Chapter

1

Pharmacokinetics and Pharmacodynamics of Drugs

Pharmacokinetics (PK) is the study of drug movements within the body. In order to produce its optimal effect, a drug must be present in an appropriate concentration at its site of action. The various steps involved in the pharmacokinetics of drugs can be remembered by an acronym DADME. The concentration of the drug at the target site depends upon the **D**ose or amount of drug, and release of active ingredient from the pharmaceutical formulation, **A**bsorption from the site of delivery into blood circulation, and **D**istribution into various fluid compartments (VdF) and tissues (VdT) of the body. The transfer of drugs across cell membranes largely depends on their dose or concentration, molecular size and shape, solubility at the site of absorption, degree of ionization and relative lipid solubility. This is followed by **M**etabolization (biotransformation, activation, inactivation) of the drug which mostly occurs in the liver. The water-soluble drug is largely **E**xcreted or eliminated in the urine (and partly in the bile, saliva, sweat, breast milk, feces) while ionized lipid-soluble agents may be stored in the body tissues.

Pharmacodynamics (PD) deals with the biological effects of drugs on various therapeutic targets or receptors. There is increasing awareness that each patient or host is unique because of genetic differences in drug metabolic pathways (Pharmacogenomics) which determines the efficacy of therapeutic agent and risk of the adverse drug reactions (ADRs). In due course of time, the drug therapy is likely to be "fine tuned"

to the concept of "personalized prescription" depending upon the genome of the patient.

Factors Modifying Absorption

The drugs in an aqueous solution are more readily absorbed than those given in an oily solution, suspension or solid form because the aqueous formulation mixes more readily with the aqueous phase at the site of absorption. Local conditions at the site of absorption alter solubility particularly in gastrointestinal tract. The concentration of a drug influences its rate of absorption. The circulation at the site of absorption also affects drug absorption. The area of absorbing surface to which a drug is exposed is one of the most important determinants of the rate of drug absorption. The absorbing surface is determined largely by the route of administration (Table 1.1).

Distribution of Drugs

The body can be considered as a series of compartments with varying accessibility to drugs. In the blood, the distribution of a drug is chiefly influenced by its lipid solubility, ionization, pH of blood, available protein binding capacity and differences in the regional blood flow. A water-soluble drug is distributed mostly in the extracellular space and it may not readily pass into cerebrospinal fluid or other body cavities. Lipid-soluble drugs are distributed throughout the intracellular and extracellular spaces.

Selective distribution of drugs occurs due to protein binding in the blood (penicillins, phenylbutazone) and in the tissues (mepacrine). In case of drugs which are not bound to proteins, distribution is confined to the extracellular space and they can be used to measure extracellular fluid volume (inulin, bromide). The drugs that are rapidly absorbed from the gut because of their lipid solubility (unionized) are known to readily diffuse into the CSF and brain. The ionized water-soluble (neostigmine, streptomycin) drugs are poorly absorbed from the gut and they show poor penetration into various body fluids. When meninges are inflamed, the penetration of all drugs into CSF is enhanced.

TABLE 1.1: Routes of administration of drugs and their practical implications

Route	*Absorption pattern*	*Special utility*	*Limitations and precautions*
Intravenous	Potentially immediate effect.	Valuable for emergency use, permits titration of dose, suitable for large volumes and irritating substances which can be administered in a diluted form.	Increased risk and chances of infection, sepsis and tissue necrosis on extravasation. Not suitable for oily and insoluble substances. It is expensive and self and ambulatory medication is not possible.
Intramuscular	Prompt absorption from aqueous solution but slow and sustained absorption from oily preparations.	Suitable for oily vehicles and some irritating substances.	May precipitate abortive polio, cause local necrosis and infection and are contraindicated in patients with a bleeding disorder. Some drugs are locally irritant and have erratic absorption (dilantin, chloramphenicol).
Subcutaneous	Prompt absorption occurs from aqueous solution but absorption is slower compared to intramuscular route.	Suitable for vaccines, insulin and some insoluble suspensions and for implantation of solid pellets.	Self-medication is possible, not suitable for large volumes, local pain and necrosis may occur.
Oral	Variable absorption depending on multiple factors.	Most common, convenient, economical and safe route. The unabsorbed drug acts at the local site.	Requires cooperation of the patient and the caretaker. The bioavailability is erratic because most drugs are metabolized in the liver after absorption and gastric juices may inactivate some drugs.

(*Contd.*)

TABLE 1.1: Routes of administration of drugs and their practical implications *(Contd.)*

Route	*Absorption pattern*	*Special utility*	*Limitations and precautions*
Sublingual	Prompt absorption of lipid-soluble drugs.	Relatively fewer molecules are required to produce drug effect because gastro-intestinal tract is bypassed.	Drugs requiring rapid effect on the heart (nitroglycerine, nifedipine) are given through this route.
Rectal	Slower absorption, 50% will pass through liver and then enter systemic circulation.	Useful in children with persistent vomiting and alteration in consciousness in domiciliary practice.	Psychological embarrassment, irritant to mucosa, irregular and incomplete absorption (paraldehyde, paracetamol, diazepam, aminophylline).
Intrathecal	Effective levels are achieved at the site of action.	Produce local effects on meninges and CNS.	Iatrogenic and chemical meningitis can occur. Large volumes cannot be given (gentamicin, human antitetanus serum).
Pulmonary (aerosol, pressurized nebulizer, inhalers and rotacaps)	Prompt local and systemic effects	Direct absorption with avoidance of hepatic transformation and systemic side effects.	Poor ability to regulate dose, cumbersome method in children, irritant to lungs. Particle size of >7 microns will not reach small bronchi and if it is <1 micron, it is likely to be exhaled.

Plasma Proteins and Tissue Binding

Many drugs circulate in the blood in two forms, free (pharmacologically active, diffusible and available for metabolism and excretion), and bound (pharmacologically inert, neither diffusible nor available for metabolism or excretion). The drugs with weak protein binding readily release the active drug as soon as the concentration of free drug falls. Thus, protein binding can be regarded as a mechanism for drug storage. Total plasma concentration (free plus bound drug) of a drug without any regard to the proportion of protein bound component can give a misleading impression, because only the free drug will diffuse into the tissues and other body fluids and provide biological activity. The claims that one penicillin gives higher total plasma concentration as compared to another, are meaningless unless it is known as to what proportion of the drug is in the bound form.

When two drugs having an identical affinity for the same binding site are given, they will compete with each other thus interfering with their bioavailability. In situations with reduced protein binding capacity (malnutrition), the concentration of a free drug may be significantly higher.

Plasma Concentration of Drugs

Plasma concentrations are specially useful and monitored when a drug may have to be taken in near toxic doses (lithium, anticonvulsants, digoxin); there are great individual variations and lack of easily measured response (antidepressants) or a potentially toxic drug is being used in the presence of renal failure (aminoglycosides), to assess compliance (anticonvulsants) and for management of poisoning (salicylates, barbiturates).

The blood is the principal vehicle for distribution of the drug into the various fluid compartments of the body. The concentration of a drug in blood (or plasma) is often related to its concentration in the target tissues. Because of ease of accessibility for samplings, plasma concentration is commonly used as a guide in clinical practice. The blood sample should be collected when a steady state has been achieved and just before the

administration of next dose of drug. The relationship between plasma concentration and tissue concentration (pharmacological effect) is closest in the case of drugs that are themselves the sole pharmacologically active compounds (not their metabolites) or drugs that act irreversibly such as monoamine oxidase inhibitors and anticholinesterases.

Half-life of a Drug

The peak plasma concentration of a drug after administration is called C_{max} and the time taken to reach the maximum concentration after its administration is called T_{max}. The period of time required for the concentration of the drug to get reduced to one-half (t½) is called biological half-life which corresponds to the duration of action of a drug. The plasma half-life of a drug depends upon how quickly the drug is eliminated from the plasma. The drug may be eliminated from the body by excretion, protein binding, metabolic inactivation or translocation to another body fluid compartment such as the intracellular fluid. The dosing interval of medications is based on the biological half-life of the drug to ensure sustained effect throughout the day. The drugs with short half-life are administered at frequent intervals while a drug like levothyroxine which has a half-life of 5–7 days is administered as a single daily dose.

Metabolism

Drugs must be eliminated from the body in a reasonable time. Those drugs which are water soluble and relatively lipid insoluble and ionised are usually excreted unchanged by the kidneys. Volatile anesthetics are highly lipid soluble and unionized drugs are reabsorbed by back diffusion from the glomerular filtrate and tend to remain in the body indefinitely unless metabolized and inactivated. Drug metabolism occurs chiefly in the liver and is of two kinds:

1. Conversion to pharmacologically inactive substances.
2. Conversion to pharmacologically active substances, e.g. cortisone, prednisone, imipramine, phenylbutazone and cyclophosphamide.

The amount and nature of drug metabolizing enzymes are genetically determined and the rate of drug metabolism varies greatly between individuals. Drugs are principally metabolized by enzymes in hepatic microsomes (a fraction of the cell endoplasmic reticulum) but also to a lesser extent by enzymes elsewhere in the body and in the blood. Two basic chemical reactions occur:

1. *Nonsynthetic*: The molecule is changed by oxidation, reduction or hydrolysis.
2. *Synthetic*: The molecule is conjugated with other substances, glucuronic acid (glucuronidation), acetic acid (acetylation), and sulphate (ethereal sulphate formation).

Phenobarbitone, phenytoin, phenylbutazone, alcohol, DDT and griseofulvin, to name a few, are enzyme inducers. Enzyme induction by alcohol is a likely explanation for tolerance shown by alcoholics to barbiturates and tolbutamide. While treating epilepsy, enzyme induction has practical implications. Drugs that depress hepatic drug metabolizing enzymes (including drugs that interfere with liver function) will potentiate the effect of certain drugs. Phenytoin metabolism is inhibited by coumarin anticoagulants, isoniazid and phenylbutazone so that phenytoin toxicity may occur when these drugs are being administered concomitantly.

Excretion

Renal excretion: The renal excretion depends upon the extent of plasma protein binding of a drug, glomerular filtration rate, amount of back diffusion from glomerular filtration (influenced by urine pH) especially when a drug is lipid soluble, active renal tubular reabsorption and active renal tubular secretion. Renal plasma flow is 12 ml/min at birth and reaches adult level of 140 ml/min by one year of age. Similarly, glomerular filteration rate (GFR) is 2–4 ml/min at birth, increases to 8–20 ml/min by 2 to 3 days and reaches adult level of 120 ml/min by 3 to 5 mon.

Biliary excretion: Many drugs excreted in the bile are often reabsorbed (enterohepatic circulation) into the circulation thus

prolonging their half-life. They are eventually excreted in the urine. High concentration of a chemotherapeutic agent is mandatory for treating infections of the biliary tract including typhoid carriers. The drugs that achieve significant concentrations in the bile include penicillins, rifampicin, erythromycin and tetracyclines.

Pulmonary excretion: Volatile lipid-soluble anesthetics and metabolites are excreted through the lungs.

Excretion/secretion in the milk: Unionized lipid-soluble drugs readily diffuse from blood to breast milk; but since the pH of the blood and milk are different (blood 7.4, milk 7.0), the total concentration of the drug is not identical in the two fluids. *In general, whatever is safely tolerated by the nursing mother, is generally safe for her suckling infant*. However, the ingestion of following drugs by the nursing mother contraindicates breastfeeding: Antithyroid drugs (except propylthiouracil), radioactive pharmaceuticals, anticancer drugs or cytotoxic agents, phenelzine, phenindione, amiodarone, tamoxifen, lithium carbonate, bromocriptine, and drugs of abuse. In most other situations when transmammary medication occurs in a suckling infant, it is best to stop the intake of offending agent to the mother and replace it by a safer alternative.

Calculation of Dose

The dose of a drug can be calculated on the basis of body weight or surface area (SA), the latter being more appropriate because it is proportional to the metabolic rate. However, because of convenience, the dose of drug is usually calculated on the basis of body weight. Because of their higher metabolic rate, children generally require higher dose per unit body weight compared to adults. There is no reliable formula for calculation of drug dosages in infants and if the proper dose of a drug is not known, it must be ascertained because the risk of intolerance is grave in infants. When available, experimentally determined or clinically established doses should be used. No method of calculation of dose provides for the individual variations in response. *The*

fixed dose combinations (FDCs) *should be avoided in children due to difficulty in administration of correct dose of each component and greater risk of toxicity*. Based on adult dose, various formulae are available to calculate the dose of drugs in children.

1. $\frac{\text{Weight of the child in kg}}{60} \times \text{adult dose}$
2. $\frac{\text{SA of the child in } M^2}{1.8} \times \text{adult dose}$
3. SA of the child in $M^2 \times 60$ = % of adult dose
4. Clark's rule: Adult dose × (weight in lbs ÷ 150)
5. Young's rule: Adult dose × (age in yrs + 12 ÷ age in yrs)
6. Fried's rule: Adult dose × (age in months ÷ 150)
7. Webster rule: Adult dose × age in yrs + 1 ÷ age in yrs + 7.

In obese children, dosing per unit body weight may create problems because they have a slow metabolic rate with reduced drug clearance. *Therefore, it is recommended to calculate the dose in obese children on the basis of their ideal body weight for their age*.

Influence of Age, Sex and Disease

Age: Preterm babies are likely to be intolerant to many drugs because the organs responsible for disposing off the drugs from the body are less efficient. Newborn babies have relatively lower renal blood flow and glomerular filtration rate than adults. A wide variety of enzyme reactions are less developed specially in the prematures. Excretion of many antibiotics is delayed. Total plasma protein and albumin concentrations are lower in the newborn than in older children. Thus binding capacity of drugs is lower so that more of the drug is free and available for diffusion into the tissues. The older children are more tolerant than adults to digitalis but tolerance to atropine and morphine is either low or normal.

Sex: Females are believed to be more liable to be excited follow- ing intake of morphine and respond poorly to antidepressant drugs. As such there are no clinically important qualitative sex differences in action of drugs but there are wide individual variations.

Diseases: Adequate knowledge regarding both the drug and the disease is essential for safe and rational therapy. Hepatic and renal insufficiency often results in defective metabolism or excretion and necessitates modification of drug dosages. Patients with malfunctioning of respiratory system are intolerant to drugs which are known to depress respiration (opiates and barbiturates). Asthmatic attack may be precipitated by cholinergic drugs, release of histamine or by blockage of beta-receptors. Myocardial damage makes a patient intolerant to therapeutic doses of digitalis and sympathomimetics. Hepatic porphyria may be precipitated by certain drugs and chemicals either by induction of hepatic ALA-synthetase enzyme or by the haem-containing drug oxidizing enzymes, cytochrome P450, e.g. phenobarbitone, sulfonamides, hydantoin, methyldopa, chloroquine, pentazocine, phenylbutazone and oral contraceptives.

In patients with shock, the drugs injected subcutaneously may not be absorbed owing to intense peripheral vaso-constriction and when shock resolves, there is pronounced effect of previously administered drug. Therefore, drugs should preferably be administered intravenously in children with shock. In patients with congestive heart failure, sodium-containing drugs like sodium salicylate, sodium penicillins and sodium-containing antacids should be avoided. A number of drugs and chemicals lead to intravascular hemolysis in patients with G-6-PD deficiency. The list of banned drugs includes primaquine, pamaquine, pentaquine, plasmoquine, sulfonamides, furazolidone, antipyrine, para-aminosalicylic acid (PAS), naphthalene, methylene blue, phenylhydrazine, probenecid and fava beans.

Pharmaceutical Formulations and Biological Availability

When a drug is prescribed, the patient does not receive the drug alone but a complex mixture along with other excipients which are added to allow the drug to be offered in a convenient, stable and easily administered form. Majority of physicians tend to ignore pharmaceutical formulations and additives or excipients

as an important factor producing variable or unexpected response to drugs. The particle size (surface area of a tablet exposed to solution), diluting substances, tablet size and the pressure used in the tableting machines can affect the biological availability of the drug.

Drug Dosages in Patients with Renal Failure

The drugs may accumulate in the body due to failure of renal excretion or they may exacerbate renal damage. Problems of safety arise especially in patients with renal failure who must be treated with drugs that are potentially toxic and which are eliminated by the kidneys. Creatinine clearance is the best guide for relationship of half-life of a drug to renal failure. If the creatinine clearance is halved, the half-life of a drug is doubled and if it is reduced to 25 percent, the half-life of the drug is quadrupled and so forth.

a. *Drugs eliminated by the kidneys:* Aminoglycosides, amphotericin B, and sulfonamides.
b. *Drugs eliminated by nonrenal mechanisms:* Chlortetracycline, erythromycin, chloramphenicol and nalidixic acid. Metabolites of these drugs may accumulate in patients with renal failure but they are safely tolerated.
c. *Drugs intermediate between (a) and (b) above:* Penicillins, cephalosporins and cotrimoxazole.

The measurement of plasma concentration of drugs is useful and desirable in patients with renal failure. The maintenance dosages of the drugs in group (a) should be reduced to about 25 percent and in case of less toxic members of group (c) to about 50 percent of the recommended dose. The priming or loading doses should be avoided in children with renal dysfunction. The interval between doses should be increased on the basis of a crude formula: Drug interval (hr) between two doses = plasma creatinine mg/dl × 8. Based on plasma creatinine and creatinine clearance values, charts can be consulted for identifying the fractional dose of the drug required in children with renal failure of varying severity.

Drugs and the Liver

Many drugs are metabolized in the liver. The metabolites may be pharmacologically active (cortisone, chloral hydrate, phenylbutazone, cyclophosphamide) or inactive (most drugs). In patients with hepatic disease, the drugs may thus become either more or less active. The drugs may interfere with hepatic functions in the following ways:

- *Interference with bilirubin metabolism:* Novobiocin inhibits bilirubin conjugation while C-17 steroid derivatives interfere with bilirubin excretion into the hepatic canaliculi. The androgens and anabolic steroids, estrogens and progestins interfere with bilirubin excretion into the hepatic canaliculi and cause reversible cholestatic jaundice.
- *Direct liver cell injury:* Carbon tetrachloride, DDT, paracetamol, arsenicals, iron, anticancer drugs and chloroform can cause hepatocellular damage.
- *Allergy or hypersensitivity or idiosyncratic reaction:*
  - Hepatitis-like reaction. Hydralazine, INH, pyrazinamide, ethionamide, NSAIDs, MAO inhibitors, etc.
  - Cholestatic injury. It is may be dose related (steroids) or allergic (phenothiazines).
  - Combined hepatocellular and cholestatic damage. Sulfonamides, PAS, and erythromycin estolate.

Prescribing in Hepatic Disease

Whenever possible it is recommended to use alternative drugs which can be safely given to children with hepatic dysfunction.

Fever: Use acetylsalicylic acid and paracetamol. NSAIDs should be avoided.

Sedation: Use diazepam or pethidine and avoid paraldehyde.

Antidepressants: Tricyclics are safer as compared to MAO inhibitors. Anticonvulsants should be used with caution.

Diuretics: It is desirable to use potassium-sparing (spironolactone) diuretics. Severe hypokalemia with worsening of hepatic status may occur with commonly used diuretics (thiazides, furosemide).

Steroids: Cortisone and prednisone may be ineffective in conventional doses because they are converted into active form (hydrocortisone and prednisolone) by the liver. Anabolic steroids and sex hormones should be used with caution because they are normally metabolized to inactive forms in the liver.

Antibiotics and chemotherapeutic agents: Antitubercular drugs should be used with caution. Penicillins and its semisynthetic derivatives, aminoglycosides and cotrimoxazole are safely tolerated by children with hepatic dysfunction.

Drug Therapy in Children with Protein–Energy Malnutrition

Malnourished children have a high incidence of intercurrent infections necessitating frequent use of drugs. The nutritional status is known to alter the biological functions in children. It is essential to know the pharmacokinetics and pharmacodynamics of drugs in malnourished children in order to ensure rational use of drugs. Due to frequent association of hypoproteinemia, the levels of free drugs are likely to be higher in children with protein–energy malnutrition (PEM). In addition, clearance of drugs by kidneys and their biotransformation by liver may be decreased. Calculation of drug dosage on the basis of body weight may be erroneous because they are likely to have relatively large surface area per unit body mass. It is advisable to calculate drug dosage on the basis of body surface area in malnourished children. The biological functions recover in a period of 4 to 6 wk following nutritional rehabilitation. Therefore, drug administration should be revised when the child has recovered. Scanty information is available regarding the pharmacokinetics of drugs in malnutrition but some drugs need special consideration when used in children with PEM.

Malnourished children should not be digitalized as they are sensitive to digitalis and its derivatives. Instead, a diuretic should be used alone while treating congestive cardiac failure. Due to decreased biotransformation in the liver, glucuronide and sulfate pathways get saturated at lower plasma concentrations of paracetamol thus posing an increased risk of toxicity. The absorption of chloramphenicol

is not altered by the nutritional status but there is a slower rate of its biotransformation by the liver. Accordingly, children with severe PEM should receive two-thirds of the recommended dose of chloramphenicol. Bioavailability of intramuscular penicillin is not altered, except in children with gross edema. It appears that in kwashiorkor, the renal clearance of penicillin is decreased and it should be administered at longer intervals. Chloroquine is bound to plasma protein to a greater extent in children with kwashiorkor than in normal children and, therefore, reduced amount of free drug is available. Nevertheless, modification in the dosages of chloroquine is not required because of its slower biotransformation in patients with kwashiorkor.

Oral Medications

Most medications are given orally and most children are fussy to take medicines because of their unpleasant taste. It needs a lot of patience and tact on the part of the mother or nurse to give them medicines. Medicines are absorbed better when given on empty stomach or in-between the meals (one hr before taking food or two hr after food) but they are preferably administered after or along meals to reduce gastric side effects and improve their tolerance (Table 1.2).

Drops formulations are preferred in young infants because small volume of the medicine need to be administered. In preschool children, syrup or suspension formulation is usually given. Dispersible tablets or mouth dissolving tablets can be given to children above 2 to 3 yr of age. Most school-going children should be able to swallow tablets or capsules but at times even an adolescent child may refuse to take a tablet. Some children are extremely prone to vomit when a medicine is given to them. Mother should hold the infant in her lap in a semi-upright position while giving medicine to him. Medicine can be given with a spoon or preferably with a plastic dropper. The exact amount to be administered should be measured with a plastic syringe or by the graduated dispenser provided by the manufacturer. Medicine should not be poured on the dorsum of the tongue but instead it should be spilled between the side of

TABLE 1.2: Drugs that should be administered on empty stomach or in-between meals

- **Antibiotics:** Penicillin G, ampicillin, ceftibuten, cloxacillin, dicloxacillin, erythromycin, azithromycin, tetracycline, cotrimoxazole, levofloxacin, antitubercular drugs especially isoniazid and rifampin.
- **Antifungal agents:** Itraconazole, ketoconazole.
- **Antiviral agents:** Dianosine, didanosine, efavirenz, indinavir, amprenavir, zidovudine.
- **Cardiovascular agents:** Digoxin, captopril, nifedipine, diltiazem, sotalol.
- **Miscellaneous drugs:** Thyroxine, omeprazole, lansoprazole, ranitidine, sucralfate, antiemetics, d-penicillamine, iron*, bisphosphonates, sildenafil, bethanechol, proton pump inhibitors, bisacodyl, etidronate, risedronate, zafirlukast, methotrexate.

*Should preferably be taken in-between the meals or at bedtime.

the tongue and the cheek. No medicine should be mixed in the milk or food because the child may stop taking the milk or food which was laced with the medicine. The medicine or crushed tablet can be mixed in honey or fruit juice.

The toddlers create the greatest fuss in taking medicines and need to be handled with understanding and firmness. The attention is diverted and child is held firmly while giving the medicine. In a struggling child, due care should be exercised to prevent choking and aspiration. *If the medicine is vomited out immediately or within 5 min after the administration, it should be readministered*. The older child should be dealt with understanding and explanation that the medicine will make him feel better and he will be able to get better or go to school sooner.

Drug Prescription

The prescription should clearly mention the name of the patient, age, sex, weight and diagnosis. The dosing matrix should provide the name and concentration of the formulation, exact dose, frequency of administration, whether taken on

empty stomach or after food, duration of therapy, etc. It is recommended to use the calibrated measuring device provided by the manufacturer or preferably a calibrated dropper or a plastic syringe to ensure precise dosing of the medication. A sample prescription for dosing matrix for Ronit 5 yr old boy weighing 16 kg with diagnosis of congenital hypothyroidism and acute respiratory infection with asthmatic bronchitis is shown in Table 1.3.

Adverse Effects of Drugs

It must be remembered that most diseases recover spontaneously and no drug is entirely safe and virtually every drug has side effects including a placebo. We should try to avoid medications unless they are unavoidable and use those drugs which have withstood the test of time.

- *Overdose:* Absolute excessive intake or relative excessive accumulation due to defective metabolism.
- *Intolerance:* Due to low threshold to normal pharmacological action.

TABLE 1.3: A sample prescription matrix

Medicines	*Empty stomach*	*After breakfast*	*After lunch*	*Evening*	*After dinner*	*Duration*
Tab thyronorm 50 µg	✓					Lifelong
Syrup crocin DS 250 mg/5 ml		✓	✓		✓	2 days, then sos
Syrup moxclav	✓			✓		5 days
Syrup levolin plus 5 ml		✓	✓		✓	7 days
Syrup rantac 75 mg/5 ml	✓			✓		7 days

Please revert back if there is any adverse reaction or intolerance to any medication.

- *Side effects:* They include undesired and unavoidable effects. The side effect may be an undesirable known therapeutic effect (e.g. drowsiness with phenobarbitone when used as an anticonvulsant) or a side effect on one occasion may be a desired effect in another situation, e.g. atropine for anesthetic premedication to dry the bronchial secretions.
- *Secondary effects:* Indirect consequences like diarrhea and deficiency of vitamins, following prolonged use of broad spectrum antibiotics.
- *Idiosyncrasy:* Inherent qualitatively abnormal reaction to a drug due to genetic abnormality, e.g. porphyria, G-6-PD deficiency and nimesulide.
- *Hypersensitivity reactions:*
  - Anaphylactoid shock. It is common following administration of penicillin and horse serum.
  - Pulmonary reactions. Antigen-antibody reactions causing local liberation of substances, including histamine and SRS-A.
  - Urticarial rashes and angioneurotic edema.
  - Serum sickness syndrome.
- *GI intolerance:* Dyspepsia, nausea, vomiting, abdominal pain, diarrhea, and constipation are the most common adverse reactions due to a variety of oral medications.
- *Blood dyscrasias:* Thrombocytopenia, granulocytopenia, agranulocytosis and aplastic anemia are rare but life-threatening.
- *Hemolysis:* Dose-related pharmacological action on normal cells, e.g. lead, some snake venoms, idiosyncracy, G-6-PD deficiency, and allergy. At times a drug (hapten) may combine with protein in the RBC membrane, i.e. PAS, quinine.
- Non-urticarial skin rashes including Stevens-Johnson syndrome.
- Drug fever
- *Syndrome resembling collagen vascular diseases:* Hydralazine, procainamide and anticonvulsants.
- *Hepatitis and cholestatic jaundice:* INH, rifampicin, erythromycin estolate, NSAIDs and chlorpromazine.

- *Miscellaneous adverse effects:* Severe hematemesis (aspirin, NSAIDs), peripheral neuritis, nephritis and toxic cataract.

Drugs and the Fetus

When a pregnant woman is administered a chemotherapeutic agent, there is unwanted and unavoidable exposure of her unborn child to the same agent. A drug which is apparently safe and well tolerated by the mother, may be harmful and damaging to the fetus. *No drug is entirely safe during first trimester of pregnancy*. While prescribing any medicines to a pregnant woman, it is mandatory to ask oneself several questions. Is medication indicated? Is the disease more dangerous as regards fetal safety compared to the known hazards of the therapeutic agent? Has the drug withstood the test of time? When a nursing mother receives some medications, her suckling infant is likely to receive variable amount of drugs secreted through the breast milk. However, whatever is safely tolerated by the nursing mother, is generally safe for her suckling infant. For a detailed list of fetal and neonatal consequences of maternal medications, please refer to Singh M, *Care of the Newborn*, Ninth Edition-2021, CBS Publishers & Distributors Pvt. Ltd., New Delhi.

Drugs in Lactating Women

TABLE 1.4: Conditions where breastfeeding should be avoided

Do not breastfeed and do not feed expressed breast milk	▪ Infant with classic galactosemia. ▪ Mother is infected with HTLV I or II. ▪ Mother has suspected or confirmed Ebola virus disease. ▪ Mother is using illicit drugs (e.g. phencyclidine or cocaine). ▪ Mother has HIV infection*.
Temporarily do not breastfeed, but may feed expressed breast milk to infant	▪ Mother has untreated active tuberculosis: Mother may resume. breastfeeding once she has been treated appropriately for 2 wk and is documented to be no longer contagious. ▪ Mother has active varicella that developed between 5 days prior to delivery and 2 days following delivery.

(*Contd.*)

TABLE 1.4: Conditions where breastfeeding should be avoided (*Contd.*)

Temporarily do not breastfeed and do not feed expressed breast milk	▪ Mother has untreated brucellosis. ▪ Mother has an active HSV infection, with lesions present on the breast. ▪ Mother is taking certain medications.

Mother is taking certain medications and vaccines

Live attenuated vaccine	*Psychoactive drugs*	*Drugs of abuse*	*Other drugs*	*Radioactive compounds*
Mpox/Smallpox (ACAM2000) Yellow fever	Citalopram Clomipramine Diazepam Doxepin Fluoxetine Fluvoxamine Lamotrigine Lithium Mirtazapine Nortriptyline Olanzapine Sertraline Venlafaxine	Alcohol Amphetamines Benzodiazepines Cocaine Heroin LSD Methamphetamine MDMA Marijuana Phencyclidine	Amiodarone Antineoplastics Gold salts Iodine Lithium Retinoids	**Temporary Cessation of Breastfeeding** ^{14}C-labeled ^{99m}Tc-labeled I-labeled (^{123}I, ^{125}I or ^{131}I-iodo hippurate) **Prolonged Cessation of Breastfeeding** I-labled (^{23}I- BMIPP, -HSA, -IPPA, -MIBG, -NaI, or -HSA) ^{201}Tl-chloride ^{67}Ga-citrate ^{22}Na, ^{75}Se

*Breastfeeding by HIV-infected women may be appropriate in resource-limited settings if breast milk replacement is not feasible, affordable, or safe.

Drugs to be Avoided in Children with G6PD Deficiency

TABLE 1.5: Medicines and other substances unsafe or safe in individuals with G6PD deficiency

Unsafe in moderate to severe G6PD deficiency	*Medicines that are probably safe*
Chlorpropamide Dabrafenib Dapsone Fluoroquinolones (ciprofloxacin, moxifloxacin, norfloxacin, ofloxacin) Methylene blue Nalidixic acid Nitrofurantoin, nifuratel, and nitrofurazone Phenazopyridine Primaquine and tafenoquine Rasburicase and pegloticase Sulfonylureas	Acetaminophen Aminophenazone (NSAIDs) Antihistamine Antipyrine Ascorbic acid Aspirin Benzhexol Chloramphenicol Chloroquine and hydroxychloroquine Colchicine Clotrimazole Diphenhydramine Isoniazid Levodopa (L-Dopa) and levodopa-carbidopa Para-aminosalicylic acid Para-aminobenzoic acid Phenylbutazone Phenytoin Probenecid Procainamide Pyrimethamine Quinine Streptomycin Sulfa-containing drugs Tiaprofenic acid Trimethoprim Tripelennamine Vitamin K
Fava beans Henna compounds (black and red Egyptian) Naphthalene (mothballs, lavatory deodorant) Phenylhydrazine Isobutyl nitrite, amyl nitrite	

For detailed list of fetal and neonatal consequences of maternal medications, please refer to Singh M, *Care of the Newborn, Ninth Edition-2021*, CBS Publishers & Distributors Pvt. Ltd., New Delhi.