Chapter

2

Basic Pharmacokinetics

Alice Kuruvilla

The therapeutic effect of a drug is related to the amount of the drug present in the tissues and blood. The drug concentration at a site is dependent on various factors such as absorption, distribution, metabolism and excretion. These points have clinical implications which should be considered when drugs are prescribed. Of particular importance is the effects on pharmacokinetics of one drug in the presence of other drugs taken concurrently.

ABSORPTION

Absorption is the process by which drug molecules gain access to the bloodstream from the site of drug administration. The proportion of a dose that reaches the systemic circulation is known as the bioavailability of the drug and produces effects on the body. Orally administered drugs are absorbed from the stomach or small bowel, and then pass through the liver, before gaining access to the systemic circulation. Therefore, drug levels may vary due to alterations of transit time in the intestine and liver. Drugs given sublingually or by rectal route, bypass liver metabolism and reach high plasma levels. This is also achieved by parenteral administration.

The presence of food influences absorption in various ways, therefore, administration of drugs with food may reduce, delay, increase or have no effect on drug absorption.

- Fatty food delays gastric emptying and absorption.
- Food may enhance the extent of absorption for poorly soluble drugs (e.g. griseofulvin)
- Food may reduce absorption for drugs degraded in the stomach (e.g. penicillin G)

While food does not interfere with absorption of many commonly used drugs, special attention needs to be given to some drugs as shown in Table 2.1.

The absorption of drugs is influenced by the following factors:

- Motility of intestines can alter drug absorption. Anti-muscarinic agents like atropine substitutes, tricyclic antidepressants and opioids increase absorption of many drugs because of reduced peristalsis and stasis. On the other hand, laxatives reduce the time spent in the intestine which leads to reduced absorption of drugs.
- Gastric pH alterations: Aluminum and magnesium salts in antacids may form insoluble complexes leading to reduced absorption of iron and tetracyclines.

Table 2.1: Relationship of drug intake with meals

Empty stomach	*Before meals*	*With meals*	*After meals*	*At bedtime*
Thyroxine Indinavir	Omeprazole	Acarbose (at the beginning of each meal)	NSAIDs aspirin	Statins
Rifampicin, 1 hour before meals Didanosine, 2 hours after meals	Sulfonylureas Sucralfate Glyptins	Fibrates, Meglitinide (within 10 minutes before meal)	Metformin	Montelukast
Alendronate	Insulin injections	Nefinavir Atazanavir	Most medications, unless specified	Insulin glargine (basal insulin)

Calcium present in milk may form chelating agents and reduce absorption of Tetracyclines.

DISTRIBUTION OF DRUGS WITHIN BODY COMPARTMENTS

- After a drug is absorbed by any route its distribution in the body depends on several factors including the size of the body compartment (water/fat) in which the drug is distributed. This is known as the volume of distribution or Vd.
- When the Vd is large, the loading dose of the drug has to be increased. Patient factors such as age, gender, muscle mass, and fat mass may influence distribution.
- Protein binding. Some drugs have a high affinity for plasma proteins. This prolongs the duration of drug effect, and may reduce the frequency of dosing.

SIGNIFICANCE OF HALF-LIFE OF DRUGS

Half-life, which is the length of time required for the concentration of a particular drug to decrease to half of its starting dose in the body, is related to distribution and excretion of drugs. As repeated doses of a drug are administered, its plasma concentration builds up and reaches a steady state.

The half-life indicates how rapidly the drug is eliminated. Knowledge about steady state concentration helps to determine dosage frequency.

DRUG METABOLISM

Metabolism is the process by which drugs are chemically changed from a lipid-soluble form suitable for absorption and distribution, to a more water-soluble form that is suitable for excretion. Most drugs are metabolized by the CYP3A4. Some drugs enhance the activity of these enzymes (enzyme induction), and others decrease their activity (enzyme inhibition). This leads to one drug affecting the metabolism of a second drug given concurrently. This may influence the therapeutic effects when two or more drugs are given on a long-term basis, e.g. phenobarbitone and carbamazepine, induce their own metabolism, therefore the drug levels reduce over time (Table 2.2).

DRUG EXCRETION

Most drugs are excreted via the kidneys after undergoing metabolism in the liver. Renal functions such as glomerular filtration rate and tubular reabsorption are influenced by

Table 2.2: Drug interactions due to altered metabolism

Drug inhibiting enzyme	*Drug affected*	*Effect on drug metabolism*	*Remarks*
Erythromycins [except azithromycin and roxithromycin]	Carbamazepine	Increased plasma levels due to decreased metabolism	Chance of toxicity
	Theophylline Terfenadine Astemizole	Increased plasma levels due to decreased metabolism	Chance of toxicity
	Warfarin	Increased plasma levels due to decreased metabolism	Chance of toxicity
Sodium valproate	Phenytoin	Displaces protein bound phenytoin and decreases its metabolism, plasma levels increased	Check blood levels and adjust dose
	Phenobarbitone lamotrigene	Inhibition of metabolism	Chance of toxicity
Isoniazid chloramphenicol	Phenytoin theophylline warfarin	Inhibition of metabolism	Chance of toxicity
Verapamil, diltiazem	Carbamazepine cyclosporine	Decreases metabolism	Chance of toxicity
Allopurinol	Azathioprine	Inhibits xanthine oxidase, therefore, increases toxicity of azathioprine	Avoid concurrent use
Norfloxacin ciprofloxacin pefloxacin	Theophylline warfarin	Inhibits metabolism	Chance of toxicity
Antifungals ketoconazole, itraconazole, fluconazole protease inhibitors	Terfenadine astemizole zidovudine	Inhibition of metabolism, results in increase in blood levels	Chance of toxicity
Metronidazole tinidazole cefoperazone griseofulvin	Alcohol	Inhibition of metabolism, disulfiram-like reactions	Avoid concurrent use

Note: More drug–drug interactions are shown in Section VIII, Appendix 1

several factors such as ageing, and co-morbid medical illnesses. The dose of the drug needs to be adjusted based on renal functions. Some drugs when given together may alter renal functions, resulting in adverse effects, e.g. diuretics and NSAIDs.

Clinically relevant examples of drug–drug interaction due to altered renal function are shown in Table 2.3.

Table 2.3: Drug interactions due to altered renal function

Drug	*Drug affected*	*Effect*	*Remarks*
Lithium	Diuretics	Sodium depletion leads to increased absorption of lithium and toxicity	Avoid concurrent use
Lithium	NSAIDs	Reduced renal excretion	Chance of toxicity
ACE inhibitors	Spironolactone	Hyperkalemia	Avoid concurrent use
Cephalosporins 3rd generation	Aminoglycosides	Increased nephrotoxicity	Adjust dose
Diuretics, leading to K loss and decreased potassium	Digoxin	Hypokalemia increases digoxin toxicity	Check electrolyte levels, supplement potassium
Probenecid	Penicillin	Reduced excretion	Beneficial effect
Azole antifungals	Sirolimus, cyclosporine	Decreased excretion	Chance of toxicity
Macrolides (erythromycin, clarithromycin)	Statins	Inhibit excretion	Chance of toxicity

Note: *See* Section VIII, Appendix 5.