interposition of uteroplacental circulation. Blood volume is markedly raised during pregnancy to 40–50% above the non-pregnant level at 30–34 weeks. As the pregnancy progresses, there are substantial changes in physiology including fluid and tissue composition.

As vasodilation increases tissue perfusion, absorption from an intramuscular site is more efficient. There is a larger space created due to total body water accumulation to 6.5 litres, causing water-soluble drugs to distribute in it. There is increased concentration free of drugs that are bound to albumin due to fall in plasma albumin levels. The free drug can be distributed, metabolized and excreted. There is deposition of body fat increasing by 4 kg acting as a reservoir for lipid-soluble drugs. The liver metabolism is rapid leading to increased clearance of drugs, such as phenytoin and theophylline. There is more rapid loss of renally excreted drugs due to doubling of renal plasma flow, e.g. amoxicillin, the dose is twice the routine dose for systemic infections.

Pharmacodynamics

A. Maternal drug actions: Heart failure is precipitated by the increased cardiac workload of pregnancy needing cardiac glycosides and diuretics. Pregnancy-induced diabetes can occur requiring therapy for control of blood glucose.

B. Therapeutic drug actions in fetus: Phototherapy is used nowadays for the treatment of neonatal-induced hyperbilirubinemia. Earlier, phenobarbital was used to induce fetal hepatic enzymes for glucuronide conjugation of bilirubin for its excretion, to reduce the incidence of jaundice in newborns. Corticosteroids are used to stimulate fetal lung maturation. Also, in pregnant mothers, zidovudine and other anti-HIV-drug treatment decreases transmission of HIV infection from mother to fetus.

C. Fetal hazards due to maternal medication during pregnancy:

i. *Fertilization and implantation stage* (Conception to 17 days—failure of pregnancy): During early embryogenesis, the drugs reach the conceptus through the tubal or uterine secretions by diffusion. Usually, blastocyst dies or there is congenital anomaly.

ii. *During organogenesis* (Second to 12 weeks): The drug can produce gross congenital malformations and even death.

From second trimester onwards: The increased drug transfer in late months of pregnancy across the placenta is due to:

- Increased free drug available for passage.
- Increased blood flow in uteroplacental circulation
- Increased surface area of placenta
- Thinness of the placental membrane.

Following guidelines are there for using drugs:

- If the benefit is more than the potential risks which can be tolerated, only then that particular drug can be used.
- Only drugs which have been approved after clinical trials and found beneficial, must be used, using the minimum therapeutic dosage for the shortest possible duration.

Maternal Medication and Fetal or Neonatal Affection

- Dependence is produced in the fetus and newborn, by chronic use of opioids by the mother.
- Females exposed to diethylstilbesterol (DES) are at increased risk of adenocarcinoma of vagina.
- Phocomelia risk by thalidomide occurs during the fourth to seventh weeks of gestation during organogenesis because during this time arms and legs develop.
- Use of antithyroid drugs can cause goiter and mental retardation.
- Use of oral antidiabetics can cause abnormalities in the eyes, CNS, skeletal systems and neonatal hypoglycemia.
- Use of aminoglycosides can cause deafness.
- Use of long-acting sulfonamides can cause jaundice and kernicterus.
- Hemolysis occurs in newborn with nitrofurantoin in presence of glucose-6-phosphate dehydrogenase deficiency.
- Vitamin D can cause cardiopathies, hypercalcemia and mental retardation.
- Chronic alcohol consumption can cause IUGR and preterm labour.

Treatment of Common Medical Illnesses during Pregnancy

- **Anemia in pregnancy:** During the second half of pregnancy, there is an increased demand for iron due to increase in plasma volume, RBC volume and Hb mass. A balanced diet rich in vitamins, iron and proteins is required. The specific therapy consists of oral iron preparations as ferrous sulfate, ferrous fumarate or ferrous succinate. Intramuscular (IM) therapy consists of:
  - Iron dextran (imferon)
  - Iron sorbitol citric acid complex (jectofer).
  - The injections are painful. The parenteral therapy is given when there is intolerance to oral iron or in severe anemia. The expected rise in Hb after therapy is 1–1.4 g/100 ml per week.
  - Folic acid supplementation 5 mg/day during pregnancy decreases the incidence of neural tube anomalies, e.g. spina bifida.
  - Heparin IV is given as anticoagulant in early pregnancy. Warfarin can be given as an anticoagulant in late pregnancy orally.
  - B2-selective agonists, corticosteroids are to be given in bronchial asthma and dextromethorphan for cough.
  - For anxiety disorders and insomnia, diazepam is given.
  - Primary hypothyroidism occurs in pregnancy due to thyroid autoimmunity mostly. Generally, therapy is started with 2–2.4 µg/kg /day. The maintenance dose is 75 and 150 µg of L-thyroxine per day. The serum TSH should be repeated every 4–6 weeks.
- For diabetes, human insulin is the preferred drug. Insulin therapy is given at a postmeal plasma glucose level of more than 140 mg % even on diet control. Before meals, glycemic goals should be around 90 mg/dl not exceeding 120 mg/dl 2 hours after meals.
- For fever and headache, take paracetamol 500 mg QID.
- For hypertension, labetolol, hydralazine and alpha methyl dopa. The dose of methyldopa is 250–300 mg, 2–3 times as needed, maximum dose 3000 mg/day and the dose of labetolol 100 mg twice daily, increase 100 mg twice daily every 2–3 days as needed, maximum dose 2400 mg/day.

- For nausea and vomiting, antacids preferred. For reflux esophagitis, antacids are preferred.
- For epilepsy, lamotrigine and levetricetam is the recommended drug. The dose of lamotrigine in pregnancy is 150–500 mg, BD. Levetiracetam 0.5 g BD, progressively increased to 1 g BD.
- For active TB during pregnancy, all first line oral drugs given for 9–18 months.
- Asymptomatic bacteriuria—amoxycillin 500 mg, TDS; nitrofurantoin—100 mg BD; cephalexin 500 mg, TDS.

Pregnant women should have a detailed ultrasound scan at 20 weeks of gestation in order to identify any fetal defects. Drug concentration should be monitored every 2 weeks after delivery until it is clear how quickly the pharmacokinetics of the drug can be returning to pre-pregnancy values. The dose should be adjusted accordingly. Prepregnant dose requirements usually can be resumed by 6 weeks postpartum.

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Chapter
8

Drug Use in Lactation

Lactation period is the most important period of a woman's life. It requires careful administration of drugs. As most drugs administered to lactating women are detectable in breast milk, careful administration of drugs is essential. Actually, all drugs present in maternal plasma will be reaching milk. Drugs are transported to milk from maternal plasma by diffusion. Lipid solubility, acid–base characteristics, protein binding profile of the drug regulates its entry into breast milk. Some drugs who attain more than 50% of maternal plasma concentration in infant plasma, alternative cow's milk should be given. Breast-feeding is stopped when unsafe drugs are perceived by the nursing mother, e.g. sedative hypnotic diazepam can prolong sleeping time of the infant. The lactating mother should optimally take a safe drug 30–60 minutes after nursing and 3–4 hours before the next milk feed to the child. Here are few examples of effect of drug intake in lactating mothers on feeding infants:

- Most antibiotics administered to lactating mothers can be detected in breast milk. Tetracycline concentration in breast milk is approximately 70% of concentration present in maternal plasma and poses permanent tooth staining risk in the infant.
- Chloramphenicol should be avoided during lactation as it causes bone marrow suppression
- Most sedatives and hypnotics reach concentration in breast milk sufficient to produce a pharmacological effect in some infants. Lethargy, sedation and poor suck reflexes in the infant can be produced at hypnotic doses of barbiturates by the mother. Diazepam can have a sedative effect on nursing infant.
- Opioids such as heroin, methadone and morphine produce narcotic dependence by entering breast milk.
- Li enters breast milk in sufficient amounts to cause toxicity—lethargy, restlessness, feeding, problem, abnormal growth and development. Breastfeeding is stopped if the mother is taking Li.
- Radioactive substances can cause thyroid suppression in infant and increase the risk of thyroid cancer. After large doses, breastfeeding is contraindicated and should be withheld for days to weeks after small doses.
- **TB in mothers:** Breastfeeding can be continued while on treatment with all anti-TB drugs. The mother should ge given full regimen while monitoring the baby. After ruling out active

TB, the infant should receive BCG vaccination and 6 months isoniazid preventive treatment. Breastfeeding by HIV-positive mother is contraindicated because it carries substantial risk of transmission to the infant.

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Chapter
9

Drug Interactions

When two or more drugs are given together for treatment of a disease, they may interact with one another and this is called drug interaction. One drug's response may be altered by prior or concomitant administration of another drug. The interaction may cause failure of treatment, additive or synergistic pharmacological effect, or a fatal toxic effect. Drug interactions are more predictable and presentable than adverse drug reactions as they have a specific time course in terms of onset and duration.

Drug interactions may be due to any one of the two important categories. First one is pharmacokinetic drug interaction, in which the drug concentration is altered at the site of action by absorption, distribution, metabolism or excretion. Second one is pharmacodynamic interactions, which occur at the level of target site, exerting synergism or antagonism. Adverse drug interactions can occur *in vitro*, e.g. heparin should not be infused with basic drugs in the infusion fluid and *in vivo*, e.g. one drug may alter the pharmacokinetics of second drug.

Important drug interactions clinically become more likely with drugs with following characteristics and conditions:

- Drugs having steep dose response curve and a small safety range as small substantial changes at the target site, e.g. receptor or enzyme caused substantial changes in effect, e.g. digoxin or lithium.
- Drugs either enzyme inducers or inhibitors.
- Drugs following saturable metabolism (zero order metabolism), when constant elimination occurs regardless of the plasma concentration, e.g. phenytoin, theophylline.
- Long-term use of drugs, where precise plasma concentrations are required, e.g. oral contraceptives, antiepileptic drugs, cardiac antiarrhythmic drugs.
- Polypharmacy in severely ill patients.
- Patients with significant liver or kidney dysfunction.
- Elderly suffering with multiple pathological conditions and receiving several drugs concurrently.

A. Drug Interaction due to Pharmacokinetic Mechanisms

a. Absorption: GIT absorption of many drugs is influenced by concurrent use of other agents having large surface area that bind or chelate, alter gastric pH, alter GIT motility, affect transport proteins such as *p*-glycoprotein.

- Atropine decreases gastric emptying and decreases intestinal absorption of other drugs.

- Prokinetic drugs that hurry gastric emptying increase GIT absorption.
- Milk, antacids and iron preparations form chelates with tetracyclines and decrease their absorption.
- Sucralfate decreases phenytoin levels due to inhibition of its GI absorption. Such drug interactions could be minimized by administering 2 drugs with a gap of 2–3 hours so that they cannot come in contact with each other in the GIT.
- H2 blockers and PPIs decrease ketoconazole absorption because they decrease gastric acidity which promotes dissolution and absorption of ketoconazole.
- An addition of epinephrine to local anesthetic injection slows down the systemic absorption of local anesthetics and prolongs its duration of effect by providing local vasoconstriction.

b. Distribution: The distribution is altered by competing with plasma protein binding and displacing from tissue binding sites, e.g. drugs like quinidine, verapamil, amiodarone displace digoxin from tissue-binding sites to increase its bioavailability. The sulfonamides displace bilirubin in neonates from its protein-binding sites causing kernicterus.

c. Metabolism: The hepatic cytochrome P450 iso-enzyme system causes most of the known drug interactions. CYT P450 is a group of heme-containing isoenzymes located on the membrane of the smooth ER (endoplasmic reticulum) mainly in liver and intestinal tract. It metabolises endogenous substances (steroids, hormones, prostaglandins, lipids, fatty acids) and involved in detoxification of exogenous compounds (especially after oral ingestion). Cyt P450 isoenzymes are used as substrates by many drugs for their metabolism. Drugs can inhibit or induce metabolism of other drugs given concurrently by competing for metabolism for available P450 isoenzyme substrates. Barbiturates, phenytoin, rifampin, troglitazone can induce cytochrome isoenzymes in liver and small intestine. The drug metabolising enzymes can be induced or inhibited leading to therapeutic failure or increased effect, respectively.

- Enzyme induction: Cytochrome P450 isoenzymes induction by any substance causes increased synthesis of that isoenzyme, resulting in increased metabolism and hepatic clearance of all substrates through that specific pathway, e.g. rifampicin, phenobarbital is capable of inducing different isoenzymes. Some drugs like carbamazepine, imipenem prompt time-dependent induction by an autoinduction process caused by increased synthesis of that isoenzyme leading to increased metabolism and hepatic clearance of all substrates through that specific pathway. Rifampin as a microsomal inducer increases CYT P450, CYP1A2, CYP2AC subfamily. It induces metabolism of many drugs like warfarin, oral contraceptives, corticosteroids, sulfonylureas, steroids, HIV protease inhibitors, theophylline, metoprolol, fluconazole, ketoconazole, clarithromycin, phenytoin. Rifampicin causes contraceptive failure. Alcohol consumption and smoking induce CYP2E1 and CYP1A2, respectively. Terfenadine and asmetizole are prodrugs that undergo extensive hepatic metabolism to active and inactive metabolites by CYP3A subfamily. Both terfenadine and asmetizole can cause torsades de pointes, a life-threatening cardiac arrhythmia.
- Enzyme inhibition: One drug may inhibit the metabolism of another drug causing increased levels of slowly metabolized drug and prolongation of potentiation of its pharmacological effects, e.g. cimetidine. Theophylline metabolism is inhibited by erythromycin by inhibition of CYP3A4. Erythromycin and clarithromycin are potent inhibitors of CYP3A4 inhibiting the metabolism of drugs, e.g. terfenadine, asmetizole, cisapride, theophylline.

- Ketoconazole and itraconazole are inhibitors of CYP3A4 and have shown to cause increased QT interval and fatal torsade's de pointes when used with asmetizole or terfenadine.
- **Excretion:** An active drug's renal excretion can also be affected by concurrent drug therapy. Other drugs that affect urinary pH, influence the renal excretion of certain drugs that are weak acids or weak bases, due to changes in ionization of drug. Some drugs are eliminated by active secretion into renal tubules.
- The changes in glomerular filtration rate, tubular reabsorption and tubular secretion affect renal drug clearance, e.g. the tubular secretion of penicillins and cephalosporins is blocked by probenecid and their action is prolonged.
- Sodium bicarbonate alkalises urine and increases excretion of acidic drugs, e.g. aspirin and barbiturates.
- Ammonium chloride or ascorbic acid acidifies urine and increases excretion of basic drugs such as morphine.
- Thiazide diuretics elevate blood glucose levels and may counteract blood sugar lowering effect of oral hypoglycemic drugs.
- The active tubular secretion of some drugs is by means of P glycoprotein, organic anion transporters (OATP), organic cation transporters (OCT). P glycoprotein effluxes drugs like digoxin, cyclosporine, dabigatran, daunorubicin and tacrolimus. The plasma concentration of these drugs can be increased by inhibiting P glycoprotein. Probenecid has high affinity for tubular organic anion transporting polypeptide (OATP) and decreases excretion of penicillin. OATP and OCT transport processes can transport their substrates from blood to tubular fluid and vice-versa.

B. Drug Interaction due to Pharmacodynamic Mechanisms

When administering drugs with similar pharmacological effects, an additive or synergistic response is usually seen leading to supra-additive effect. If the two drugs have opposite pharmacological effects, it leads to antagonism (leading to decreased effects) known as pharmacodynamic interactions.

Additive effect: The effect of two drugs add up. Amlodipine + atenolol as antihypertensive.

Supra-additive effect: The effect of combination is greater than the individual effect of the components, e.g. sulfamethoxazole + trimethoprim. Both are bacteriostatic drugs but the combination becomes bactericidal.

Combined toxicity: The use of two or more drugs in combination can produce toxic effects on the same organ, causing organ damage. The concurrent administration of two nephrotoxic drugs can produce kidney damage. Loop diuretics increase the ototoxicity of aminoglycosides. Use of two CNS depressants, e.g. BZPs and antihistamines may cause excess sedation. Metoclopramide increases extrapyramidal side effects of phenothiazines. Potassium sparing diuretics and angiotensin-converting enzymes (ACEs) given together cause severe hyperkalemia.

Antagonism: CNS-stimulant drugs and CNS-depressant drugs antagonize each other's action.

Drug–food interaction: Some of the drug–food interactions are of significant importance.

1. Monoamine oxidase inhibitors (MAOIs) cause hypertensive reactions in person taking tyramine rich food, e.g. matured cheese, red wines.

2. Grape fruit and oranges inhibit CYP3A4 isoenzyme system and increase bioavailability of drugs like indinavir, saquinavir and midazolam.
3. A rich protein diet produces acidic urine which promotes excretion of basic drugs. Low protein diet provides alkaline urine which promotes excretion of acidic drugs, e.g. aspirin.
4. Food, orange juice, coffee, tea markedly decrease the bioavailability of alendronate. Hence, the drug is administered empty stomach with plain water only.

Drug Herbal Interactions

Gingko biloba increases the bleeding tendency with concurrent use of antiplatelet and anticoagulant drugs.

St. John's wart causes phototoxicity when used with tetracyclines, sulfonamides and proton pump inhibitors.

Administration of garlic/ginger with anti-coagulant and anti-platelets should be avoided because of risk of bleeding.

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