Shree H.N.Shukla institute of Pharmaceutical Education & Research Rajkot

B.Pharm

Semester IV

Subject Name: Pharmacology I
Subject code:BP404TP

TOPIC:

a. Pharmacodynamics- Principles and mechanisms of drug action. Receptor theories and classification of receptors, regulation of receptors. drug receptors interactions signal transduction mechanisms, G-protein–coupled receptors, ion channel receptor, transmembrane enzyme linked receptors, transmembrane JAK-STAT binding receptor and receptors that regulate transcription factors, dose response relationship, therapeutic index, combined effects of drugs and factors modifying drug action.

b. Adverse drug reactions.

c. Drug interactions (pharmacokinetic and pharmacodynamic)

d. Drug discovery and clinical evaluation of new drugs -Drug discovery phase, preclinical evaluation phase, clinical trial phase, phases of clinical trials and pharmacovigilance.

PHARMACODYNAMICS

Pharmacodynamics (Greek pharmacon: drug; dynamis: power). It covers all aspects relating to 'what the drug does to the body'. It is the study of drugs – their mechanism of action, pharmacological actions and adverse effects.

TYPES OF EFFECTS OF A DRUG

1. **Stimulation**: Some drugs act by increasing the activity of specific organ/system, e.g. adrenaline stimulates the heart resulting in an increase in heart rate and force of contraction.

2. **Depression**: Some drugs act by decreasing the activity of specific organ/system, e.g. alcohol, barbiturates, general anaesthetics, etc. depress the central nervous system.

3. **Irritation**: Certain agents on topical application can cause irritation of the skin and adjacent tissues. When an agent on application to the skin relieves deep seated pain, it is known as counterirritant, e.g. eucalyptus oil, methyl salicylate, etc. They are useful in sprain, joint pain and myalgia.

They exert their action by

reflexly increasing local circulation in deeper structures.

blocking impulse conduction in the spinal cord.

4. **Cytotoxic**: Drugs are selectively toxic for the infecting organism/cancer cells, e.g. antibiotics/anticancer drugs.

5. **Replacement**: When there is a deficiency of endogenous substances, they can be replaced by drugs, e.g. insulin in diabetes mellitus, thyroxine in cretinism and myxoedema, etc.

MECHANISM OF DRUG ACTION

Nonreceptor-Mediated Mechanism of Action of Drugs

1. **By physical action**:

a. **Osmosis**: Some drugs act by exerting an osmotic effect, e.g. 20% mannitol in cerebral oedema and acute congestive glaucoma.

b. **Adsorption**: Activated charcoal adsorbs toxins; hence, it is used in the treatment of drug poisoning.

c. **Demulcent**: Cough syrup produces a soothing effect in pharyngitis by coating the inflamed mucosa.

d. **Radioactivity**: Radioactive isotopes emit rays and destroy the tissues, e.g. 131I in hyperthyroidism.

2. **By chemical action**:

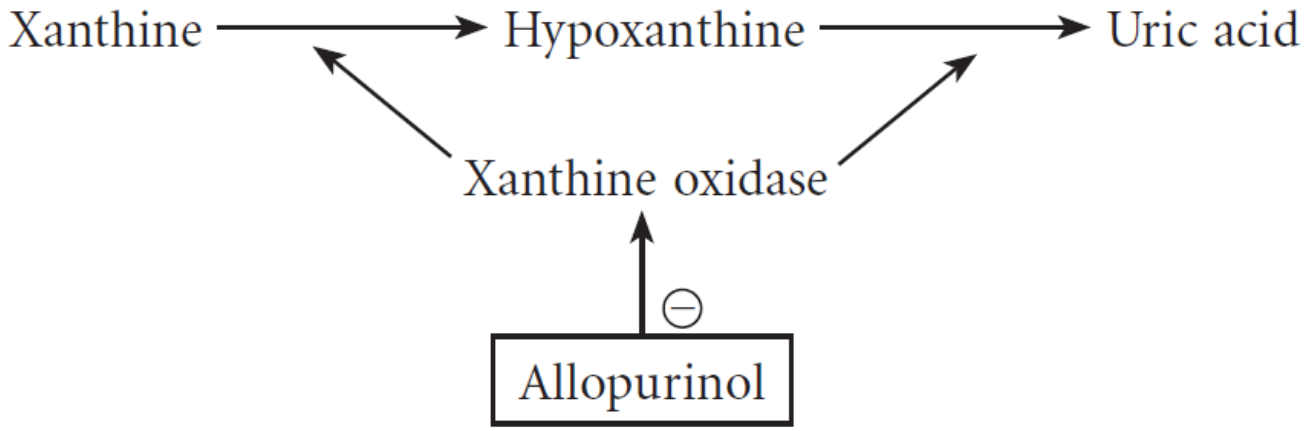
a. Antacids are weak bases – they neutralize gastric acid – useful in peptic ulcer.

b. Metals like iron, copper, mercury, etc. are eliminated from the body with the help of chelating agents. These agents trap metals and form water-soluble complexes, which are rapidly excreted from the body, e.g. dimercaprol (BAL) in arsenic poisoning, desferrioxamine in iron poisoning and d-penicillamine in copper poisoning.

3. Through enzymes: Some drugs act by inhibiting the enzyme activity.

a. Angiotensin-converting enzyme (ACE) inhibitors, such as captopril, enalapril, etc. act by inhibiting ACE. They are used in the treatment of hypertension, congestive heart failure, etc.

b. Xanthine and hypoxanthine are oxidized to uric acid by the enzyme xanthine oxidase, which is inhibited by allopurinol. Allopurinol (competitive inhibitor) is used in the treatment of chronic gout to reduce the synthesis of uric acid.



4. **Through ion channels**: Some drugs directly bind to ion channels and alter the flow of ions, e.g. local anaesthetics block sodium channels in neuronal membrane to produce local anaesthesia.

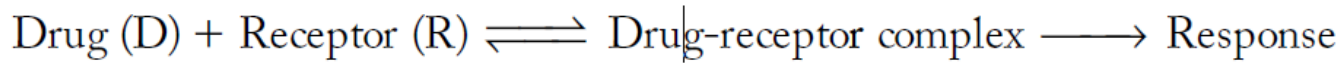
5. **Through antibody production**: Vaccines produce their effect by stimulating the formation of antibodies, e.g. vaccine against tuberculosis (BCG), oral polio vaccine, etc.

6. **Transporters**: Some drugs produce their effect by binding to transporters. Selective serotonin reuptake inhibitors (SSRIs) n bind to 5-HT transporter n block 5-HT reuptake into neurons n antidepressant effect.

7. **Others**: Drugs, like colchicine, bind to tubulin and prevent migration of neutrophils (hence useful in acute gout).

Receptor-Mediated Mechanism of Action of Drugs

Receptors are macromolecules, present either on the cell surface, cytoplasm or in the nucleus with which the drug binds and interacts to produce cellular changes.



For example, adrenergic receptors (" and $), cholinergic receptors (muscarinic and nicotinic), opioid receptors, etc.

Affinity: The ability of the drug to get bound to receptor is known as affinity.

Intrinsic activity: The ability of the drug to produce pharmacological action after combining with the receptor is known as intrinsic activity of the drug.

Agonist: A drug that is capable of producing pharmacological action after binding to the receptor is called an agonist. Agonist has high affinity + high intrinsic activity (e.g. morphine and adrenaline).

Antagonist: A drug that prevents binding of agonist to its receptor or blocks its effect/s is called an antagonist. It does not by itself produce any effect.

Competitive antagonist has high affinity without intrinsic activity (e.g. naloxone and atropine). It produces receptor blockade.

Partial agonist: A drug that binds to the receptor but produces an effect less than that of an agonist is called partial agonist. It inhibits the effect of agonist. Partial agonist has affinity + less intrinsic activity (e.g. pindolol and buprenorphine).

Inverse agonist: It has full affinity towards the receptor but produces effect opposite to that of an agonist, e.g. benzodiazepines (BZDs) produce antianxiety and anticonvulsant

effects by interacting with BZD receptors, but $-carbolines act as inverse agonist at BZD receptor and produce anxiety and convulsions. Inverse agonist has affinity + intrinsic activity between 0 and –1 (e.g. $-carboline).

RECEPTOR FAMILIES

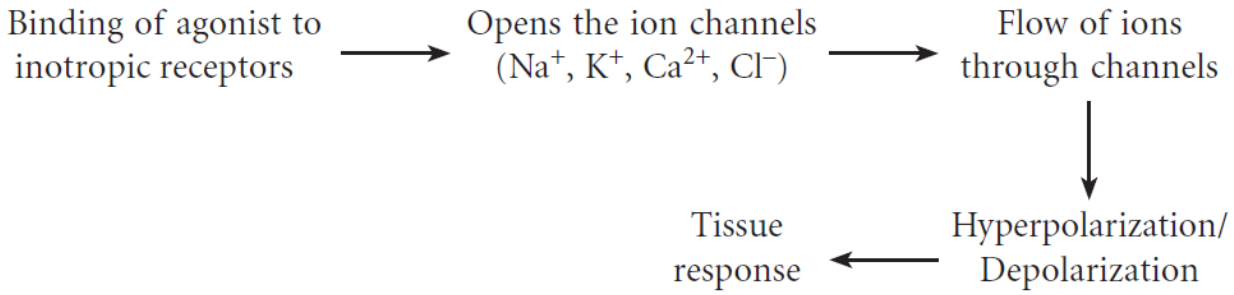
1. Ligand-gated ion channels (inotropic receptors)

2. G protein-coupled receptors (GPCRs; metabotropic receptors)

3. Enzymatic receptors

4. Receptor-regulating gene expression (transcription factors) or the nuclear receptor

Ligand-Gated Ion Channels (Inotropic Receptors). Examples are nicotinic (NM) acetylcholine receptors at neuromuscular junction, GABA (gamma amino butyric acid) and glutamate receptors in the CNS.



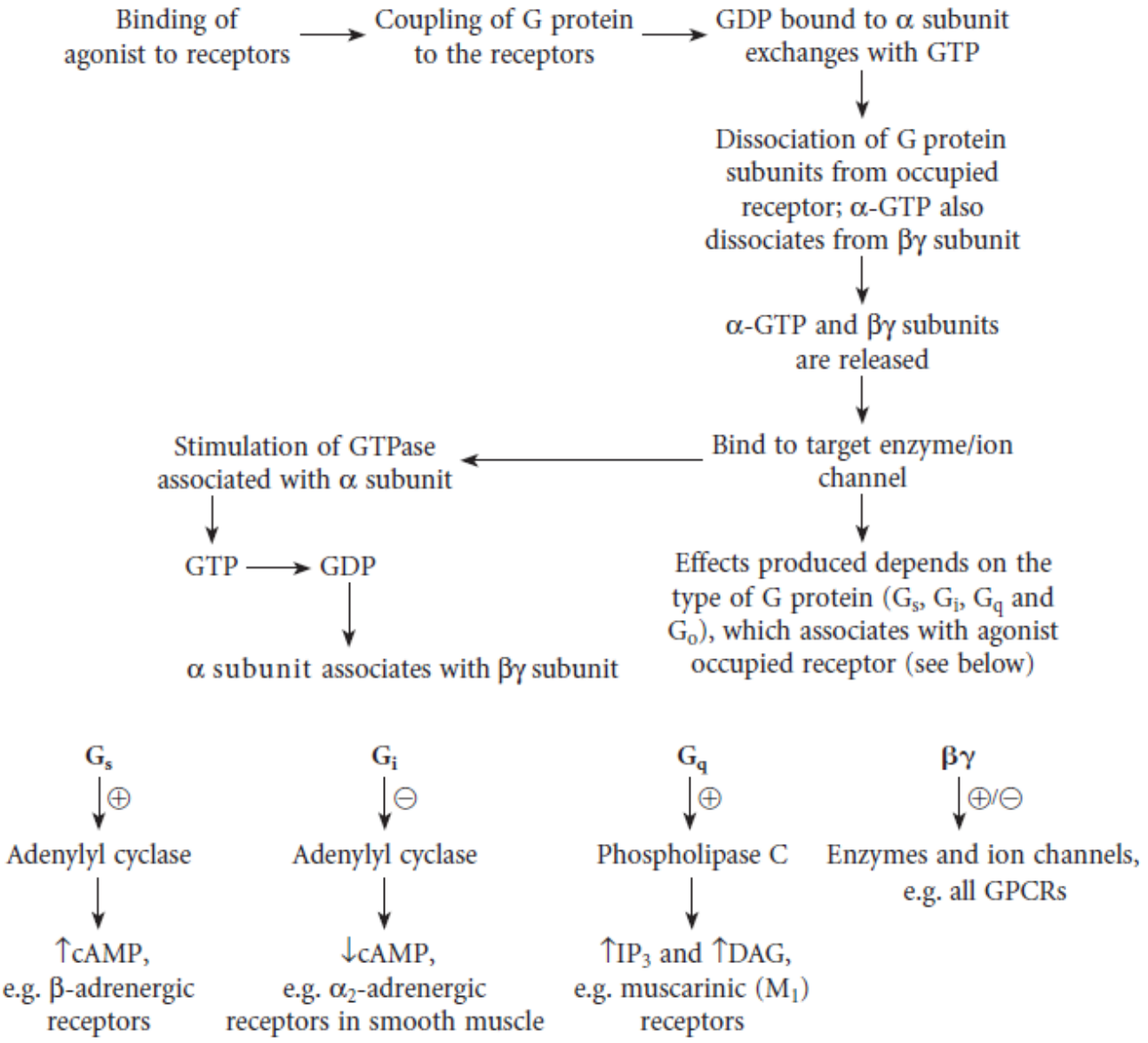
The onset of action of a drug is fastest through this receptor.

G Protein-Coupled Receptors (GPCRs, Metabotropic Receptors). GPCRs are transmembrane receptors which control cell function via adenylyl cyclase, phospholipase C, ion channels, etc. They are coupled to intracellular effectors through G proteins. G proteins are membrane proteins and have three subunits (", $, %) with GDP bound to ALPHA subunit.

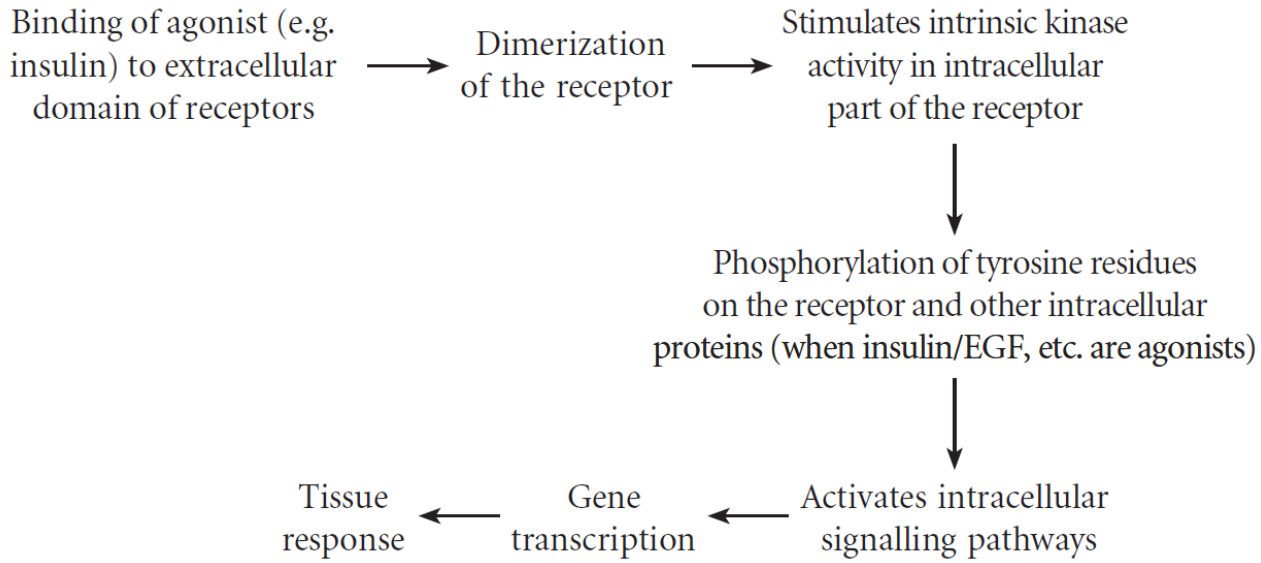
Table 1.5 ■ **Characteristics of various receptor families**

	Ligand-gated ion channels	G protein-coupled receptors	Enzymatic receptors	Nuclear receptors
Location	Membrane	Membrane	Membrane	Intracellular
Effector	Ion channel	Channel or enzyme	Enzyme	Gene transcription
Examples	Nicotinic, $GABA_A$ receptors	Muscarinic, adrenergic receptors	Insulin epidermal growth factor receptors	Steroid, thyroid hormone receptors
Time required for response	Milliseconds	Seconds	Minutes to hours	Hours

The agonist that binds to the receptor is the first messenger. It results in the formation or recruitment of molecules (second messengers) that initiate the signalling mechanism in a cell. Examples of second messengers are cAMP (generated by adenylyl cyclase), cGMP (generated by guanylyl cyclase), Ca2#, IP3-DAG (generated by phospholipase C), nitric oxide, etc.


Binding of agonist to receptors
Coupling of G protein to the receptors
GDP bound to α subunit exchanges with GTP
Dissociation of G protein subunits from occupied receptor; α-GTP also dissociates from βγ subunit
α-GTP and βγ subunits are released
Bind to target enzyme/ion channel
Stimulation of GTPase associated with α subunit
GTP → GDP
α subunit associates with βγ subunit
Effects produced depends on the type of G protein (G_s, G_i, G_q and G_o), which associates with agonist occupied receptor (see below)
G_s
⊕
Adenylyl cyclase
↑cAMP, e.g. β-adrenergic receptors
G_i
⊖
Adenylyl cyclase
↓cAMP, e.g. α_2-adrenergic receptors in smooth muscle
G_q
⊕
Phospholipase C
↑IP_3 and ↑DAG, e.g. muscarinic (M_1) receptors
βγ
⊕/⊖
Enzymes and ion channels, e.g. all GPCRs

Transmembrane Enzyme-Linked Receptors. Transmembrane enzyme-linked receptors have enzymatic activity in their intracellular portion. The enzyme is mainly tyrosine kinase, e.g. receptor tyrosine kinases for insulin, epidermal growth factor, etc.).



Transmembrane JAK (Janus kinase)-STAT (signal transducer and activator of transcription) receptors, e.g. receptors for cytokines, growth hormone, etc. These receptors do not have intrinsic enzymatic activity in their intracellular part. On activation, they dimerize followed by their binding to kinases in the cytoplasm, e.g. JAK n phosphorylates tyrosine residues on the receptor n binding of receptor to STAT which gets phosphorylated n dissociation of STAT from receptor n binds to gene to alter transcription.

Nuclear Receptors – Regulate Gene Expression. Examples: receptors for thyroxine, vitamins A and D, sex steroids and glucocorticoids. Steroids n bind to receptors in cytoplasm n steroid-receptor complex n migrates to nucleus n binds to specific site on the DNA n regulate protein synthesis n response

Regulation of Receptors

Table 1.6 ■ **Regulation of receptors**

Receptor downregulation	Receptor upregulation
Prolonged use of agonists ↓ ↓↓ Receptor number and sensitivity ↓ ↓↓ Drug effect For example, chronic use of salbutamol downregulates β_2-adrenoceptors, which may be responsible for decreased effect of salbutamol in asthmatics.	Prolonged use of antagonists ↓ ↑↑ Receptor number and sensitivity; On sudden stoppage of the antagonist ↓ ↑↑ Response to agonist For example, when propranolol is stopped after prolonged use, some patients experience symptoms, such as nervousness, anxiety, palpitation, tachycardia, rise in BP, increased incidence of angina or even myocardial infarction may be precipitated. This is due to upregulation or supersensitivity of β-adrenoceptors to catecholamines. Therefore, propranolol should not be discontinued abruptly.

DOSE–RESPONSE RELATIONSHIP

The pharmacological effect of a drug depends on its concentration at the site of action, which in turn is determined by dose of the drug administered. Such a relationship is called 'dose–response relationship.

TYPES OF DOSE–RESPONSE CURVES

1. Graded dose–response: This curve when plotted on a graph takes the form of a rectangular hyperbola, whereas log dose–response curve (DRC) is sigmoid shaped.

2. Quantal DRC: Certain pharmacological effects which cannot be quantified but can only be said to be present or absent (all or none) are called as quantal responses, e.g. a drug causing ovulation.

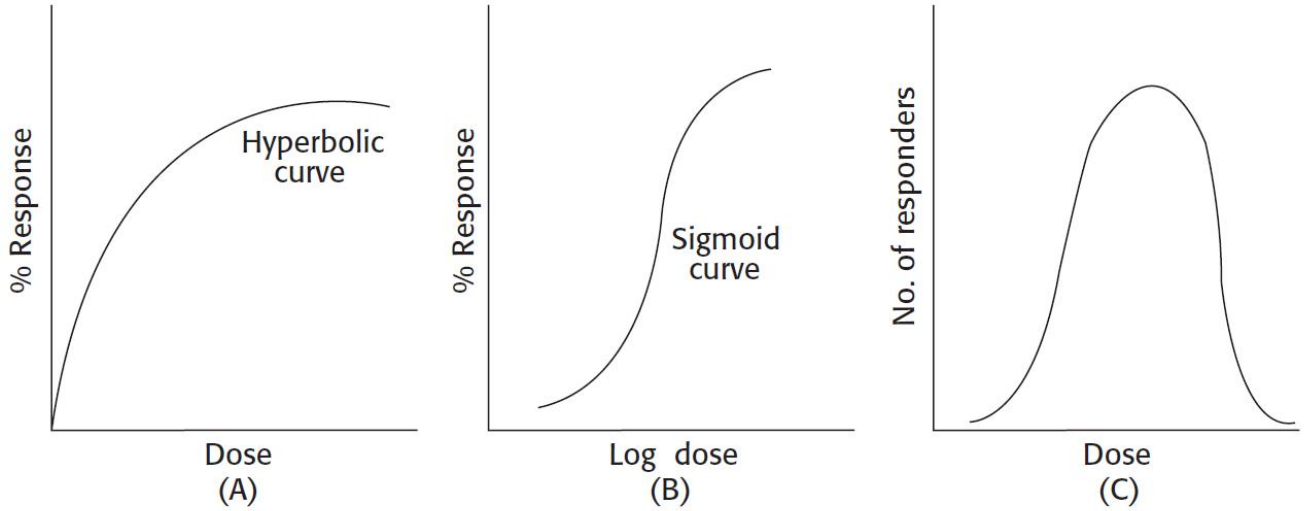


Fig. 1.7 (A) Dose–response curve. (B) Log dose–response curve. (C) Quantal dose–response curve.

Therapeutic Index

Therapeutic index (TI) is an index of drug safety.

$$TI = \frac{\text{Median lethal dose } (LD_{50}) \text{ of the drug}}{\text{Median effective dose } (ED_{50}) \text{ of the drug}}$$

It is the ratio of median lethal dose to the median effective dose.

1. **LD50**: It is the dose of a drug, which is lethal for 50% of the population.

2. **ED50**: It is the dose of drug, which produces the desired effect in 50% of the population.

Higher the value of therapeutic index, safer is the drug, e.g. penicillin G has a high therapeutic index; digitalis, lithium and phenytoin have narrow therapeutic index.

Drug Potency

The amount of a drug required to produce a desired response is called potency of the drug. Lower the dose required for a given response, more potent is the drug, e.g. analgesic dose of morphine is 10 mg and that of pethidine is 100 mg. Therefore, morphine is ten times more potent than pethidine as an analgesic. DRC of drug A (morphine) and drug B (pethidine, rightward DRC) as analgesic is compared.

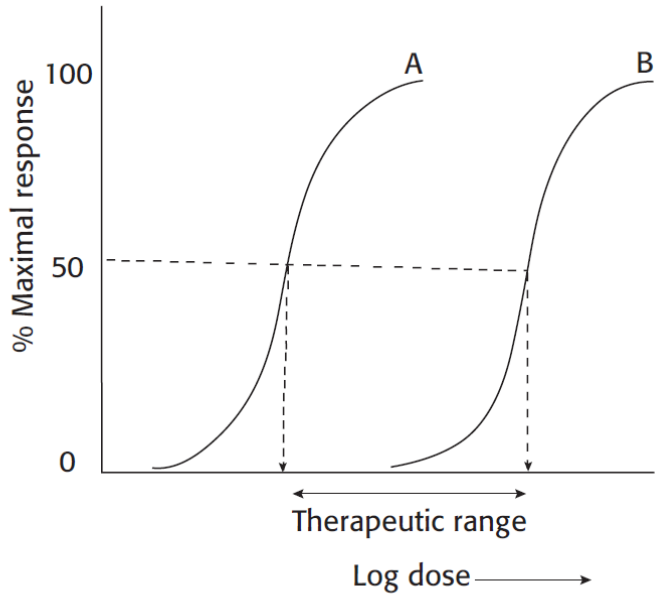


Fig. 1.8 Dose–response curves of therapeutic effect (A) and adverse effect (B).

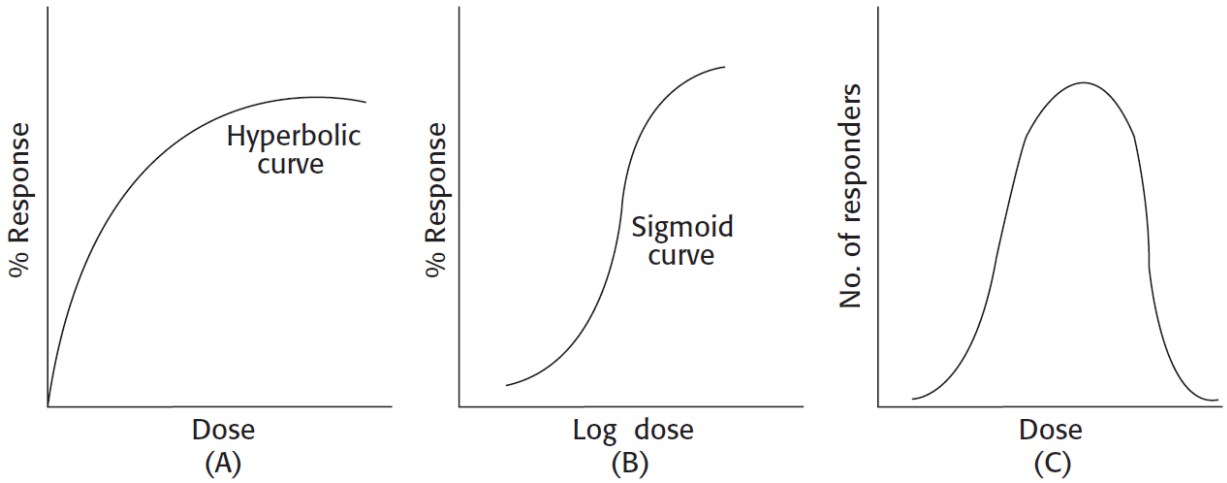


Fig. 1.7 (A) Dose–response curve. (B) Log dose–response curve. (C) Quantal dose–response curve.

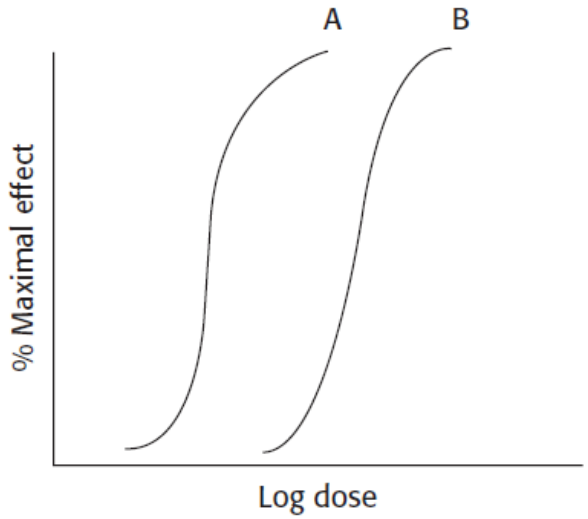


Fig. 1.9 Relative potency of two drugs.

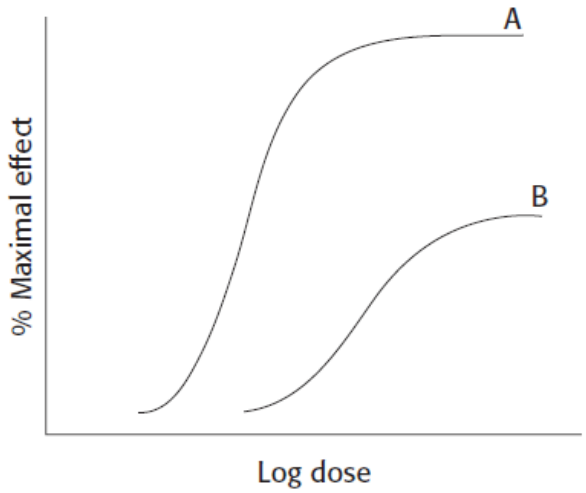


Fig. 1.10 Relative efficacy of two drugs.

Drug Efficacy

It is the maximum effect of a drug, e.g. morphine is more efficacious than aspirin as an analgesic. DRC of drug A (morphine) and drug B (aspirin) as an analgesic is compared.

Therapeutic Range

It is the range of concentration of the drug which produces desired response with minimal toxicity.

COMBINED EFFECT OF DRUGS

A combination of two or more drugs can result in an increase or a decrease in response.

Increased Response

1. **Additive effect**: The combined effect of two or more drugs is equal to the sum of their individual effect.

Effect of drugs A +B = Effect of drug A +Effect of drug B

For example, combination of ibuprofen and paracetamol as analgesic.

2. **Potentiation (supra-additive)**: The enhancement of action of one drug by another drug which is inactive is called potentiation.

Effect of drugs A + B > Effect of drug A + Effect of drug B

For example, levodopa + carbidopa; acetylcholine +physostigmine.

Carbidopa and physostigmine inhibit breakdown of levodopa and acetylcholine, respectively, thus enhancing their effects.

3. **Synergism**: When two or more drugs are administered simultaneously, their combined

effect is greater than that elicited by either drug alone.

For example, sulphamethoxazole + trimethoprim; pyrimethamine + sulphadoxine.

Decreased Response (Drug Antagonism)

In antagonism, the effect of one drug is decreased or abolished in the presence of

another drug.

1. **Physical antagonism**: The opposing action of two drugs is due to their physical property, e.g. adsorption of alkaloids by activated charcoal – useful in alkaloid poisoning.

2. **Chemical antagonism**: The opposing action of two drugs is due to their chemical property, e.g. antacids are weak bases; they neutralize gastric acid and are useful in peptic ulcer; chelating agents complex metals and are useful in heavy metal poisoning (dimercaprol in arsenic poisoning).

3. **Physiological (functional) antagonism**: Here, two drugs act at different receptors or by different mechanisms on the same physiological system and produce opposite effects, e.g. insulin and glucagon on blood sugar; adrenaline and histamine on bronchial smooth muscle – histamine produces bronchoconstriction (via histamine receptors), whereas adrenaline produces bronchodilatation by acting through adrenergic ($2) receptors – hence, adrenaline helps to reverse bronchospasm in anaphylactic shock.

4. **Receptor antagonism**: The antagonist binds to the same receptor as the agonist and inhibits its effects. It can be competitive or noncompetitive.

a. **Competitive antagonism (equilibrium type)**: In competitive antagonism, both agonist and the antagonist bind reversibly to same site on the receptor.

For example,

Acetylcholine ⟶ Muscarinic receptors ⟵ Atropine

Morphine (Agonists) ⟶ Opioid receptors ⟵ Naloxone (Antagonists)

Equilibrium type of competitive antagonism can be overcome (reversible) by increasing concentration of the agonist. The log DRC of the agonist shows a rightward parallel shift in the presence of competitive antagonist.

Nonequilibrium antagonism: The antagonist binds to the same site on the receptor as agonist but binding is irreversible. The antagonist forms strong covalent bond with the receptor, e.g. phenoxybenzamine is an irreversible antagonist of adrenaline at " receptors.

b. **Noncompetitive antagonism**: The antagonist binds to a different site on the receptor and prevents the agonist from interacting with the receptor. In this type, the antagonistic effect cannot be overcome by increasing the concentration of the agonist. There is a flattening of the DRC in noncompetitive antagonism, e.g. diazepam and bicuculline.

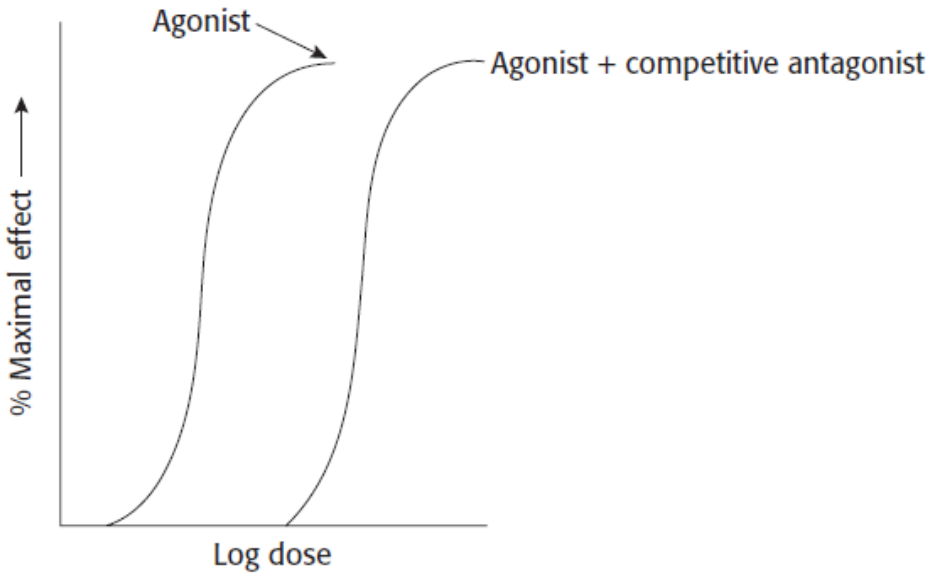


Fig. 1.11 Competitive antagonism. (Adapted from Alfred Gilman Sr. and Louis S. Goodman: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 12th edition, Mcgraw Hill, 2018.)

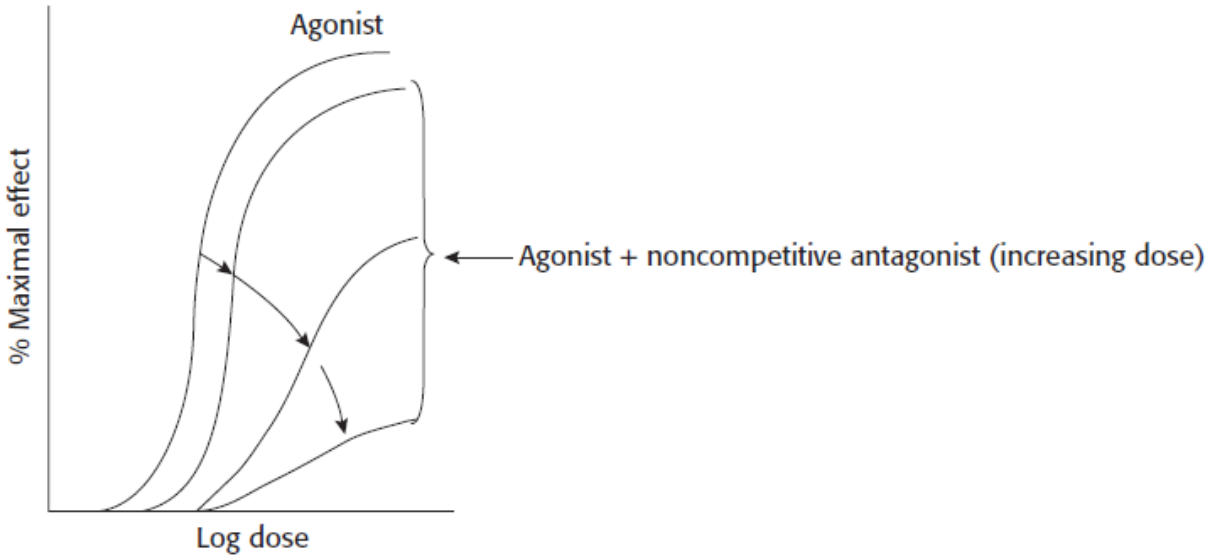


Fig. 1.12 Noncompetitive antagonism. (Adapted from Alfred Gilman Sr. and Louis S. Goodman: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 12e.)

Factors Modifying Drug Action

There are a number of factors which can influence drug response. Individuals may often show quantitative variations in drug response but rarely show qualitative variations.

DRUG FACTORS

1. **Route of administration**: When a drug is administered by different routes, it commonly exhibits quantitative variations, but sometimes it may also result in qualitative variations in response.

   a. **Quantitative variation**: Oral dose of drugs are usually larger than intravenous dose (since i.v. route produces 100% bioavailability), e.g. for analgesic effect, intravenous dose of morphine required is 5–10 mg whereas oral dose is 30–60 mg. Onset of drug action following intravenous administration is rapid.

Table 1.7 ■ **Factors influencing drug response**

Drug factors	Patient factors
• Route of administration	• Age
• Presence of other drugs	• Body weight
• Cumulation	• Sex
	• Environment
	• Genetic factor
	• Psychological factor
	• Pathological state
	• Tolerance
	• Drug dependence

b. Qualitative variation: The drug may produce an entirely different response when administered by different routes, e.g. magnesium sulphate administered orally produces purgative effect; parenterally, it causes CNS depression and on local application reduces oedema in the inflamed area.

2. Presence of other drugs: See addition, potentiation, synergism and antagonism.

3. Cumulation: If the elimination of a drug is slow, then repeated administration of such drug will result in its accumulation in the body causing toxicity, e.g. digoxin, emetine and chloroquine.

PATIENT FACTORS

1. **Age**: In neonates, metabolizing function of liver and excretory function of kidney is not fully developed, e.g. chloramphenicol can cause grey baby syndrome when given to neonates as the metabolizing enzymes are not fully developed. In adults, penicillin G is given 6 hourly, but in infants it is given 12 hourly as the excretory function is not completely developed. In the elderly, renal and hepatic functions progressively decline. The incidence of adverse effect of drugs is also relatively more, and hence drug doses have to be reduced accordingly, e.g. dose of aminoglycosides in elderly is less than normal adult dose. The dose of a drug for a child can be calculated as follows:

$$\text{Young's formula: Child dose} = \frac{\text{Age}}{\text{Age} + 12} \times \text{adult dose}$$

$$\text{Dilling's formula: Child dose} = \frac{\text{Age}}{20} \times \text{adult dose}$$

2. **Body weight and body surface**: An average dose of a drug is usually calculated in terms of body weight (mg/kg).

$$\text{Dose} = \frac{\text{Body weight (kg)}}{70} \times \text{Average adult dose}$$

In obese individuals and in patients with dehydration or oedema, dose calculation on the basis of body weight is not very appropriate. A more accurate method for calculating a dose is on the basis of the body surface area (BSA) of the patient. Nomograms are available to calculate BSA from height and weight of the patient. Since it is inconvenient to calculate BSA, dose is routinely calculated on body weight basis. Dose of anticancer drugs and a few other drugs are calculated on the basis of BSA.

3. **Sex**: Drugs like $ blockers, diuretics and clonidine can cause decreased libido in males.

4. **Diet and environmental factors**: Milk reduces absorption of tetracyclines; fatty meal increases the absorption of griseofulvin (antifungal agent). Cigarette smoke induces hepatic microsomal enzymes and increases metabolism of drugs, such as theophylline. So, the dose of the drug administered may be inadequate in smokers.

5. **Genetic factor**: For example, fast and slow acetylators of isoniazid, prolonged succinylcholine apnoea, primaquine induced haemolysis in G6PD deficiency individuals. Other examples are as follows-

Acute porphyria

Barbiturates may precipitate attacks of acute intermittent porphyria in susceptible individuals by inducing ALA (aminolevulinic acid) synthase enzyme that catalyses the production of porphyrins.

Malignant hyperthermia

In some patients, dangerous rise in body temperature (malignant hyperthermia) may occur especially when halothane–succinylcholine combination is used due to genetic abnormality.

In person with shallow anterior chamber/and or narrow iridocorneal angle, mydriatics may precipitate acute congestive glaucoma.

There is an increased risk of bleeding with coumarin anticoagulants due reduced activity of metabolizing enzyme, CYP2C9.

6. **Psychological factor**: Personality of the doctor as well as the patient can affect response to a drug. Some patients respond to inert dosage forms (placebo) in conditions like pain, bronchial asthma, anxiety, etc.

Placebo effect: 'Placebo' is a Latin term that means 'I will please'. It is a dummy medicine

having no pharmacological activity. The effect produced by placebo is called placebo effect. Sugar tablets and distilled water injection are used as placebos.

1) **Uses**

a) Placebos are used for the relief of subjective symptoms like anxiety, headache,

tremors, pain, insomnia, etc.

b) Placebos are used in clinical trials in order to minimize bias.

2) **Factors affecting placebo effect are**:

a) Patient factor: Patients with neurotic symptoms often respond to placebos.

b) Drug factor: The placebo response can be affected by the physical presentation or route of administration of the drug, e.g. colourful tablets, such as red, blue, green and injectable preparations give better placebo effect.

c) Doctor factor: Personality of the doctor, motivation, way of instruction, doctor–patient relationship, etc. are important factors that also affect response to placebo.

7. **Pathological states**:

a. GI disorders: Achlorhydria reduces the absorption of weakly acidic drugs in stomach by causing their ionization. In malabsorption syndrome, absorption of some drugs is reduced.

b. Liver disease: In chronic liver diseases, metabolism of drugs is greatly reduced. This will increase bioavailability of drugs having high first-pass metabolism, e.g. propranolol.

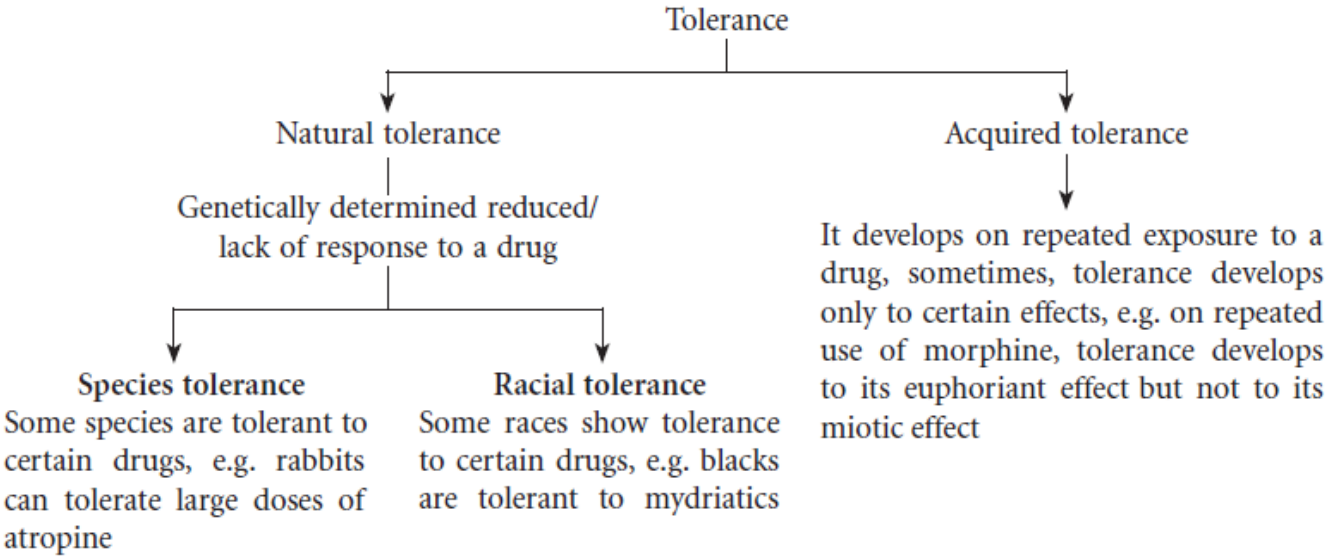
c. Renal failure: Clearance of drugs that are excreted through kidney is impaired,

e.g. the incidence of nephrotoxicity and ototoxicity with aminoglycosides is more in the presence of renal failure.

d. Absorption of iron from the gut is increased in iron deficiency anaemia.

8. **Tolerance**: It means 'need for larger doses of a drug to produce a given response'. Tolerance develops to nasal decongestant effect of ephedrine on repeated use. Patients on organic nitrates for angina develop tolerance on long-term therapy. Tolerance is commonly seen with drugs like morphine, alcohol, amphetamine, etc.

a. Types of tolerance



b. **Mechanism of development of tolerance**: It could be pharmacokinetic or pharmacodynamic tolerance.

1) **Pharmacokinetic tolerance (dispositional tolerance)**: It is due to reduced concentration of the drug at the site of action – may be as a result of decreased absorption, increased metabolism and excretion. For example, rifampin induces the metabolizing enzyme of oral contraceptives, enhances their metabolism, leading to contraceptive failure.

2) **Pharmacodynamic tolerance (functional tolerance)**: The drug effect is reduced, which may be due to downregulation of receptors or decrease in receptor-coupled signal transduction. Repeated use of opioids, barbiturates, etc. results in the development of tolerance due to decrease in the number of receptors (downregulation).

c. **Cross-tolerance**: The phenomenon of tolerance exhibited by closely related (structural and mechanistic) drugs is called cross-tolerance, e.g. among nitrates, among opioids, between ether and alcohol.

d. **Tachyphylaxis (tachy ! rapid; phylaxis! protection; acute tolerance):** Repeated use of certain drugs at short intervals may result in rapid decrease in pharmacological response. This is known as tachyphylaxis or acute tolerance, e.g. tyramine, ephedrine and amphetamine. These drugs act by releasing noradrenaline from adrenergic nerve endings. Repeated administration of the drug causes gradual depletion of the neurotransmitter and hence reduction in the response.

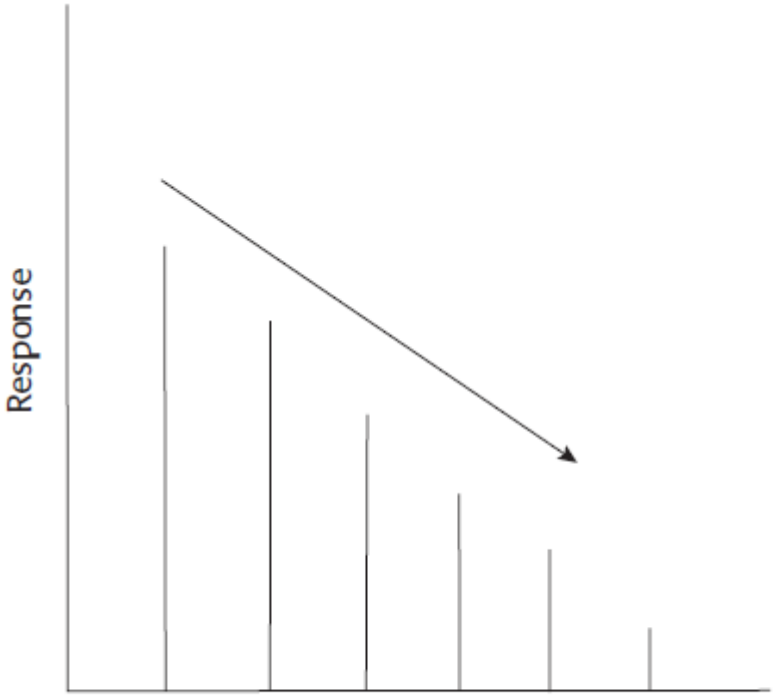
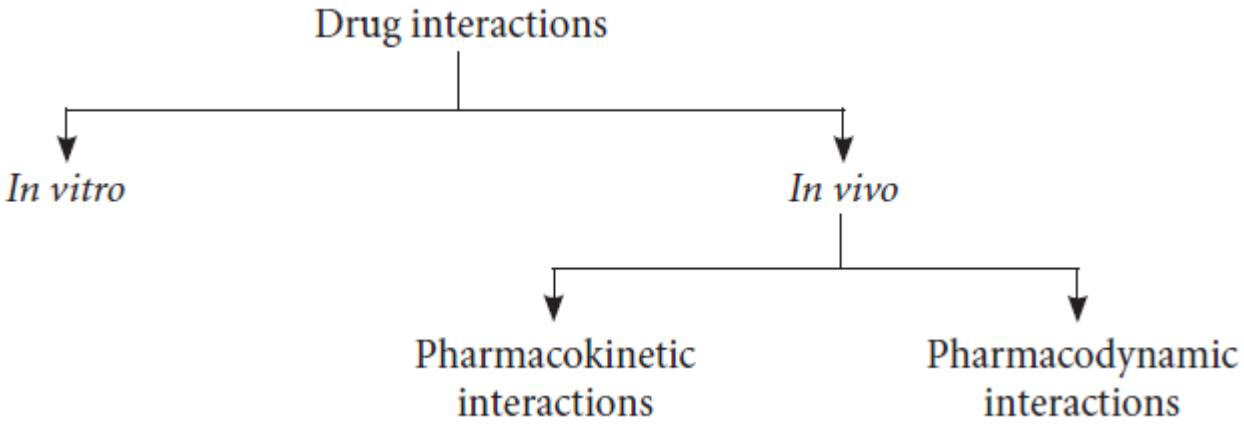


Fig. 1.13 Tachyphylaxis. BP, blood pressure.

DRUG INTERACTION

When two or more drugs are given simultaneously, the effects of one drug may be altered by another drug. Drug interactions can occur in vitro (outside the body) or in vivo (inside the body).



Drug interactions can result in either beneficial or harmful effects.

Pharmaceutical interactions: These can occur as a result of incompatibility (physical or chemical) of a drug with an intravenous solution or when two or more drugs are mixed in the same syringe/i.v. infusion. This may result in precipitation or inactivation of one or more drugs. Phenytoin should not be administered in dextrose solution as it gets precipitated. Dextrose solution is not suitable for i.v. infusion of ampicillin as it is unstable at acidic pH of dextrose. Gentamicin and carbenicillin should not be given in the same infusion as it may result in loss of potency.

Pharmacokinetic interactions: These occur when one drug alters the absorption, distribution, metabolism or excretion of another drug.

Absorption: Antacids (containing aluminium, magnesium and calcium), iron, etc. interfere with the absorption of tetracyclines by forming unabsorbable complexes with it. Some drugs affect absorption of other drugs by altering GI motility. Metoclopramide increases the rate of gastric emptying and promotes absorption of aspirin.

Distribution: Plasma protein binding can cause displacement interactions. More than one drug can bind to the same site on plasma protein. The drug with higher affinity will displace the one with lower affinity. This results in increase in concentration of unbound drug, e.g. salicylates displace warfarin from binding sites resulting in increased free warfarin levels and enhanced anticoagulant effect.

Metabolism: This occurs when metabolism of one drug is increased (enzyme induction) or decreased (enzyme inhibition) by another drug, e.g. carbamazepine induces the metabolizing enzyme of warfarin, thus enhancing its metabolism and leading to decreased anticoagulant effect. Erythromycin inhibits the metabolizing enzyme of carbamazepine and may increase its toxicity.

Excretion: Most of them occur in kidney.

Salicylates interfere with the excretion of methotrexate and potentiate its toxicity.

Probenecid decreases renal tubular secretion of penicillins/cephalosporins and prolongs their duration of action (beneficial interaction).

Pharmacodynamic interactions: The interaction is due to action of drugs on receptors or physiological system. This may result in either additive, synergistic or antagonistic effects. The interaction may result in harmful effects, e.g. enhanced nephrotoxicity seen with the concurrent use of aminoglycosides and amphotericin B; it may also result in beneficial effect, e.g. levodopa and carbidopa in parkinsonism.

RATIONAL USE OF MEDICINES

According to WHO, rational use of medicines requires that 'patients receive medications appropriate to their clinical needs in doses that meet their own individual requirements For an adequate period of time and at the lowest cost to them and their community'.

It involves the administration of right drug, right dose, right duration, right cost to

the right patient.

EXAMPLES OF IRRATIONAL PRESCRIBING

Drug not prescribed as per standard treatment guidelines.

Unnecessary use of drugs, e.g. antibiotics for viral infections.

Underuse of drugs, e.g. not prescribing oral rehydration solution in acute diarrhoea.

Incorrect use of a drug, e.g. selection of wrong drug, use of incorrect route and dose of a drug.

Use of medicines with doubtful efficacy, e.g. appetite stimulants.

Prescribing banned drugs, e.g. cisapride.

Use of irrational combinations, e.g. ampicillin and cloxacillin for staphylococcal

infections.

Prescribing expensive medicines unnecessarily when cheaper, equally effective drugs are available.

Polypharmacy. Hazards of Irrational Use of Drugs

Therapeutic failure.

Increased incidence of adverse drug reactions (ADRs).

Emergence of drug-resistant microorganisms.

Increase in cost of treatment.

Financial burden to society.

Loss of patient's faith in the doctor.

Rational Prescribing (WHO)

A diagnosis has to be made.

The problem has to be defined.

The therapeutic goals to be achieved, e.g. relief of symptoms, cure, etc. has to be set.

The right drug - appropriate route, dose and duration of treatment has to be selected. Write a complete prescription.

Proper instructions and information about the drug should be given.

Monitor therapy.

Adverse Drug Effects

Adverse effect is defined as any undesirable or unwanted effect of a drug.

The WHO suggested definition of ADR and adverse event (AE) are as follows:

ADR: Any response which is noxious, unintended and which occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.

AE: Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have causal relationship with the treatment.

TYPES OF ADVERSE DRUG REACTIONS

Predictable Reactions (Type A or Augmented Reactions)

These are predictable reactions to a drug which are related to its pharmacological actions. They include side effects, secondary effects and toxic effects.

Unpredictable Reactions (Type B or Bizarre Reactions)

These are nondose-related unpredictable reactions to a drug. They are not related to the pharmacological actions of the drug. Allergic reactions and idiosyncrasy are unpredictable reactions.

Predictable Reactions

Side effects: These are unwanted pharmacological effects of a drug, that are seen with therapeutic doses, e.g. atropine used in the treatment of heart block also produces dryness of mouth, blurring of vision, urinary retention, etc., which are the side effects.

Secondary effects: The primary action of a drug may result in other effects, e.g. immunosuppression by corticosteroids can lead to development of opportunistic infections, e.g. oral candidiasis.

Toxic effects: These are the effects of a drug, which are either due to overdosage or chronic use, e.g. bleeding due to chronic use/overdosage of anticoagulants and nephrotoxicity with aminoglycosides especially in patients with renal failure.

Unpredictable Reactions

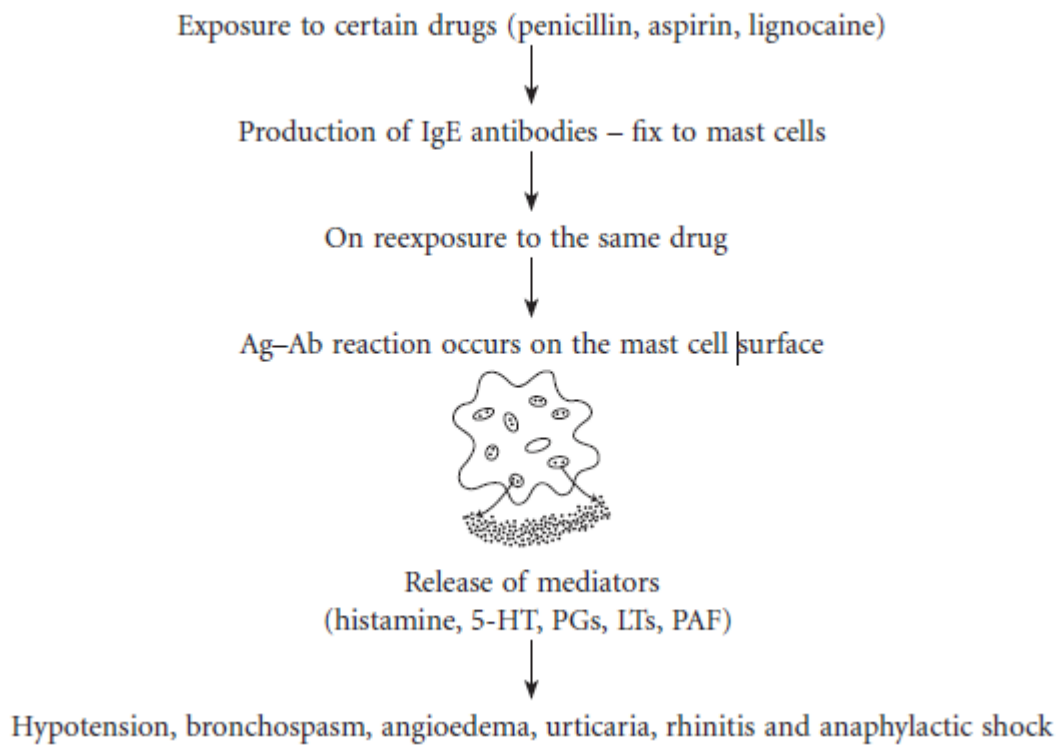
Drug allergy: It is an abnormal response (local or systemic), mediated by immune system, to a drug/foreign antigen. Different types of hypersensitivity reactions are discussed below.

Those associated with humoral antibodies: types I, II and III.

Those associated with cell-mediated immunity: type IV (delayed hypersensitivity).

Type I hypersensitivity (immediate type, anaphylactic) reactions

It is a rapidly occurring reaction, hence called immediate hypersensitivity reaction. The manifestations are itching, urticaria, hay fever, asthma or even anaphylactic shock. Itching, rhinitis and urticaria are treated with antihistamines,



Hypotension, bronchospasm, angioedema, urticaria, rhinitis and anaphylactic shock Anaphylactic shock is a medical emergency and should be treated promptly with:

1. Inj. adrenaline (1:1000) 0.3–0.5 mL intramuscularly.

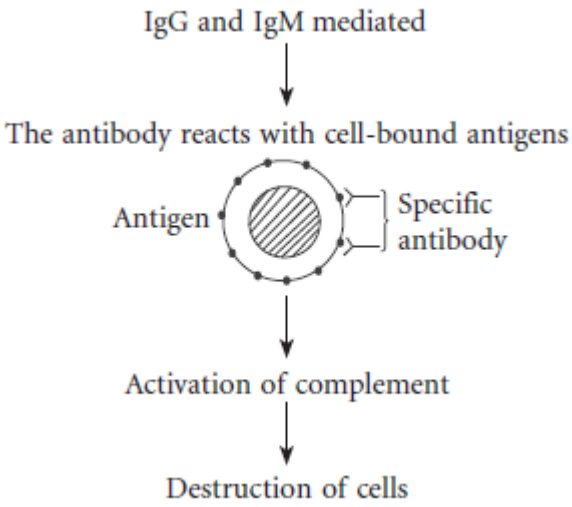
2. Inj. hydrocortisone 100–200 mg intravenously.

3. Inj. pheniramine 45 mg intramuscularly/intravenously.

4. Maintenance of patent airway, intravenous fluids.

Type II hypersensitivity (cytotoxic) reactions

The antibodies (IgG and IgM) react with cell-bound antigen and cause activation of complement, which destroys the cells.



Examples are: blood transfusion reactions, haemolytic anaemias produced by quinine, quinidine, cephalosporins, etc.

Type III hypersensitivity (Arthus, serum sickness) reactions

In this type of reaction, antibodies involved are mainly IgG.

AG: AB complexes are formed n Fix complement n Deposition of complexes on vascular endothelium n Destructive inflammatory response.

For example, serum sickness (fever, urticaria, joint pain, lymphadenopathy) with penicillins and sulphonamides; acute interstitial nephritis with nonsteroidal anti-inflammatory drugs (NSAIDs) and Stevens–Johnson syndrome with sulphonamides.

Type IV hypersensitivity (cell-mediated or delayed hypersensitivity) reactions

It is mediated by sensitized T lymphocytes. Reexposure to the antigen leads to a local inflammatory response. The manifestations usually occur 1–2 days after exposure to the sensitizing antigen, e.g. contact dermatitis due to local anaesthetic creams, topical antibiotics and antifungal agents.

Types II, III and IV reactions are treated with glucocorticoids.

Idiosyncrasy

It is usually a genetically determined abnormal reaction to drugs, e.g. aplastic anaemia caused by chloramphenicol, prolonged succinylcholine apnoea, haemolytic anaemia seen with primaquine and sulphonamides.

Drug dependence

WHO defines drug dependence as ‘a state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug characterized by behavioural and other response that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects and sometimes to avoid the discomfort of its absence’, e.g. opioids, alcohol, barbiturates, amphetamine, etc. The dependence could be psychological or physical.

a. **Psychological dependence**: There is an intense desire to continue taking the drug as the patients feel that their well-being depends on the drug.

b. **Physical dependence**: Repeated drug use produces physiological changes in the body, which makes continuous presence of the drug in the body necessary to maintain normal

function. Abrupt stoppage of the drug results in an imbalance wherein the body has to readjust to the absence of the drug resulting in the development of signs and symptoms known as withdrawal syndrome. The withdrawal signs and symptoms are generally opposite to the effects produced by the drug.

Principles of treatment of drug dependence are:

1. Hospitalization.

2. Substitution therapy: For example, methadone substitution for morphine addiction.

3. Aversion therapy: Disulfiram for alcohol addiction.

4. Psychotherapy

5. General measures: Maintain nutrition, family support and rehabilitation.

Iatrogenic diseases

It is physician-induced disease ('iatros' is a Greek word, means 'physician') due to drug therapy, e.g. parkinsonism due to metoclopramide; acute gastritis and peptic ulcer due to NSAIDs.

Table 1.8 ■ **Teratogenic effects of some drugs (Note the 'T's)**

Drug	Teratogenic effect
Thalidomide	Phocomelia
Tetracyclines	Yellowish discolouration of teeth
Antithyroid drugs	Fetal goitre

Teratogenicity

Certain drugs when given during pregnancy may cross the placenta and produce various dangerous effects in the fetus. This is called teratogenesis.

Administration of drugs during early pregnancy (conception to 16 days) could

result in abortion; during 2–8 weeks of gestation, it can affect organogenesis

and produce structural abnormalities; during second and third trimester, drugs

can affect growth and development of the fetus. Hence, drug administration

during pregnancy should be restricted.

The USFDA (Food and Drug Administration) had placed drugs in various categories (A, B, C, D, X) depending on the risk of the drug to cause birth defects.

Category X drugs (e.g. warfarin, methotrexate) was contraindicated for use during pregnancy as risk to fetus was proven and outweighed benefits of its use. This system is being replaced by a revised labelling rule which will provide latest information about a drug pertaining to its use during pregnancy.

Carcinogenicity and mutagenicity

The ability of a drug to cause cancer is carcinogenicity and the agent is known as carcinogen. The abnormalities of genetic material in a cell produced by a drug is known as mutagenicity, e.g. anticancer drugs and oestrogens.

Photosensitivity reactions

It is a drug-induced cutaneous reaction (photoallergy/phototoxicity) following exposure to ultraviolet radiation. Sulphonamides cause photoallergy on exposure to light; they produce dermatitis due to immune response (cell mediated).

Doxycycline and fluoroquinolones can cause phototoxicity – a local reaction (erythema, blisters) occurs on exposure to UV light. Use of sunscreen and avoidance of exposure to sunlight is advised. Calamine lotion and topical steroids are used for treatment.

Hepatotoxicity

Some of the hepatotoxic drugs are isoniazid, rifampicin, pyrazinamide, halothane, paracetamol, etc.

Nephrotoxicity (Vancomycin, aminoglycosides, cisplatin, cyclosporine, amphotericin

B, tetracyclines [Fanconi syndrome], indinavir, gold salts, nystatin, etc. are nephrotoxic drugs)*

Ototoxicity

It can occur with aminoglycosides, loop diuretics, cisplatin, etc.

Ocular toxicity

Ethambutol, chloroquine, glucocorticoids, etc. can cause ocular toxicity.

Pharmacovigilance

It is the 'science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems' (WHO). The aim of pharmacovigilance is to improve patient care and safety related to use of drugs, promote rational use of medicines, develop regulations for use of drugs and educate health care professionals about ADRs.

Causality assessment: Some of the commonly used tools for causality assessment are

Naranjo's scale and WHO scale.

The National Pharmacovigilance Centre is located at Ghaziabad. The International Centre is Uppsala Monitoring Centre in Sweden. Any health care professional, e.g. doctors, dentists, nurses and pharmacists can report a suspected adverse drug event. Patients can also report ADRs.

New Drug Development

Preclinical studies in animals: Before undertaking clinical trials, sufficient data about the drug must be obtained by testing it in animals. Animal studies generate pharmacodynamic, pharmacokinetic and toxicological data of the drug.

TOXICITY STUDIES

Acute toxicity studies Acute toxicity is carried out in two animal species (one rodent, one nonrodent). Single, graded doses are administered to small groups of animals using two routes – one that is to be used in humans. It is done to determine the general behaviour and median lethal dose (LD50) following exposure to the test drug. LD50 is the dose required to kill 50% of the animals. It is determined in a 24-hour period after administration of the drug.

Subacute toxicity studies

These are done in two species of animals to determine the maximum tolerated dose, identify target organ of toxicity and nature of toxicities. The test drug is administered daily for a period depending on the duration of treatment in humans. Animals are examined for general effects (food intake, change in the body weight, etc.), biochemical and haematological parameters are monitored; histological examination is done.

Chronic toxicity studies

Drugs are administered in two species (one rodent and one nonrodent) for 6–12 months. Monitoring is done as in subacute toxicity studies.

Special toxicity studies

These include tests for carcinogenicity, mutagenicity and teratogenic effects of the drug. It also includes effects on reproduction.

CLINICAL TRIALS

After completion of preclinical testing of the drug, the company files an investigational new drug (IND) application with the regulatory authority for permission to test the

drug in humans. A drug should be scientifically and ethically evaluated by testing in human beings for safety and efficacy prior to its use in man for therapeutic purposes. Such study in humans is referred to as clinical trial. The principles of bioethics should be upheld during clinical trials. They include autonomy, beneficence, nonmaleficence and justice. Clinical trials are conducted in four phases, I–IV. Usually, the information obtained from one phase is analysed before proceeding to the next phase.

Phase I

This phase involves testing of the drug in humans for the first time. It is carried out in about 10–100 participants. This is usually carried out in healthy volunteers. For drugs with potential toxicity, e.g. anticancer drugs, phase I trials are carried out in cancer patients. The main objective of this phase is to determine safety of the drug and the maximum tolerated dose. Pharmacokinetic and pharmacodynamic data can be obtained. It is usually carried out by a clinical pharmacologist. No blinding is done (open label study).

Phase II (Therapeutic Exploratory Study)

It is carried out for the first time in patients with target disease for which the drug is intended to be used. It is conducted in about 50–500 patients and usually in three to four centres. The main objective of this phase is to assess the effectiveness of the drug and to determine effective dose range. Further evaluation of safety and pharmacokinetics is also done. The study is randomized and controlled, may be blinded.

Phase III (Therapeutic Confirmation Trial)

The aim is to confirm the efficacy of the drug in large number of patients of either sex. It is conducted in multiple centres. It is generally randomized, double blind comparative trial. Further data on kinetics and drug interactions can be obtained. Permission for marketing the drug is granted after successful completion of phase III trials.

Phase IV (Postmarketing Surveillance)

Once the drug is approved for marketing, postmarketing surveillance is carried out to obtain additional data about benefit and risk of a drug following its long-term use in a larger number of patients. It provides information on adverse reactions, drug interactions, new indications and evaluation of different formulations. Postmarketing surveillance helps to estimate incidence of adverse reactions, detect previously unknown adverse reactions and identify risk factors for the adverse reactions. There are ADR monitoring centres in different parts of the country. The ADRs observed in the patient should be reported to these centres. The drug company has to submit postmarketing data for the drug at regular intervals to the regulatory agency to continue its use. Besides clinical trials, other types of clinical studies are case control study, cohort study and meta-analysis.

GOOD CLINICAL PRACTICE

International Council for Harmonization – Good Clinical Practice (ICH–GCP) guidelines is an international ethical and scientific standard for designing, conducting, monitoring, terminating, auditing, reporting and recording trials. It ensures that the data generated from the trials is credible, accurate and the rights, integrity and confidentiality of the participants are protected.

INFORMED CONSENT

Prior to enrolling the patient in the trial, the investigator should obtain informed consent from the subject. It is a process by which a subject voluntarily confirms his/her willingness to participate in a trial after having been informed of all aspects of the trial relevant to the subject's decision to participate in the trial. The consent should be obtained by the investigator in the subject's language without exerting undue influence.

The informed consent is documented by means of a written, signed and dated (by both investigator and subject) informed consent form. If a subject is illiterate, his legally accepted representative or an impartial witness should be present during informed consent process. The thumb impression of the subject is taken and his legally accepted representative should sign and date the informed consent form. In case of young children and mentally ill patients, consent is obtained from their guardian or legal representative.

ETHICS COMMITTEE

It is a committee or board designated by the institution to review research proposals and

conduct periodic review of research involving humans so as to ensure the protection of the rights and welfare of human subjects. The number of persons in an ethics committee is about 7–15. A minimum of five persons are required to form the quorum. Composition

1. Chairperson (from outside the institution to maintain independence of the committee)

2. Basic medical scientists (preferably one pharmacologist)

3. Clinicians

4. Legal expert or retired judge

5. Social scientist/philosopher/ethicist/theologist

6. Lay person from the community

7. Member secretary

RANDOMIZATION

It is a process where the subjects are randomly assigned to treatment groups in a clinical

trial using a chance mechanism. This is usually done by a computer. The investigator has no role in deciding the allocation of a particular treatment to a particular patient in the trial. Randomization is done to avoid bias in the constitution of trial group.

BLINDING

The purpose of blinding in a trial is to eliminate bias. It is done to conceal the identity of the drug from the investigator and the subject. It could be single blind or double blind.

In a double blind trial, both the investigator and the subject do not know the identity

of the drug administered to the subject. In a single blind trial, the subject is unaware of

the identity of the drug administered to him. A randomized double blind trial is a standard design for most of the clinical trials.