Chapter 66 Chelating Agents

These are drugs which complex metallic ions, forming ring structures within their molecule (Greek *Chele* = Crab; the compound holds the metal like a crab's claw). They are primarily used in heavy metal poisonings.

Those compounds which form stable, non-toxic and easily excreted complexes with toxic metals are valuable in poisonings. The useful agents contain two or more reactive groups (ligands) which can hold the metal from at least two sides so that a ring is formed. When the ring is 5–7 membered, it is most stable.

Ligand is a functional group capable of forming coordinate bond, i.e. a covalent bond in which both the shared electrons are donated by the ligand—generally O, N, or S atoms in hydroxyl, carboxyl, keto, sulfhydryl, disulfide, amino or phosphate groups.

Heavy metals exert their toxic effects by combining with and inactivating functional groups (ligands) of enzymes or other critical biomolecules. Chelating agents compete with body ligands for the heavy metal. They differ in their affinity for different metals. Clinically useful agents should have a higher affinity for the toxic metal than for calcium, because Ca^{2+} is readily available in plasma and extracellular fluid. They should also have higher affinity than the body ligands for the toxic metal. Moreover, to be effective in metal poisoning, their distribution in the body should correspond to that of the metal to be chelated, and they should be water soluble.

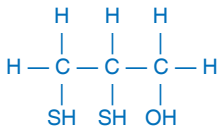
Efficacy of all chelating agents in promoting excretion of the toxic metal and in reversing toxic manifestations declines rapidly as the interval between entry of the metal in the body and the administration of the chelator increases.

Chelating agents useful as drugs are:

Dimercaprol (BAL)	Calcium disodium DTPA
Dimercaptosuccinic acid (Succimer)	Penicillamine
Disodium edetate	Desferrioxamine
Calcium disodium edetate	Deferiprone

Dimercaprol (British antilewisite; BAL)

It is an oily, pungent smelling, viscous liquid, developed during World War II by Britishers as an antidote to the arsenical war gas *lewisite*. The two SH groups of dimercaprol bind those metals which produce their toxicity by interacting with sulfhydryl containing enzymes in the body, i.e. As, Hg, Au, Bi, Ni, Sb, Cu. The complex of 2 molecules of dimercaprol with one metal ion is more stable than 1:1 complex. It is, therefore, desirable to maintain excess of dimercaprol in plasma to allow formation of 2 : 1 complex. The dimercaprol-metal complex spontaneously dissociates releasing the metal at a slow rate; also dimercaprol is partly oxidized in the body: further emphasizing the necessity to have excess dimercaprol available. But due to dose dependent toxicity of dimercaprol, large amounts should not be given at a time.



DIMERCAPROL

Uses

1. Poisoning by As, Hg, Au, Bi, Ni, Sb: it is administered i.m., 5 mg/kg *stat*, followed by 2–3 mg/kg every 4–8 hours for 2 days, then once

or twice a day for 10 days. It is partly oxidized and glucuronide conjugated, but mainly excreted as such in 4–6 hours. Earlier the treatment is instituted, the better it is. Because the dimercaprol-metal complex dissociates faster in acidic urine and the released metal can damage the kidney, urine is alkalinized during dimercaprol therapy.

2. As an adjuvant to Cal. disod. edetate in lead poisoning.

3. As an adjuvant to penicillamine in Cu poisoning and in Wilson's disease—300 mg/day i.m. for 10 days every second month.

BAL INJ 100 mg/2 ml (in arachis oil) inj.

It is contraindicated in iron and cadmium poisoning, because the dimercaprol-Fe and dimercaprol-Cd complex is itself toxic.

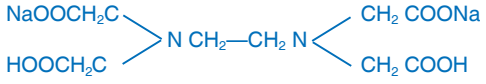
Adverse effects These are frequent, dose related and distressing, but generally not damaging.

Rise in BP, tachycardia, vomiting, tingling and burning sensations, inflammation of mucous membranes, sweating, cramps, headache and anxiety.

Antihistaminics given 30 min before dimercaprol injection, reduce the intensity of adverse effects.

Dimercaptosuccinic acid (Succimer) It is similar to dimercaprol in chelating properties, water soluble, less toxic and orally effective. Its efficacy has been demonstrated in As, Hg and Pb poisoning. It has been marketed in USA and some other countries, but not in India for the treatment of lead intoxication. Side effects are nausea, anorexia and loose motions.

Disodium edetate (Na_2EDTA) It is the disodium salt of ethylene diamine tetraacetic acid (EDTA). It is a potent chelator of calcium—causes tetany on i.v. injection. When a slow infusion is given, tetany does not occur, because calcium is withdrawn from bones. It can be used for emergency control of hypercalcaemia: 50 mg/kg i.v. infusion over 2–4 hours, but bisphosphonates are preferred.



DISODIUM EDETATE

Calcium disodium edetate (Ca Na_2 EDTA)

It is the calcium chelate of Na_2 EDTA. Because this chelating agent has higher affinity for metals like Pb, Zn, Cd, Mn, Cu and some radioactive metals, it can remove them from the body by exchanging with Ca held by it. It is highly ionized, therefore distributed only extracellularly and rapidly excreted in urine by glomerular filtration ($t½ \leq 1$ hour) carrying the toxic metal along. It is not metabolized. Because of its ionic nature, Ca Na_2 EDTA is not absorbed from the g.i.t.—must be given parenterally. Since i.m. injection is painful, preferred route is i.v. It does not enter brain or CSF. Thus, it can remove toxic metals only from accessible sites.

Uses

1. *Lead poisoning* This is the most important indication for $CaNa_2$EDTA; 1 gm is diluted to 200–300 ml in saline or glucose solution and infused i.v. over 1 hour twice daily for 3–5 days. The urinary excretion of Pb is promptly increased, but declines quickly as the metal is removed from accessible sites (primarily bone). A second course of $CaNa_2$EDTA may be repeated after 5–7 days, allowing time for Pb to redistribute to extracellular sites.

2. It is also useful in Fe, Zn, Cu, Mn and radioactive metal, but not Hg poisoning, because Hg is more firmly bound to body constituents and is localized in areas not accessible to $CaNa_2$ EDTA.

Adverse effects $CaNa_2$ EDTA does not produce tetany and is relatively safe.

Kidney damage with proximal tubular necrosis is the most important problem. This is roughly dose-related and may be due to the toxic metal partly dissociating in the tubule. It can be minimized by maintaining high urine flow.

An acute febrile reaction with chills, bodyache, malaise, tiredness occurs in some individuals.

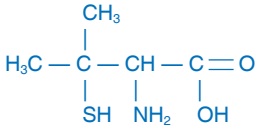
Anaphylactoid reaction with fall in BP and congestion of eyes and nose is also reported.

Calcium disodium DTPA Diethylene triamine penta acetic acid (DTPA, Pentetic acid) is a congener of EDTA. It has higher affinity for many heavy metals than EDTA. Its calcium chelate has been used in metal poisonings (especially radioactive metals like uranium, plutonium) which

do not respond to $CaNa_2EDTA$. However, because of its limited distribution in the body, results are not impressive.

Penicillamine

It is dimethyl cysteine, obtained as a degradation product of penicillin. It was found to have strong copper chelating property and was used in 1956 for Wilson's disease. It selectively chelates Cu, Hg, Pb and Zn. The d-isomer is used therapeutically, because the l-isomer and the recemate produce optic neuritis and are more toxic. It is adequately absorbed after oral administration, little metabolized in the body and excreted in urine and faeces. When given to patients with heavy metal toxicity, excretion of the metal is enhanced.



PENICILLAMINE

Uses

1. Wilson's disease (Hepatolenticular degeneration): This is due to genetic deficiency of ceruloplasmin, a protein which normally binds and disposes off Cu from the body. In its absence, plasma concentration of free Cu is high which gets deposited in liver, substantia nigra, basal ganglia of brain, and causes local degeneration. Life long therapy is needed to prevent progression of the disease.

Dose: 0.5–1 g daily in divided doses 1 hour before or 2 hour after meals to avoid chelation of dietary metals.

ARTAMIN, CILAMIN 250 mg cap, ARTIN 150, 250 mg cap.

Pot. sulfide 20–40 mg may be given with each meal to decrease the absorption of dietary copper.

2. Copper/mercury poisoning: 1–1.5 g/day is given for a few days. It is the drug of choice for Cu poisoning and alternative drug to dimercaprol/succimer for Hg poisoning.
3. Chronic lead poisoning: It may be used as an adjuvant to $CaNa_2EDTA$, but succimer is preferred.
4. Cystinuria and cystine stones: It promotes the excretion of cysteine and prevents its precipitation in the urinary tract, because penicillamine-cysteine complex is more soluble than dicysteine (cystine).
5. Scleroderma: Penicillamine benefits by increasing soluble collagen.

It was used as a disease modifying drug in rheumatoid arthritis, but has been replaced now by safer drugs (*see* p. 212).

Adverse effects Short-term administration (as metal chelator) of penicillamine does not cause much problem. Various cutaneous reactions, itching and febrile episodes may occur. However, long-term use produces pronounced toxicity. Dermatological, renal, haematological and collagen tissue toxicities are prominent.

Desferrioxamine

Ferrioxamine is a long chain iron containing complex obtained from an actinomycete. Chemical removal of iron from it yields desferrioxamine which has very high affinity for iron: 1g is capable of chelating 85 mg of elemental iron. The straight chain desferrioxamine molecule winds round ferric iron and forms a stable nontoxic complex which is excreted in urine. It removes loosely bound iron as well as that from haemosiderin and ferritin, but not from haemoglobin or cytochrome. Another desirable property is its low affinity for calcium.

Little of orally administered desferrioxamine is absorbed. Parenterally administered desferrioxamine is partly metabolized and rapidly excreted in urine.

Uses

1. Acute iron poisoning: mostly in children. This is the most important indication—may be life saving (*see* p. 606).
2. Transfusion siderosis: occurs in thalassemia patients who receive repeated blood transfusion. Desferrioxamine 0.5–1 g/day i.m. helps to excrete the chronic iron overload; may also be infused i.v. concurrently with blood transfusion—2 g per unit of blood.

Adverse effects Desferrioxamine can cause histamine release → fall in BP, flushing, itching,

urticaria, rashes. A variety of allergic reactions are reported. Changes in lens and retina can occur on repeated use.

Other side effects are abdominal pain, loose motions, muscle cramps, fever and dysuria.

DESFERAL 0.5 g/vial inj.

Deferiprone

It is an orally active iron chelator which has simplified the treatment of transfusion siderosis in thalassemia patients. Excessive haemolysis occurs in these patients, and they have to be given repeated blood transfusions. An iron chelator has to be used to clear the resulting iron overload. Oral deferiprone is a somewhat less effective alternative to injected desferrioxamine. Side effects and cost of treatment are reduced. Deferiprone has also been indicated for acute iron poisoning (less effective than desferrioxamine) and for iron load in liver cirrhosis.

Dose: 50–100 mg/kg daily in 2–4 divided doses.

KELFER 250, 500 mg caps.

Side effects are anorexia, vomiting, altered taste, joint pain, reversible neutropenia, rarely agranulocytosis. However, long-term safety is not yet known.

Chapter 67 Vitamins

Vitamins are nonenergy yielding organic compounds, essential for normal human metabolism, that must be supplied in small quantities in the diet. This definition excludes the inorganic essential trace minerals and essential amino acids and fatty acids which are required in much larger quantities. Other substances needed for proper growth of microorganisms or cells in culture are called 'growth factors'. The different chemical forms and precursors of a vitamin can be called its *Vitamers* (analogy—isomers).

The importance of vitamins as drugs is primarily in the prevention and treatment of deficiency diseases. Some vitamins do have other empirical uses in pharmacological doses. Vitamin deficiencies occur due to inadequate intake, malabsorption, increased tissue needs, increased excretion, certain genetic abnormalities and drug-vitamin interactions.

Vitamins, as a class, are over-promoted, over-prescribed and over-used. Myths like 'vitamins energise the body', 'any physical illness is accompanied by vitamin deficiency', 'vitamin intake in normal diet is precariously marginal', 'vitamins are harmless', are rampant.

Vitamins are traditionally divided into two groups:

(a) *Fat-soluble* (A, D, E, K): These (except vit K) are stored in the body for prolonged periods and are liable to cause cumulative toxicity after regular ingestion of large amounts. Some interact with specific cellular receptors analogous to hormones.

(b) *Water-soluble* (B complex, C): These are meagerly stored: excess is excreted with little chance of toxicity. They act as cofactors for specific enzymes of intermediary metabolism.

Chemical forms and preparations of vitamins are listed in Table 67.1.

FAT-SOLUBLE VITAMINS

VITAMIN A

Chemistry and source Vitamin A occurs in nature in several forms. *Retinol* (Vit. A_1) is an unsaturated alcohol containing an 'ionone' ring. Marine fish (cod, shark, halibut) liver oils are rich sources. Appreciable amounts are present in egg yolk, milk and butter.

Dehydroretinol (Vit A_2) is present in fresh water fishes. *Carotenoids* are pigments found in green plants (carrot, turnip, spinach), β *Carotene* is the most important carotenoid. It is inactive as such, one molecule splits to provide two molecules of retinol. Man on normal diet gets half of his vit A as retinol esters and half from carotenoids.

1 µg of retinol = 3.3 IU of vit. A activity

It is now called 1 *Retinol Equivalent* = 6 µg of dietary carotene (because of incomplete utilization of the provitamin).

Absorption and fate Retinyl palmitate, the chief retinyl ester in diet, is hydrolysed in intestines to retinol which is absorbed by carrier transport and reesterified. Aided by bile, it passes into lacteals. Absorption is normally complete, but not in steatorrhoea, bile deficiency and from protein poor diet. Retinol ester circulates in chylomicrons and is stored in liver cells. Free retinol released by hepatocytes combines with *retinol binding protein* (*RBP* a plasma globulin) and is transported to the target cells. On entering them, it gets bound to the *cellular retinol binding protein* (*CRBP*). Small amount is conjugated with glucuronic acid, excreted in bile, undergoes enterohepatic circulation. Minute quantities of water soluble metabolites are excreted in urine and faeces.

In contrast to retinol, only 30% of dietary β carotene is absorbed. It is split into two molecules of *retinal* in the intestinal wall; only half of this is reduced to retinol and utilized.

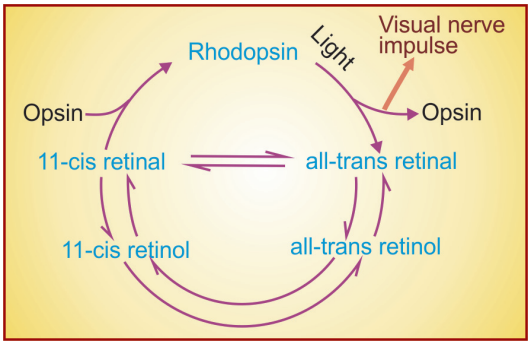


Fig. 67.1: The role of vit. A in visual cycle

Physiological role and actions

(a) *Visual cycle* Retinal generated by reversible oxidation of retinol is a component of the light sensitive pigment *Rhodopsin* which is synthesized by rods during dark adaptation. This pigment gets bleached and split into its components by dim light and in the process generates a nerve impulse through a G-protein called *Transducin*. Retinal so released is reutilized. A similar pigment (Iodopsin) is synthesized in the cones—responsible for vision in bright light, colour vision and primary dark adaptation. In vit. A deficiency rods are affected more than cones; irreversible structural changes with permanent night blindness occur if the deprivation is long-term.

(b) *Epithelial tissue* Vit. A promotes differentiation and maintains structural integrity of epithelia all over the body. It also promotes mucus secretion, inhibits keratinization and improves resistance to infection. It appears to have the ability to retard development of malignancies of epithelial structures. Vit A is also required for bone growth.

(c) *Reproduction* Retinol is needed for maintenance of spermatogenesis and foetal development.

(d) *Immunity* Increased susceptibility to infection occurs in vit A deficiency. Physiological amount of vit A appears to be required for proper antibody response, normal lymphocyte proliferation and killer cell function.

Deficiency symptoms Since vit. A is stored in liver, deficiency symptoms appear only after long-term deprivation, but vit A deficiency is quite prevalent, especially among infants and children in developing countries. Manifestations are:

- Xerosis (dryness) of eye, 'Bitot's spots', keratomalacia (softening of cornea), corneal opacities, night blindness (nyctalopia) progressing to total blindness.
- Dry and rough skin with papules (phrynoderma), hyperkeratinization, atrophy of sweat glands.
- Keratinization of bronchopulmonary epithelium, increased susceptibility to infection.
- Unhealthy gastrointestinal mucosa, diarrhoea.
- Increased tendency to urinary stone formation due to shedding of ureteric epithelial lining which acts as a nidus.
- Sterility due to faulty spermatogenesis, abortions, foetal malformations.
- Growth retardation, impairment of special senses.

Therapeutic uses

1. Prophylaxis of vit A deficiency during infancy, pregnancy, lactation, hepatobiliary diseases, steatorrhoea: 3000–5000 IU/day.
2. Treatment of established vit A deficiency: 50,000–100,000 IU i.m or orally for 1–3 days followed by intermittent supplemental doses.
3. Skin diseases like acne, psoriasis, ichthyosis. Retinoic acid (*see* below) and 2nd or 3rd generation retinoids are used.

Interactions

(i) Vit E promotes storage and utilization of retinol and decreases its toxicity.
(ii) Regular use of liquid paraffin by carrying through with it vit A can result in deficiency.
(iii) Long-term oral neomycin induces steatorrhoea and interferes with vit A absorption.

Hypervitaminosis A Regular ingestion of gross excess of retinol (100,000 IU daily for months) has produced toxicity—nausea, vomiting, itching,

erythema, dermatitis, exfoliation, hair loss, bone and joint pains, loss of appetite, irritability, bleeding, increased intracranial tension and chronic liver disease. Excess retinol is also teratogenic in animals and man. Daily intake should not exceed 20,000 IU.

Acute poisoning has been described after consumption of polar bear liver which contains 30,000 IU/g vit A. Single massive ingestion (> 1 million IU) produces intense headache, drowsiness, irritability, rise in intracranial tension, vomiting, liver enlargement and shedding of skin. Due to saturation of RBP, excess retinol esters circulate in the free state or loosely associated with lipoprotein. These have surfactant property which damages tissues.

Treatment consists of stopping further ingestion, supportive measures, and vit E which promotes storage of retinol in tissues and speeds recovery. Most signs regress in a week, some persist for months. Excess intake of carotenoids does not produce hypervitaminosis A, because conversion to retinol has a ceiling.

Retinoic acid (vit A acid) Retinoic acid has vit A activity in epithelial tissues and promotes growth, but is inactive in eye and reproductive organs. All-trans retinoic acid (Tretinoin) is used topically, while 13-cis retinoic acid (Isotretinoin) is given orally for acne (*see* Ch. 64). Unlike retinol, it is not stored but rapidly metabolized and excreted in bile and urine.

The *cellular retinoic acid binding protein* (*CRABP*) is different from CRBP, is present in skin and other tissues but not in retina—this may be the reason for the inability of retinoic acid to participate in visual cycle.

Retinoid receptors Retinol and retinoic acid act through *nuclear retinoid receptors* which function in a manner analogous to the steroid receptors: activation results in modulation of protein synthesis. In the target cells (epithelial, gonadal, fibroblast) synthesis of certain proteins is enhanced while that of other proteins is depressed—accounting for the structural and functional changes. Two distinct families of retinoid receptors, *viz. Retinoic acid receptors (RARs)* and *Retinoid X receptors (RXRs)* have been identified with differing affinities for different retinoids.

VITAMIN E

Chemistry and source A number of tocopherols, of which α tocopherol is the most abundant and potent, have vit E activity. The *d*-isomer is more potent than *l*-isomer. Wheat germ oil is the richest source, others are cereals, nuts, spinach and egg yolk.

1 mg of *d* α-tocopherol is called α-tocopherol equivalent = 1.49 IU of vit E.

The daily requirement of vit. E is estimated at 10 mg. It is increased by high intake of polyunsaturated fats.

Absorption and fate Vit. E is absorbed from intestine through lymph with the help of bile; it circulates in plasma in association with β-lipoprotein, is stored in tissues and excreted slowly in bile and urine as metabolites.

Physiological role and actions Vit E acts as *antioxidant*, protecting unsaturated lipids in cell membranes, coenzyme Q, etc. from free radical oxidation damage and curbing generation of toxic peroxidation products. Feeding animals with polyunsaturated fats increases vit E requirement, while antioxidants like cystein, methionine, selenium, chromenols prevent some vit E deficiency symptoms in animals. However, vit E might be having some more specific action or a structural role in biological membranes, because other deficiency symptoms are not relieved by these unrelated antioxidants.

Deficiency symptoms Experimental vit E deficiency in animals produces recurrent abortion, degenerative changes in spinal cord, skeletal muscles and heart, and haemolytic anaemia. No clear-cut vit E deficiency syndrome has been described in humans, but vit E deficiency has been implicated in certain neuromuscular diseases in children, neurological defects in hepatobiliary disease and some cases of haemolytic anaemia.

Therapeutic uses

1. Primary vit E deficiency does not occur clinically. Supplemental doses (10–30 mg/ day) may be given to patients at risk (*see* above).
2. G-6-PD deficiency—prolonged treatment with 100 mg/day increases survival time of erythrocytes.

3. Acanthocytosis—100 mg /week i.m: normalizes oxidative fragility of erythrocytes.
4. The risk of *retrolental fibroplasia* in premature infants exposed to high oxygen concentrations can be reduced by 100 mg/kg/day oral vitamin E.
5. Alongwith vit A to enhance its absorption and storage, and in hypervitaminosis A to reduce its toxicity.
6. Large doses (400–600 mg/day) have been reported to afford symptomatic improvement in intermittent claudication, fibrocystic breast disease and nocturnal muscle cramps.

For its antioxidant property, vit E has been promoted for recurrent abortion, sterility, menopausal syndrome, toxaemia of pregnancy, atherosclerosis, ischaemic heart disease, cancer prevention, several skin diseases, prevention of neurodegenerative disorders, postherpetic neuralgia, scleroderma and many other conditions, but without convincing evidence of benefit.

Toxicity Even large doses of vit E for long periods have not produced any significant toxicity, but creatinuria and impaired wound healing have been reported; abdominal cramps, loose motions and lethargy have been described as side effects of vit. E.

Vit E can interfere with iron therapy.

Antioxidant vitamins (vit E, β carotene, vit C) in prevention of cardiovascular disease and cancer

Antioxidants are believed to quench free radicals. Free radicals are atoms or molecules with 'singlet', i.e. unpaired electron which makes them highly reactive. Oxidative free radicals are generated by metabolic reactions—create a chain reaction leading to membrane lipid peroxidation, DNA damage, etc. Free radical oxidation has been implicated in atherosclerosis (oxidized LDL is more atherogenic), cancers, neurodegenerative diseases and inflammatory bowel diseases. Many endogenous and dietary compounds like superoxide dismutase, ferritin, transferrin, ceruloplasmin, α tocopherol, β carotene and ascorbic acid have antioxidant and free radical scavenging properties. On this theoretical basis supported by some epidemiological observations, cohort studies and prospective trials β carotene, vit C and especially vit E have been claimed to protect against atherosclerosis leading to coronary artery disease as well as many types of cancers (lung, breast, mouth, skin, esophagus, stomach, etc.). As a result, vit E and others are being aggressively promoted and many physicians are prescribing them for prophylaxis of these conditions. Learning from mass media, people on their own also are consuming them on a large scale. However, the evidence of a beneficial effect is highly contradictory.

Several large observational studies (involving tens of thousands of subjects) and their meta-analysis have failed to demonstrate any benefit of antioxidant vitamins in terms of cardiovascular event/cancer prevention in well nourished population. On the other hand, there is some indication of increased risk of CHF with >400 mg/day α tocopherol and increased risk of hip fracture among postmenopausal women with high dose of vit A. Therefore, it would be well advised to adopt a healthy lifestyle, *viz.* eating sufficient fruits and vegetables, doing regular exercise, avoiding overweight and smoking, rather than consuming antioxidant medications.

A large number of antioxidant proprietary preparations (ANTOXID, CAROFIT, GLACE, VITOXID, REVOX, CARNITOR, CARNIVIT-E, etc.) containing widely variable amounts of β-carotene, vit A acetate, vit E, vit C, selenium, zinc, copper, manganese, carnitine (a substance synthesized in liver and kidney, and involved in intracellular transport of long-chain fatty acids) are briskly promoted and consumed, but with no credible evidence of benefit, and may be some potential harm.

WATER-SOLUBLE VITAMINS

THE VITAMIN B COMPLEX GROUP

Thiamine (Aneurine, vit B_1)

Chemistry and source A colourless, crystalline compound containing a pyrimidine and a thiazole ring. It is present in the outer layers of cereals (rice polishing), pulses, nuts, green vegetables, yeasts, egg and meat.

TABLE 67.1 Chemical forms, stability, daily allowance and non-combination preparations of vitamins

Vitamin	*Chemical forms*	*Thermostability*	*Daily allowance (adult males)*	*Preparations*
		Fat-Soluble Vitamins		
A	Retinol (A_1) Dehydroretinol (A_2) β-Carotene (provit)	Stable in absence of air	1000 µg (4000 IU)	AQUASOL-A 50,000 IU cap, 100,000 IU in 2 ml inj. AROVIT 50,000 IU tab, 150,000 IU/ml drops, 100,000 IU/ 2 ml inj. CAROFRAL 50,000 IU tab, 100,000 IU/2 ml inj.
D	Calciferol (D_2) Cholecalciferol (D_3) Calcitriol	Stable	5 µg (200 IU) 1 µg	ACRACHITOL, OSTELIN FORTE 300,000 IU/ml & 600,000 IU/ml inj (1 ml amp.), CALCIROL 60,000 IU in 1 g granules. CALTROL, ROCALTROL 0.25 µg cap, CALCIBEST 1 µg/ml inj.
E	α-Tocopherol	Stable; air and UV light decompose	10 mg	EVION 100, 200, 400, 600 mg pearls, 50 mg/ml paed. drops. VITEOLIN, ECAP 200, 400 mg pearls, cap., EROVIT, ETOPLEX, EPHYNA 200, 400 mg caps.
K	Phytonadione (K_1) (Phylloquinone) Menaquinones (K_2) Menadione (K_3) Acetomenaphthone	Stable, decomposed by light	50–100 µg	VITAMIN-K, KENADIONE 10 mg/ml inj. KAPILIN 10 mg tab., ACETOMENADIONE 5, 10 mg tab.
		Water-Soluble Vitamins		
B_1	Thiamine	Relatively labile	1.5 mg	BERIN 50, 100 mg tab, 100 mg/ml inj. (10 ml vial) BENEURON 5 mg cap., BETABION 100 mg tab.
B_2	Riboflavin	Relatively stable	1.7 mg	LIPABOL 20 mg tab. RIBOFLAVIN 10 mg/ml inj.
B_3	Nicotinic acid, Nicotinamide, Tryptophan (provit.) — Niacin	Stable	20 mg	NICOTINIC ACID 25, 50 mg tab., NIALIP 250, 375, 500 mg tab NICOTINAMIDE 25, 50 mg tab.
B_6	Pyridoxine Pyridoxal Pyridoxamine	Stable in absence of air	2 mg	PYRIDOXINE HCl 50 mg/2 ml inj., 10 mg tab. BENADON 40 mg tab, PYRICONTIN 100 mg tab
	Pantothenic acid	Labile	4–7 mg	CALCIUM PANTOTHENATE 50 mg tab., 50 mg/2 ml inj.
	Biotin	Stable	0.1–0.2 mg	
	Folic acid Folinic acid	Labile	0.2 mg	FOLVITE, FACITAB 5 mg tab. CALCIUM LEUCOVORIN 3 mg/ml inj.
B_{12}	Cyanocobalamin Hydroxocobalamin Methylcobalamin	Stable	2 µg	MACRABIN 35 µg/ml liq: 100, 500, 1000 µg inj., REDISOL-H, MACRABIN-H 500, 1000 µg inj. VITAMIN B_{12} 500, 1000 µg in 10 ml vial. METHYLCOBAL, BIOCOBAL, DIACOBAL, 500 µg cap
C	Ascorbic acid	Labile in solution	60 mg	CECON 500 mg tab, 100 mg/ml drops. CELIN 50, 100, 500 mg tab., CHEWCEE 500 mg tab REDOXON 200, 500 mg tab, 500 mg/5 ml inj.

Absorption and fate Physiological amounts are absorbed by active transport. When large doses are given orally, some passive diffusion also occurs. Limited amounts are stored in tissues. About 1 mg/day is degraded in the body, excess is rapidly excreted in urine.

Physiological role After conversion in the body to *Thiamine pyrophosphate,* it acts as a coenzyme in carbohydrate metabolism: decarboxylation of ketoacids and hexose monophosphate shunt. Requirement is dependent upon carbohydrate intake—about 0.3 mg/ 1000 K cal. It also appears to play some role in neuromuscular transmission.

Pyrithiamine and *oxythiamine* are synthetic thiamine antagonists. Tea also contains a thiamine antagonist.

Deficiency symptoms The syndrome of thiamine deficiency beriberi is seen in *dry* and *wet* forms:

Dry beriberi: Neurological symptoms are prominent—polyneuritis with numbness, tingling, hyperesthesia, muscular weakness and atrophy resulting in 'wrist drop', 'foot drop', paralysis of whole limb, mental changes, sluggishness, poor memory, loss of appetite and constipation.

Wet beriberi: Cardiovascular system is primarily affected—palpitation, breathlessness, high output cardiac failure and ECG changes. Protein deficiency is commonly associated and adds to the generalised anasarka due to CHF.

Therapeutic uses

1. Prophylactically (2–10 mg daily) in infants, pregnant women, chronic diarrhoeas, patients on parenteral alimentation. Glucose infusion unmasks marginal thiamine deficiency.
2. Beriberi—100 mg/day i.m. or i.v. till symptoms regress—then maintenance doses orally.
3. Acute alcoholic intoxication: thiamine 100 mg is added to each vac of glucose solution infused. Most neurological symptoms in chronic alcoholics are due to thiamine deficiency—peripheral neuritis, Wernick's encephalopathy, Korsakoff's psychosis: give 100 mg/day parenterally.
4. In neurological and cardiovascular disorders, hyperemesis gravidarum, chronic anorexia and obstinate constipation—thiamine has been used even without definite proof of its deficiency—symptoms improve dramatically if thiamine deficiency has been causative.

Adverse effects Thiamine is nontoxic. Sensitivity reactions sometimes occur on parenteral injection.

Riboflavin (vit B_2)

Chemistry and source A yellow flavone compound found in milk, egg, liver, green leafy vegetables, grains.

Absorption and fate Well absorbed by active transport and phosphorylated in the intestine. Riboflavin phosphate (Flavin mononucleotide: FMN) is formed in other tissues as well. Body does not significantly store riboflavin; larger doses are excreted unchanged in urine. Thiamine and riboflavin are both synthesized by colonic bacteria but this does not become available to the host.

Actions and physiological role Flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) are coenzymes for flavoproteins involved in many oxidation-reduction reactions. Thiamine and riboflavin are devoid of pharmacological actions.

Deficiency symptoms Riboflavin deficiency generally occurs in association with other deficiencies. Characteristic lesions are angular stomatitis; sore and raw tongue, lips, throat, ulcers in mouth; vascularization of cornea. Dry scaly skin, loss of hair; anaemia and neuropathy develop later.

Therapeutic uses To prevent and treat ariboflavinosis (2–20 mg/day oral or parenteral), generally along with other B complex members. There is no proof of benefit in any other condition.

Niacin (vit B_3)

Chemistry and source Niacin refers to *Nicotinic acid* as well as *Nicotinamide*—pyridine compounds, initially termed pellagra preventing factor. Sources are liver, fish, meat, cereal husk, nuts and pulses.

The amino acid *tryptophan* (mainly from animal protein) can be regarded as a provitamin, as it is partially converted in the body to nicotinic acid (60 mg tryptophan = 1 mg nicotinic acid). Maize eaters have suffered from pellagra because corn flour is poor in tryptophan and it is believed to contain a niacin antagonist. Thus, daily requirement of niacin is affected by the amount of tryptophan in diet.

Absorption and fate Niacin is completely absorbed from gastrointestinal tract. Physiological amounts are metabolized in the body, while large doses are excreted unchanged in urine. Modest amounts are stored in liver.

Physiological role and actions Nicotinic acid is readily converted to its amide which is a

component of the coenzyme *Nicotinamide-adenine-dinucleotide* (NAD) and its *phosphate* (NADP) involved in oxidation-reduction reactions. These pyridine nucleotides act as hydrogen acceptors in the electron transport chain in tissue respiration, glycolysis and fat synthesis. Flavoproteins regenerate them by oxidizing NADH and NADPH.

Nicotinic acid (but not nicotinamide) in large doses is a vasodilator, particularly of cutaneous vessels. It also lowers plasma lipids (*see* Ch. 45).

Deficiency symptoms Niacin deficiency produces 'Pellagra', cardinal manifestations of which are:

Dermatitis—sunburn like dermal rash on hands, legs and face which later turn black, crack and peal.

Diarrhoea—with enteritis, stomatitis, glossitis, salivation, nausea and vomiting.

Dementia—with hallucinations preceded by headache, insomnia, poor memory, motor and sensory disturbances.

Anaemia and hypoproteinaemia are common in pellagra. Chronic alcoholics are particularly at risk of developing pellagra, because in addition to dietary deficiency, niacin absorption is impaired in them. Other B vitamin deficiencies are often associated.

Therapeutic uses

1. Prophylactically (20–50 mg/day oral) in people at risk of developing pellagra.
2. Treatment of pellagra—200 to 500 mg/day in divided doses orally or parenterally. Striking improvement occurs in 1–2 days, but skin lesions take weeks to months. Nicotinamide is preferred, especially for injection, because it does not cause flushing and other side effects seen with nicotinic acid.
3. Hartnup's disease: in which tryptophan transport is impaired, and in carcinoid tumours which use up tryptophan for manufacturing 5-HT, need niacin supplementation.
4. Nicotinic acid (not nicotinamide) has been used in peripheral vascular disease and as hypolipidaemic (Ch. 45).

Adverse effects Nicotinic acid, in pharmacological doses, has many side effects and toxicities (p. 640). Nicotinamide is innocuous.

Pyridoxine (vit B_6)

Chemistry and source *Pyridoxine, Pyriodoxal* and *Pyridoxamine* are related naturally occurring pyridine compounds that have vit B_6 activity. Dietary sources are—liver, meat, egg, soybean, vegetables and whole grain.

Absorption and fate All three forms of the vitamin are well absorbed from the intestine. They are oxidized in the body and excreted as pyridoxic acid. Little is stored.

Physiological role and actions Pyridoxine and pyridoxamine are readily oxidized to pyridoxal, which is then phosphorylated to *pyridoxal phosphate*—the coenzyme form. Pyridoxal dependent enzymes include transaminases and decarboxylases involved in synthesis of nonessential amino acids, tryptophan and sulfur containing amino acid metabolism, formation of 5-HT, dopamine, histamine, GABA and aminolevulinic acid (first step in the synthesis of haeme). High protein diet increases pyridoxine requirement.

Pyridoxine has been shown to interact with steroid hormone receptors, but its clinical implication is not clear. Prolonged intake of large doses of pyridoxine can give rise to dependence, and mega doses (0.2–2.0 g/day) have been linked with sensory neuropathy. Otherwise, pyridoxine is free from pharmacological actions and side effects. However, suppression of lactation has been noted in nonsuckling postpartal women given high doses of pyridoxine: may be due to increased dopamine action on pituitary lactotropes.

Drug interactions

1. Isoniazid reacts with pyridoxal to form a hydrazone, and thus inhibits generation of pyridoxal phosphate. Isoniazid also combines with pyridoxal phosphate to interfere with its coenzyme

function. Due to formation of hydrazones, the renal excretion of pyridoxine compounds is increased. Thus, isoniazid therapy produces a pyridoxine deficiency state.
2. Hydralazine, cycloserine and penicillamine also interfere with pyridoxine utilization and action.
3. Oral contraceptives reduce pyridoxal phosphate levels in some women.
4. Pyridoxine, by promoting formation of dopamine from levodopa in peripheral tissues, reduces its availability in the brain, abolishing the therapeutic effect in parkinsonism, but not when a peripheral decarboxylase inhibitor is combined with it.
5. 4-deoxypyridoxine is a vit B_6 antagonist.

Deficiency symptoms Deficiency of vit B_6 usually occurs in association with that of other B vitamins. Symptoms ascribed to pyridoxine deficiency are—seborrheic dermatitis, glossitis, growth retardation, mental confusion, lowered seizure threshold or convulsions (due to fall in brain GABA levels), peripheral neuritis and anaemia.

Therapeutic uses

1. Prophylactically (2–5 mg daily) in alcoholics, infants and patients with deficiency of other B vitamins.
2. To prevent and treat (10–50 mg/day) isoniazid, hydralazine and cycloserine induced neurological disturbances. Acute isoniazid poisoning has been successfully treated with massive doses (in grams) of pyridoxine.
3. To treat mental symptoms in women on oral contraceptives (50 mg daily).
4. Pyridoxine responsive anaemia (due to defective haeme synthesis) and homocystinuria are rare genetic disorders that are benefited by large doses of pyridoxine (50–200 mg/day).
5. Convulsions in infants and children.

Pantothenic acid

Pantothenic acid is an organic acid, widely distributed in food sources, especially liver, mutton, egg yolk and vegetables. It is quickly absorbed and excreted unchanged in urine with little storage.

It is a component of coenzyme-A which functions in carbohydrate, fat, steroid and porphyrin metabolism by catalysing acetate transfer reactions. Clinical deficiency of pantothenic acid is not known. Experimental deficiency in man causes insomnia, intermittent diarrhoea, flatulence, vomiting, leg cramps and paresthesias. Calcium/sodium pantothenate is included in B complex and multivitamin preparations. Intravenous calcium pantothenate has been tried in paralytic ileus.

Biotin

Biotin is a sulfur containing organic acid found in egg yolk, liver, nuts and many other articles of food. Some of the biotin synthesized by intestinal bacteria is also absorbed. It is well absorbed from intestine and excreted mainly unchanged in urine. Not much is stored in the body. *Avidin*, a heat labile protein in egg white, binds and prevents the absorption of biotin. Some other biotin antagonists are also known.

Biotin is a coenzyme for several carboxylases involved in carbohydrate and fat metabolism. Deficiency symptoms include seborrheic dermatitis, alopecia, anorexia, glossitis and muscular pain. Spontaneous deficiency of biotin has been noted only in subjects consuming only raw egg white and in patients on total parenteral nutrition. Except for these unusual instances and rare genetic abnormalities of biotin dependent enzymes, there are no clearly defined therapeutic uses of biotin. It is present in some multivitamin preparations.

VITAMIN C (ASCORBIC ACID)

Chemistry and source Ascorbic acid is a 6 carbon organic acid with structural similarity to glucose. It is a potent reducing agent and *l*-form is biologically active. Citrus fruits (lemons, oranges) and black currants are the richest sources; others are tomato, potato, green chillies, cabbage and other vegetables. Human milk is richer in vit C (25–50 mg/L) than cow's milk.

Absorption and fate It is nearly completely absorbed from g.i.t. and widely distributed extra- and intracellularly. Plasma concentration and total body store of vit C is related to daily intake. The usual 60 mg/day intake results in about 0.8 mg/dl in plasma and 1.5 g in the body as a whole. Increasing proportions are excreted in urine with higher intakes. Body is not able to store more than 2.5 g. It is partly oxidized to active (dehydroascorbic acid) and inactive (oxalic acid) metabolites.

Physiological role and actions Vit C plays a role in many oxidative and other metabolic

TABLE 67.2 **Combination preparations of vitamins**

Proprietary name		Dose unit	Vit. A (IU)	Vit. D (IU)	Vit. E (mg)	Thiamine (mg)	Riboflavin (mg)	Niacin (mg)	Pyridoxine (mg)	Pantothenic (mg)	Biotin (mg)	Folic acid (mg)	B_{12} (µg)	Vit. C (mg)
ABDEC DROPS		per 0.6 ml	5,000	400	–	1	1	10	0.6	3	–	–	–	50
ADEXOLIN	cap	per cap.	5,000	400	–	–	–	–	–	–	–	–	–	–
AQUASOL-A-D	drops	per ml	24,000	1,000	–	–	–	–	–	–	–	–	–	–
AQUASOL-A-E	cap	per cap.	30,000	–	50	–	–	–	–	–	–	–	–	–
BECOSULES	cap	per cap.	–	–	–	10	10	50	3	12.5	–	1	5	150
"	syrup	per 5 ml	–	–	–	2	2.5	20	2	6	–	–	–	75
BECOZYME C FORTE	tab.	per tab.	–	–	–	15	15	50	3	16.3	0.15	–	10	150
BEJECTAL	inj.	per ml	–	–	–	10	2	75	5	5	–	–	–	–
EDINOL	cap	per cap.	10,000	1,000	15	10	10	50	3	10	–	1	5	150
MULTIVITAPLEX	elixir	per 5 ml	2,500	200	–	2	2.5	20	1	5	–	–	–	50
" FORTE	cap.	per cap.	10,000	400	15	5	5	50	1.5	5	–	1	5	75
COBADEX FORTE	cap.	per cap	–	–	–	10	10	100	3	50	–	1.5	15	–
COBADEX SYRUP	syr	per 5 ml	–	–	–	5	2.5	50	1.5	5	–	–	–	–
KINETONE	liq.	per 15 ml	2000	200	7.5	2	3	–	1.5	–	–	–	1	–
OPTINEURON	inj.	per 3 ml	–	–	–	100	5	100	100	50	–	–	1000	–
STRESS CAPS	cap.	per cap	–	–	–	10	10	100	2	20	–	–	5	150
NEUROXIN-12	inj.	per 10 ml	–	–	–	30	–	–	14	–	–	–	500	–
" FORTE	inj.	per 3 ml	–	–	–	100	5	100	100	50	–	–	1000	–
NEUROBION	tab	per tab	–	–	–	10	10	45	3	50	–	–	15	–
POLYBION	cap.	per cap.	–	–	–	10	10	100	3	50	–	1.5	15	150
"	inj.	per 2 ml	–	–	–	10	4	40	4	6	–	–	8	–
ROVIGON	tab.	per tab.	10,000	–	70	–	–	–	–	–	–	–	–	–
SCLEROBION	tab.	per tab.	10,000	–	25	–	–	–	3	–	–	–	–	–
VIMAGNA	drops	per ml	2,000	200	–	0.8	0.8	13	0.8	1.7	–	–	–	20

Combined formulations of vitamins with analgesics, antiinflammatory drugs, tranquilizers and antitubercular drugs (except isoniazid + pyridoxine) are banned in India.

reactions, e.g. hydroxylation of proline and lysine residues of protocollagen—essential for formation and stabilization of collagen triple helix; hydroxylation of carnitine, conversion of folic acid to folinic acid, biosynthesis of adrenal steroids, catecholamines, oxytocin and vasopressin and metabolism of cyclic nucleotides and prostaglandins. It directly stimulates collagen synthesis and is very important for maintenance of intercellular connective tissue. A number of ill-defined actions have been ascribed to ascorbic acid in mega doses, but none is proven.

Deficiency symptoms Severe vit C deficiency *Scurvy*, once prevalent among sailors is now seen only in malnourished infants, children, elderly, alcoholics and drug addicts. Symptoms stem primarily from connective tissue defect: increased capillary fragility—swollen and bleeding gums, petechial and subperiosteal haemorrhages, deformed teeth, brittle bones, impaired wound healing, anaemia and growth retardation.

Therapeutic uses

1. Prevention of ascorbic acid deficiency in individuals at risk (*see* above) and in infants: 50–100 mg/ day. Vit C or orange juice can be routinely included in infant diet.
2. Treatment of scurvy—0.5–1.5 g/day.
3. Postoperatively (500 mg daily): though vit C does not enhance normal healing, suboptimal healing can be guarded against. It has also been found to accelerate healing of bedsores and chronic leg ulcers. Requirement of ascorbic acid is increased in postinjury periods.
4. Anaemia: Ascorbic acid enhances iron absorption and is frequently combined with ferrous salts (maintains them in reduced state). Anaemia of scurvy is corrected by ascorbic acid, but it has no adjuvant value in other anaemias.
5. To acidify urine (1 g TDS–QID) in urinary tract infections (*see* Ch. 54).
6. Large doses (2–6 g/day) of ascorbic acid have been tried for a variety of purposes (common cold to cancer) with inconsistent results. No definite beneficial effect has been noted in asthma, cataract, cancer, atherosclerosis, psychological symptoms, infertility, etc. However, severity of common cold symptoms may be somewhat reduced, but not the duration of illness or its incidence. Improved working capacity at submaximal workloads has been found in athletes but endurance is not increased.

Adverse effects Ascorbic acid is well tolerated in usual doses. Mega doses given for long periods can cause 'rebound scurvy' on stoppage—probably due to enhancement of its own metabolism or tissue acclimatization. The risk of urinary oxalate stones may be increased. High doses may also be cytotoxic when added to iron preparations.

Vitamin D (Ch. 24), vit K (Ch. 44), folic acid and vit B_{12} (Ch. 43) have been considered in earlier chapters.

Chapter 68 Vaccines and Sera

Vaccines and sera are biological products which act by reinforcing the immunological defence of the body against foreign agencies (mostly infecting organisms or their toxins).

Vaccines impart *active immunity*—act as antigens which induce production of specific antibodies by the recipient himself.

Antisera and *Immune globulins* impart passive *immunity*—readymade antibodies (produced by another person or animal who has been actively immunized) are transferred.

Active immunization is more efficacious and longer lasting than passive immunization, but the former needs a latent period of one to many weeks, whereas the latter affords immediate protection. Antisera are, therefore, curative also, whereas vaccines are only prophylactic. Acutely ill, debilitated or immunocompromised individuals may not be able to generate an adequate antibody response and require passive protection.

Vaccines and sera are potentially dangerous products and mostly used in public health programmes—their manufacture, quality control, distribution and sale is strictly supervised by State health authorities. These biologicals are standardized by bioassay and need storage in cold to maintain potency.

VACCINES

Vaccines are antigenic materials consisting of the whole microorganism or one of its products. Vaccines are of 3 types:

(i) *Killed (Inactivated) vaccines*: consist of microorganisms killed by heat or chemicals. They generally require to be given by a series of injections for primary immunization. The immunity is relatively shorter-lasting; booster doses are mostly needed at intervals of months or years.

(ii) *Live attenuated vaccines*: consist of live bacteria or viruses which have been rendered avirulent. They nevertheless grow and multiply in the body of the host to a limited extent. Live vaccines usually produced long-lasting immunity. In individuals with impaired host defence, e.g.

(a) Leukaemia or other malignancies, especially those receiving cytotoxic chemotherapy.
(b) Systemic lupus erythematosus.
(c) Corticosteroid recipients.
(d) AIDS and other immune deficiency states.

The limited virulence of organisms in the live vaccine may be sufficient to cause a disease; live vaccines are contraindicated in them.

Two live vaccines, if not given together, should preferably be administered with a gap of 1 month.

(iii) *Toxoids*: are modified bacterial exotoxins so that toxicity is lost but antigenicity is retained. The term 'vaccine' is sometimes restricted to preparations of whole microorganisms and toxoids are enumerated separately.

Active immunization with vaccines may fail to 'take' during corticosteroid or immunosuppressant medication and should be avoided. Vaccination should be deferred in the presence of any acute (especially respiratory) infection and during pregnancy. Antibiotics added during production of vaccines and present in trace amounts in viral vaccines may cause reaction in individuals sensitive to these. Egg proteins (in vaccines prepared on chick embryo) and other materials used for vaccine culture may be responsible for allergic reactions. Adrenaline injection (1 in 1000) should be available to control allergic reaction to the vaccine, if it occurs.

Killed (inactivated) vaccines	Live attenuated vaccines
BACTERIAL	
Typhoid-paratyphoid (TAB)	Bacillus Calmette-Guérin (BCG)
Vi Typhoid polysaccharide	Typhoid-Ty 21a
Cholera	
Whooping cough (Pertussis)	
Meningococcal	
Haemophilus influenzae type b	
Plague	
VIRAL	
Poliomyelitis inactivated (IPV, Salk)	Poliomyelitis oral live (OPV, Sabin)
Rabies (Neural tissue)	Mumps (live attenuated)
Rabies (Chick embryo cell, PCEV)	Measles (live attenuated)
Rabies (Human diploid cell, HDCV)	Rubella (live attenuated)
Rabies (Vero cell, PVRV)	Varicella (live attenuated)
Influenza	
Hepatitis B	
Hepatitis A	
TOXOIDS	
Tetanus (fluid/adsorbed)	
Diphtheria (adsorbed)	
COMBINED VACCINES	
Double antigen (DT-DA)	
Triple antigen (DPT)	
Measles, mumps, rubella (MMR)	
Pentavalent vaccine (DPT + Hepatitis B + *H. influenzae* type b)	

SECTION 14

The antibodies developed in response to live or killed vaccines inactivate the bacteria/virus when it subsequently enters the body, while those induced by toxoids neutralize the elaborated exotoxin. The latent period between vaccination and development of immunity and the period for which it lasts depends primarily on the organism, but varies somewhat in different individuals. Viral vaccines and toxoids generally afford more prolonged protection than bacterial vaccines. The important vaccines are described briefly.

BACTERIAL VACCINES

1. Typhoid-Paratyphoid A, B (TAB vaccine) It is a sterile suspension, 1 ml containing 1×10^9 *S. typhi* and 7.5×10^8 each of *S. paratyphi* A and B organisms in 5, 10 ml vials. *Dose*—0.5 ml s.c., 2–3 injections at 2–4 weeks intervals. Local tenderness, fever and malaise lasting 1–2 days are common after the first dose. It is estimated to be 70% effective in preventing enteric fever for 1 year. Booster doses may be given every 2–3 years.

2. Vi Typhoid polysaccharide vaccine It contains purified Vi capsular antigen of *S. typhi*. A single 0.5 ml s.c./i.m. dose affords 72% protection at 18 months and 60% protection at 3 years. It produces much less local and systemic side effects than TAB and induces longer lasting immunity, but does not protect against paratyphoid A and B. Thus, it is an improvement over the whole cell TAB vaccine. However, it is not approved for use in children below 2 years and in pregnant women.

VACTYPH, TYPHIM Vi, TYPHIVAX 0.025 mg in 0.5 ml inj; repeat after 3 years.

3. 'Typhoid-Ty21a' oral vaccine This is a newer live oral typhoid vaccine prepared from Ty 21a attenuated strain of *S. typhi* which lacks the Vi polysaccharide and is nonpathogenic. The attenuation is due to absence of the enzyme

Uridine diphosphate galactose-4 epimerase which is essential for the production of lipopolysaccharide 'O' antigens. It is avirulent. By lodging in the intestinal mucosa it protects against *S. typhi* invasion of the gut in addition to imparting systemic immunity. High cell mediated and modest antibody mediated immunity is produced. Administered as 3 doses on alternate days in the form of enteric coated capsules it affords protection for 3 years. Efficacy is better than TAB. Trials in India and other countries have reported 67–90% protection at 3 years. Side effects are negligible: only 2% cases have reported diarrhoea, abdominal pain or rashes. It is much more convenient, safer and longer acting. It is not approved for use in children below 5 years and in pregnant women.

TYPHORAL *S. typhi* strain Ty21A 10^9 organism per cap; 3 caps taken in 3 doses on alternate days in between meals.

4. Cholera vaccine It is a suspension of phenol/formalin killed Inaba and Ogawa strains of *V. cholerae*, each ml containing 8×10^9 organisms in 5, 10, 30 ml vials. *Dose:* 0.5 ml s.c. or i.m. followed by 1 ml 1–4 weeks later, or a single dose of 1 ml for mass innoculation. Immunity, sufficient to prevent clinical disease, is produced only in 50% of those innoculated, and lasts 6 months or so—sufficient to tide over an epidemic. Cholera innoculation during congregations (*melas*) has not reduced the incidence of the disease (because it takes 2–3 weeks for immunity to develop): this practice has been discontinued. It also does not prevent carrier state. Transient local soreness, low grade fever, aches and pains lasting 1–2 days are common. Neurological complications are rare.

Two new oral cholera vaccines have been produced: killed whole cell/recombinant B subunit (WC/r BS) and live CVD-103 HgR vaccine. Both these vaccines are highly immunogenic, safer than the present cholera vaccine and provide immunity upto 3 years. Cumulative protective efficacy of 86% at 3 weeks and 50% at 3 years have been estimated. They have been made available in Europe, but not yet in India.

5. Whooping cough (pertussis) vaccine It is killed 2×10^{10} organisms/ml suspension of *B. pertussis* organisms. *Dose* 0.25–0.5 ml s.c. or i.m. thrice at 4 week intervals in infants and children below 5 years (whooping cough is very rare after 5 years age).

It also induces a state of diminished β adrenergic reactivity and aids sensitization to other antigens.

In addition to local pain and induration, severe systemic (even fatal) reactions have been reported, but extremely rarely—high fever with hypotonic hyporesponsive child, convulsions, alterations of consciousness and focal neurological signs. Once any such reaction has occurred, further doses are contraindicated. It is also contraindicated in children with history of convulsions or other neurological disease.

It is a component of triple antigen: seldom used separately.

6. Meningococcal A&C vaccine It contains purified capsular polysaccharide of *N. meningitidis* group A and C, 50 µg of each per unit in single dose and 10 dose vials. One dose (0.5 ml s.c. or i.m.) is indicated for prophylaxis of meningitis during an epidemic caused by group A or C meningococci.

MENINGOCOCCAL A & C, MENCEVAX A & C 0.5 ml amp, 5 ml vial.

7. Haemophilus influenzae type b (Hib) vaccine It contains medium oligosaccharide of *H. influenzae* type b (10 µg) conjugated with nontoxic protein (25 µg) of CRM_{197} mutant *C. diphtheriae* toxin along with alum. hydrox. adjuvant. It is indicated for protection of infants and children against *H. influenzae* meningitis, pneumonia, etc. Infants 2–6 months are given 3 doses (0.5 ml i.m.) at 8 week gaps, 7–11 months 2 doses, while those older than 1 yr require only 1 dose. Good antibody response and protection has been obtained in > 90% recipients.

VAXEM-HIB, HIB-TITER 0.5 ml and 5 ml vials

8. Antiplague vaccine formalized It contains 2×10^9 *Y. pestis* organisms per ml, killed by formaline, in 10 ml vial. *Dose*—1 ml i.m. twice 1–2 weeks apart or 2 ml single dose. Local and systemic reactions are relatively frequent and increase with the number of booster doses. Immunity lasts 6–8 months—sufficient to cover an epidemic. Plague is now rare, so is the need for this vaccine.

9. Bacillus Calmette-Guérin (BCG) vaccine It is a live vaccine bearing an attenuated bovine strain of *M. tuberculosis*, developed in 1921 by Calmette and Guérin in France. It is supplied as 0.5–1 mg dry powder (1–2.5 × 10^7 colony forming units) in ampules to be suspended in 1 ml of sterile water; 0.05 ml (in neonate) 0.1 ml (older individuals) is injected intracutaneously in the left deltoid region at birth. In children and adults tuberculine testing is done beforehand and BCG is given only to negative responders.

A red painless papule appears after 7–10 days; reaches about 8 mm diameter in 5 weeks with swelling of axillary lymph node; may ulcerate, but scales and dries in 3 months; totally heals in 6 months. The protection afforded by BCG is partial and neither permanent nor entirely predictable. It has been widely used to enhance resistance to tubercular infection, but doubt has been cast about its utility in adults, though children appear to be benefited.

BCG has also been used to enhance immunity nonspecifically by stimulating the reticuloendothelial system: employed as adjuvant in immunotherapy of cancer and some other conditions. It is contraindicated in tuberculine positive individuals, in those with compromised host defence including HIV positive children, and during pregnancy.

VIRAL VACCINES

1. Poliomyelitis The virus (type 1, 2, 3) is grown in monkey kidney cell culture and two vaccines are prepared from it.

(a) *Oral poliovirus vaccine (OPV; Sabin vaccine)* It is the live virus available in 10 ml and 50 ml vials; each dose is 2 drops, dropped directly in the mouth. The virus multiplies in the intestines and produces active immunity, simulating natural infection, without producing symptoms of the disease. For primary immunization OPV is now generally given at birth and then at 6, 10 and 14 weeks. Booster doses are given between 15–18 months and at school entry. OPV is the vaccine of choice for active immunization of children because it is simple to administer, is well accepted, induces systemic as well as intestinal immunity (the portal of entry of disease virus) and is highly efficacious. The intestinal immunity also eliminates carrier state and thus limits spread of the disease. It is advised to postpone the vaccine in presence of vomiting and diarrhoea. Vaccine associated paralysis occurs extremely rarely.

Simultaneous vaccination of all infants and children upto 5 years age (pulse polio programme) has eradicated the wild virus in many countries by colonizing all susceptible intestines by the vaccine virus. This programme is underway in India.

(b) *Inactivated poliomyelitis vaccine (IPV, Salk vaccine)* It is inactivated suspension of the virus which is preferred over OPV only for:

(i) primary immunization in adults (risk of vaccine associated paralysis following OPV is higher in adults).
(ii) in persons with compromized immune system.

Three doses of 1 ml each are injected s.c. in the deltoid region at 4–6 week intervals and a fourth is given 6–12 months later. Booster doses are given every 5 years. Fever and local pain are common. Allergic reactions sometimes occur, probably to the animal protein present in the vaccine.

2. Rabies Four rabies vaccines have been produced.

a. *Antirabic vaccine carbolized (Semple vaccine)* Also called 'Neural tissue vaccine' (NTV), it is a 5% suspension of sheep brain substance containing carbolic acid fixed rabies virus. Though long considered obsolete because of poorer efficacy, need for 14 daily painful large volume (2–5 ml) injections into the anterior abdominal wall, and risk of serious (even fatal) vaccine associated allergic encephalomyelitis, it continued to be used in Government hospitals in India till mid 2005, after which it has been discontinued.

b. *Purified chick embryo cell vaccine (PCEV)* It consists of Flury-LEP strain of rabies virus grown on chick fibroblasts and inactivated by β-propiolactone; available as 2.5 IU in 1 ml amp (RABIPUR). The efficacy of this vaccine is nearly equal to HDCV, and it produces local reactions in ~5% cases. However, rare neuroparalytic complications have been reported. Local pain, erythema, swelling and lymph node enlargement can occur.

c. *Human diploid cell vaccine (HDCV)* It is lyophilized inactivated rabies virus grown in human diploid cell culture. The vial containing 2.5 IU is freshly suspended in 1 ml of diluent.

A local reaction—redness and slight induration lasting 1–2 days occurs in 10% cases. Fever and arthralgia is reported in 1%. HDCV is ~100% effective and well tolerated. Vaccine associated encephalitis does not occur.

d. *Purified vero cell rabies vaccine (PVRV)* This contains inactivated wistar rabies PM/WI38-1-503-3M strain grown on vero continuous cell line (VERORAB 1 ml; VEROVAX-R 0.5 ml).

Post-exposure prophylaxis: This is given to all nonimmunised animal-bite cases suspected to have been exposed to the rabies virus. The intradermal (i.d.) regimen for all tissue culture rabies vaccines called the 'Thai regimen' that has been recommended by the WHO since 1992, has been approved and notified by the Government of India in 2006. This regimen requires only 1/5 dose of the earlier used i.m. regimen, is less expensive, more convenient and equally efficacious. In this regimen 0.1 ml of PCEV or PVRV or 0.2 ml of HDCV is injected i.d. at 2 sites (over deltoid of both arms) on days 0, 3 and 7 followed by 1 site injection on day 28 (or 30) and day 90, (2 + 2 + 2 + 1 + 1 = 8 injections). Thus, no injection is given on day 14 as in earlier i.m. regimen which employed 1 ml PCEV/HDCV or 0.5 ml PVRV per injection on days 0, 3, 7, 14, 30, 90.

Because rabies vaccines take 10–14 days to develop protective antibodies, concurrent administration of rabies immunoglobulin (RIG) is recommended in category III bites, where risk of contacting rabies is high.

An alternative 8 site i.d. regimen (Oxford regimen) is advocated for an earlier antibody response, particularly when RIG is not available for postexposure treatment. In this regimen 0.1 ml of PCEV or HDCV (but not PVRV) is injected at 8 sites (over both deltoids, suprascapular region, thighs and abdomen) on day 0. On 7th day 4 sites are injected followed by one site injection on day 28 and 90 (total 14 injections).

Pre-exposure prophylaxis (Primary vaccination): This is usually recommended for veterinary workers and animal handlers, who are at high risk of animal bites. Three i.d. injections of 0.1 ml each of PCEV/HDCV/PVRV are given on days 0, 7 and 28. Booster doses are recommended every 2 years so long as the person remains at risk.

Post-exposure prophylaxis in already vaccinated subjects: This is given when an immunized person is bitten by a suspected animal. Three 0.1 ml i.d. injections are given on days 0, 3 and 7.

Local treatment of bite wound: Early local treatment of bite wound is essential in addition to the vaccine ± RIG. The wound should be thoroughly washed with soap under running water for at least 5 min, followed by application of an antiseptic (alcohol/povidone iodine/cetrimide). Cauterization with carbolic acid is contraindicated. In category III bites, RIG should be infiltrated locally in the depth and around the wound to inactivate the locally present virus. Suturing of the wound should be avoided, at least for 2 days.

3. Influenza virus vaccine Contains inactivated influenza virus A and B. Immunization may be done annually or during an epidemic: 2 injections of 0.5–1 ml i.m. 1–2 months apart. Influenza virus undergoes frequent antigenic changes; hence the efficacy of the vaccine is inconsistent. It is indicated only in high risk cases.

Adverse reactions are commoner in children—local tenderness and induration occurs in 30%. Fever, malaise and myalgia lasting 1–2 days is less frequent. Allergic reactions to the egg protein present in the vaccine occur rarely.

4. Hepatitis B vaccine The new hepatitis B vaccine (ENGERIX-B) is prepared in yeast cells by recombinant DNA technique and contains aluminium hydroxide adsorbed hepatitis B virus surface antigen 20 µg in 1 ml suspension. Three 1 ml injections in the deltoid muscle given at 0, 1 and 6 months produce protective antibody titers in 99% subjects. Children <10 yr are given 0.5 ml doses in the thigh. Now included in universal immunization for all, but is especially indicated in persons who come in contact with blood, blood products and other body fluids (surgeons, dentists, blood bank personnel, laboratory technicians and other health care workers, haemophilics, haemodialysis patients,

drug addicts, etc). Induration and soreness at injection site and occasional fever and malaise are the adverse effects.

5. Hepatitis A vaccine It is prepared by inactivating with formaldehyde hepatitis A virus grown in human diploid cell culture. A single 0.5 ml i.m. injection in deltoid muscle affords protection, but a booster dose ater 6 month is recommended.

AVAXIM 0.5 ml prefilled syringe, HAVRIX 0.5 ml inj.

6. Mumps virus vaccine live attenuated It is prepared from mumps virus grown in cell culture of chick embryo. A single dose of 5000 $TCID_{50}$ (tissue culture infectious dose 50%) affords protection for 10 years; revaccination is not required. Clinical disease may occur if the vaccine is given *after exposure* to natural mumps. It is generally combined with measles and rubella vaccine (MMR), and is not recommended below 1 year of age. A mild febrile reaction occurs occasionally.

7. Measles vaccine live attenuated This is also a vaccine grown on chick embryo; available in single dose vials containing 1000 $TCID_{50}$ of *Edmonston Schwarz* strain (ROUVAX, RIMEVAX) or *Edmonston zagreb* strain (M-VAC) for s.c. injection over right deltoid region. It produces a modified infection—fever, rash and coryza may appear after 5–10 days; immunity lasts 8 years and no booster doses are required. It is recommended in children 9 months or older. Ordinarily, adults need not be immunized. Malnourished, chronically ill and tuberculous children must be protected to minimize the risk of serious complications of natural measles. Some protection is afforded even if given after exposure. It should be given with caution to children with history of febrile convulsions or parental history of epilepsy.

8. Rubella vaccine (R-VAC) It contains live attenuated rubella virus Wistar RA27/3 strain 1000 $TCID_{50}$ per 0.5 ml inj. for deep s.c. or i.m. injection in upper arm. It is used especially in girls from 1 yr age to puberty—for immunization against German measles; mostly as combined MMR vaccine. It is contraindicated during pregnancy, febrile illness and in untreated tuberculosis patients. Reactions are fever, malaise, sore throat, joint pain and lymphadenopathy.

9. Measles-Mumps-Rubella (MMR) vaccine Two preparations of this combined live vaccine are available: have similar efficacy.

TRIMOVAX lyophilized measles 1000 $TCID_{50}$ of Schwarz strain, mumps 5000 $TCID_{50}$ and rubella 1000 $TCID_{50}$ per unit dose (0.5 ml) vial.

TRESIVAC lyophilized measles 5000 $TCID_{50}$ of Edmonston Zagreb strain, mumps 5000 $TCID_{50}$ and rubella 4000 $TCID_{50}$ per unit dose (0.5 ml) vial.

A single dose injected s.c. over right deltoid is indicated in children older than 12 months for protection against these 3 diseases. Mild fever, rash, enlargement of cervical/occipital lymph nodes and parotid glands and local induration may occur after ~5 days. It is absolutely contraindicated during pregnancy; adult female vaccinees should not conceive for at least 2 months.

10. Varicella vaccine It is lyophilised live attenuated OKa strain of varicella-zoster virus grown in human diploid cell culture, containing $10^{3.3}$ PFU (plaque forming units) of the virus. A single dose induces antibody response in > 98% children and affords protection for 10 years.

Dose: 0.5 ml s.c. single dose for children 1–12 years, and 2 doses 6–10 weeks apart in those >12 years.

VARILRIX, OKAVAX 0.5 ml inj.

Contraindicated during pregnancy, in those with lymphocytopenia and within 1 month of measles vaccination. Mild local reaction, papular eruption and short-lasting fever occurs in 4–5% children.

TOXOIDS

1. Tetanus toxoid It is formaline treated exotoxin of tetanus bacilli; indicated for routine immunization in all children and adults. Two types of preparations—*fluid* and *adsorbed* are available. The adsorbed toxoid is superior—induces higher antibody titers and more prolonged immunity. *Dose:* 0.5 ml, preferable route is i.m., can also be given s.c.

For primary immunization—Tetanus toxoid adsorbed (0.5 ml amp. 10 ml vial), 2 doses are given 4–6 weeks apart, or Tetanus toxoid fluid (1 ml amp, 10 ml vial) 3 doses at interval of 3–4 weeks. Booster dose should be given after 1 year and then every 10 years. In non-immunized or inadequately immunized individuals the toxoid should be given after any injury likely to introduce tetanus bacilli. Concomitant administration of chloramphenicol is avoided, as it may interfere with antibody response.

Reactions—Local erythema, pain and induration is not uncommon. Axillary lymph nodes may enlarge. Fever, chills, malaise, aches and pains occur occasionally, especially in adults. Paresis and other neurological complications are rare.

2. Diphtheria toxoid adsorbed It is modified diphtheria exotoxin adsorbed onto aluminium hydroxide. It is indicated in infants and children below 6 years of age. Older individuals seldom require protection against diphtheria. For primary immunization 2–3 injections of 0.5 ml i.m. are given 4–6 weeks apart, booster dose after 1 year and then at school entry. Reactions are similar to those caused by tetanus toxoid.

MIXED ANTIGENS

1. Double antigen (DT-DA) It consists of alum precipitated toxoids of tetanus and diphtheria, available in 0.5 ml ampule and 5 ml vial (DUAL ANTIGEN). It is used in children above 5 years and in younger children in place of triple antigen when pertussis vaccine is contraindicated. *Dose:* 0.5 ml i.m.

2. Triple antigen (DPT) It is a mixture of toxoids of tetanus and diphtheria with pertussis vaccine (TRIPVAC: Diphtheria toxoid 25 Lf, tetanus toxoid 5 Lf, *B. pertussis* 20,000 million in 0.5 ml amp; also 10 ml multidose vial).

It is the preparation of choice for primary active immunization against the 3 diseases in children below 5 years age. *Dose*–0.5 ml i.m. in the anterolateral aspect of mid thigh or right deltoid, 2–3 injections 4–8 weeks apart, between 3–9 months age and one at 18 months. Reactions, precautions and contraindications mentioned under the individual vaccines apply to triple antigen as well.

3. Pentavalent vaccine It contains toxoids of tetanus and diphtheria along with pertussis vaccine, hepatitis B vaccine and *Haemophilus influenzae* type b (Hib) vaccine. Used in place to triple antigen for primary immunization of infants, it affords protection against two additional common infections, and reduces the total number of injections that the infant receives for protection against these 5 infections. Pentavalent vaccine has been used in many countries, and now Government of India is introducing it in a phased manner in its universal immunization programme for infants and children. However, recently few infant deaths have been reported, though the relationship between these and the vaccine is not clear. Nevertheless, some experts have raised concern about its safety.

A routine immunization schedule for infants and children is given in the box.

Routine immunization schedule for infants and children

At birth	BCG + OPV (first dose) + Hepatitis B (after 12–24 hours)
At 6 weeks	DPT + OPV + Hepatitis B
At 10, 14 weeks	DPT + OPV
At 6 months	Hepatitis B
At 9 months	Measles
At 15–18 months	DPT + MMR + OPV (booster dose)
At 4–5 years (School entry)	DT-DA + OPV (booster dose) Typhoid (TAB 2 doses/ Vi 1 dose/Ty 21a 3 doses) optional
At 10 years	TT + TAB/Vi/Ty 21a (optional)
At 16 years	TT
For pregnant women	
16–24 weeks	TT (1st dose)
24–34 weeks	TT (2nd dose)

ANTISERA AND IMMUNE GLOBULINS

Antisera are purified and concentrated preparations of serum of horses actively immunized against a specific antigen.

Immediate type of allergic reactions (urticaria, angioedema, respiratory distress, anaphylaxis) can occur with any antiserum; adrenaline (1:1000 amp.) should be at hand while injecting them. Prior to each administration, history of reaction to any 'serum' preparation should be elicited and an intracutaneous/scratch test should be performed. A positive test contraindicates administration but a negative test does not completely rule out systemic sensitivity.

Serum sickness with fever, rash, joint pain, lymphadenopathy appearing 7–12 days later is more frequent after large doses and repeated administration. An overall incidence of 5–10% is reported.

Local pain, erythema and arthus type reaction without constitutional symptoms may also occur 7–10 days after i.m. injection.

Immune globulins (IGs) are separated human gamma globulins which carry the antibodies. These may be nonspecific (normal) or specific (hyperimmune) against a particular antigen. These are *more efficacious* than the corresponding antisera. Hypersensitivity reactions are very rare with IGs. Skin tests may be misleading and are not needed. However, large doses and repeated injections do increase risk; adrenaline should be available. Transient local tenderness and stiffness of injected muscle is occasional. Serum sickness does not occur with human IGs.

Antisera (from horse)
Tetanus antitoxin (ATS)
Gas gangrene antitoxin (AGS)
Diphtheria antitoxin (ADS)
Antirabies serum (ARS)
Antisnake venom polyvalent
Immune globulins (human)
Normal human gamma globulin
Anti-D immune globulin
Tetanus immune globulin
Rabies immune globulin
Hepatitis-B immune globulin

1. Normal human gamma globulin

It is concentrated IG obtained by fractionation in cold from pooled human plasma. Indications for its use are—viral hepatitis A and B (prophylaxis), measles, mumps, poliomyelitis and chickenpox (prophylaxis and modification of course of illness), and has some beneficial action in burns. It is especially valuable in agammaglobulinemia, premature infants and in patients of leukemia or those undergoing immunosuppression. It can augment the response to antibiotics in debilitated patients with bacterial infections.

Dose: 0.02–1 ml/kg i.m. for different indications.

GAMMALIN, GLOBUNAL, Sii GAMMA GLOBULIN, GAMAFINE 10%, 16.5% injection in 1, 2 ml amps.

An intravenous preparation (Sii I.V.GG 0.1–0.4 g/kg/day) has been made available for conditions requiring high doses which cannot be injected i.m.

2. Anti-D immune globulin

(*see* p. 885).

3. Tetanus

(a) *Tetanus immune globulin (human)* It is indicated for prophylaxis in non-immunized persons receiving a contaminated wound who are at high risk of developing tetanus. The t½ of this antitoxin is 4 weeks and significant blood levels are maintained for upto 14 weeks. It is more efficacious and longer acting than the equine antitoxin (ATS). If tetanus toxoid is given at the same time (but at a different site), development of primary immune response to the toxoid is not interfered with. It has also been used for the treatment of clinical tetanus, but the efficacy is variable. Intrathecal administration has also been tried.

Dose: prophylactic 250–500 IU, therapeutic 3000–6000 IU i.m. and/or 250-500 IU intrathecal.

Sii TIG 250 IU (liquid), 500 IU (lyophilized), TETNAL 250 IU/2 ml inj., TETAGAM 250 IU/ml inj.

(b) *Tetanus antitoxin (antitetanic serum, ATS)* It is obtained from horse; is inferior to human antitoxin and should be used for the above indications only when tetanus immuneglobulin is not available.

Dose: prophylactic 1500–3000 IU, i.m. or s.c.; therapeutic 50,000–100,000 IU part i.v. and rest i.m.

TETANUS ANTITOXIN 750 IU, 1500 IU, 5000 IU, 10,000 IU, 20,000 IU, and 50,000 IU in 1–10 ml ampoules.

TETANUS IMMUNE SERUM (enzyme refined, equine) 10,000 and 20,000 IU vials.

4. Rabies

(a) *Antirabies serum (ARS)* Also called 'equine rabies immune globulin' (ERIG) is refined, concentrated and lyophilized serum from horses hyperimmunized by repeated injections of fixed rabies virus. It is indicated promptly after suspected exposure and is given simultaneously with rabies vaccine to nonimmunized individuals.

Dose—40 IU/kg infiltrated round the wound and excess is injected i.m.; single dose at the initiation of antirabic therapy along with rabies vaccine. It is inferior to HRIG and should be used only when HRIG is not available.

IMORAB 1000 IU/5 ml inj.

(b) *Rabies immune globulin human (HRIG)* It is used in the same manner as ARS and is superior to it with longer t½. *Dose*—20 IU/kg, on day 0 only, infiltrated round the bite; excess may be injected i.m. elsewhere. Passive protection with HRIG or ARS is needed because active immunity takes 2 or more weeks to develop.

BERIRAB-P 300 IU/2 ml and 750 IU/5 ml inj; RABGLOB 300 IU/2 ml inj.

5. Hepatitis B immune globulin

It is 10–18% solution of human IG containing a high titer of antibody to hepatitis B surface antigen. It is a better prophylactic than normal human gamma globulin: indicated in individuals acutely exposed to HBsAg positive blood or blood products. Hepatitis B vaccine should be given concurrently.

Dose: 1000–2000 IU (adults), 32–48 IU/kg (children) to be administered within 7 days of exposure.

HEPAGLOB 100 IU (0.5 ml) 200 IU (1 ml) per vial for i.m. inj.

6. Diphtheria antitoxin (Antidiphtheritic serum ADS)

It is obtained from horse and is used therapeutically in clinical diphtheria without waiting for bacteriological report, because each hour's delay increases the dose requirement and decreases beneficial effects: damage already caused by the toxin is not reversed. The antitoxin neutralizes the exotoxin released at the site of infection and that circulating in blood but not that fixed to tissues.

Dose: 20,000–40,000 IU i.m. or i.v. for pharyngeal/laryngeal disease of upto 48 hour duration. Higher dose (upto 100,000 IU may be needed).

DIPHTHERIA ANTITOXIN 10,000 IU in 10 ml amp.

Appropriate antimicrobials should also be given. Unprotected child contacts should be given ADS (1000 IU) along with diphtheria toxoid for prophylaxis.

7. Gas gangrene antitoxin (Anti gas gangrene serum, AGS)

It is enzyme refined equine antitoxin against *Cl. edematiens, Cl. perfringens* and *Cl. septicum*.

Dose: prophylactic 10,000 IU; therapeutic 30,000–75,000 IU s.c./i.m./i.v.

AGGS 10,000 IU amp.

8. Antisnake venom (ASV) serum polyvalent

It is available as purified, enzyme refined and concentrated equine globulins in lyophilized vials with 10 ml ampule of distilled water. After reconstitution, each ml neutralizes:

0.6 mg of standard Cobra (*Naja naja*) venom.
0.6 mg of standard Russel's viper (*Vipera russelli*) venom.
0.45 mg of standard Sawscaled viper (*Echis carinatus*) venom.
0.45 mg of standard Krait (*Bungarus caeruleus*) venom.

ANTISNAKE VENOM SERUM POLYVALENT, ASVS

Dose: 20 ml i.v. (1 ml/min injection) repeated at 1–6 hourly intervals till symptoms of envenomation disappear: upto 300 ml may be required in viper bites, while still larger amounts (upto 900 ml) have been used in cobra bites, but it is important to continue ASV treatment till evidence of envenomation persists. In case of viper bite some serum should also be infiltrated around the site to prevent venom induced gangrene.

Allergic reactions, including anaphylactic shock, to the serum are possible. When time permits, sensitivity test should be done; otherwise adrenaline may be injected s.c. concurrently. An antihistaminic and a glucocorticoid may also be given prophylactically.

Chapter 69 Drug Interactions

Drug interaction refers to modification of response to one drug by another when they are administered simultaneously or in quick succession. The modification is mostly quantitative, i.e. the response is either increased or decreased in intensity, but sometimes, it is qualitative, i.e. an abnormal or a different type of response is produced. The possibility of drug interaction arises whenever a patient concurrently receives more than one drug, and the chances increase with the number of drugs taken.

Many medical conditions are treated with a combination of drugs. The components of the combination are so selected that they complement each other's action, e.g. an antibiotic is used along with an analgesic to treat a painful infective condition; adrenaline is combined with lidocaine for local anaesthesia; antitubercular drugs are combined to prevent drug resistance; mixed aerobic-anaerobic bacterial infections are treated with a combination of antimicrobials. More commonly, multiple drugs are used to treat a patient who is suffering from two or more diseases at the same time. The chances of unintended/adverse drug interactions are greater in this later situation, because an assortment of different drugs may be administered to a patient depending on his/her diseases/symptoms.

Several drug interactions are desirable and deliberately employed in therapeutics, e.g. the synergistic action of ACE inhibitors + diuretics to treat hypertension or sulfamethoxazole + trimethoprim to treat bacterial infection or furosemide + amiloride to prevent hypokalaemia. These are well-recognized interactions and do not pose any undue risk to the patient. The focus of attention in this chapter are drug interactions which may interfere with the therapeutic outcome or be responsible for adverse effects, or may even be fatal (bleeding due to excessive anticoagulant action).

The severity of drug interactions in most cases is highly unpredictable. However the doctor must know which drugs are not to be prescribed concurrently. More importantly, a large section of patients may be receiving one or several drugs for their chronic medical conditions like hypertension, diabetes, arthritis, etc. (*see* box for regular medication drug classes employed commonly). The physician may prescribe certain drugs which may interact with those already being taken by the patient and result in adverse consequences. It is, therefore, imperative for the doctor to elicit a detailed drug history of the patient and record all the medication that he/she is currently on. The list of potential adverse drug interactions is already quite long and constantly growing. It is practically impossible for anyone to know/remember all possible drug interactions. Fortunately, the clinically important and common drug interactions that may be encountered in routine practice are relatively few. Some of these are listed in Table 69.1. More exhaustive

Regular medication drugs
(Likely to be involved in drug interactions)

1. Antidiabetics
2. Antihypertensives
3. Antianginal drugs
4. Antiarthritic drugs
5. Antiepileptic drugs
6. Antiparkinsonian drugs
7. Oral contraceptives
8. Anticoagulants
9. Antiasthmatic drugs
10. Psychopharmacological agents
11. Antipeptic ulcer/reflux drugs
12. Corticosteroids
13. Antitubercular drugs
14. Anti-HIV drugs

compilations and documentation are available in specialized books, monographs, review articles and computer database on the subject, but these also need constant updating.

Certain types of drugs (*see* box) can be identified that are most likely to be involved in clinically important drug interactions. The physician may take special care and pay attention to the possibility of drug interactions when the patient is receiving one or more of such medications, or when the doctor intends to prescribe any of such drugs.

Types of drugs most likely to be involved in clinically important drug interactions

- Drugs with narrow safety margin, e.g. aminoglycoside antibiotics, digoxin, lithium
- Drugs affecting closely regulated body functions, e.g. antihypertensives, antidiabetics, anticoagulants
- Highly plasma protein bound drugs like NSAIDs, oral anticoagulants, sulfonylureas
- Drugs metabolized by saturation kinetics, e.g. phenytoin, theophylline

MECHANISM OF DRUG INTERACTIONS

Drug interactions can be broadly divided into *pharmacokinetic* and *pharmacodynamic* interactions. In certain cases, however, the mechanisms are complex and may not be well understood. Few interactions take place even outside the body when drug solutions are mixed before administration.

Pharmacokinetic interactions

These interactions alter the concentration of the object drug at its site of action (and consequently the intensity of response) by affecting its absorption, distribution, metabolism or excretion.

Absorption Absorption of an orally administered drug can be affected by other concurrently ingested drugs. This is mostly due to formation of insoluble and poorly absorbed complexes in the gut lumen, as occurs between tetracyclines and calcium/iron salts, antacids or sucralfate. Phenytoin absorption is decreased by sucralfate due to binding in the g.i. lumen. Such interactions

Pharmacokinetic interactions

- Alteration of absorption or first-pass metabolism
- Displacement of plasma protein bound drug
- Alteration of drug binding to tissues affecting volume of distribution and clearance
- Inhibition/induction of metabolism
- Alteration of excretion

can be minimized by administering the two drugs with a gap of 2–3 hours so that they do not come in contact with each other in the g.i.t. Ketoconazole absorption is reduced by H_2 blockers and proton pump inhibitors because they decrease gastric acidity which promotes dissolution and absorption of ketoconazole. Antibiotics like ampicillin, tetracyclines, cotrimoxazole markedly reduce gut flora that normally deconjugates oral contraceptive steroids secreted in the bile as glucuronides and permits their enterohepatic circulation. Several instances of contraceptive failure have been reported with concurrent use of these antibiotics due to lowering of the contraceptive blood levels. Alteration of gut motility by atropinic drugs, tricyclic antidepressants, opioids and prokinetic drugs like metoclopramide or cisapride can also affect drug absorption.

Distribution Interactions involving drug distribution are primarily due to displacement of one drug from its binding sites on plasma proteins by another drug. Drugs highly bound to plasma proteins that have a relatively small volume of distribution like oral anticoagulants, sulfonylureas, certain NSAIDs and antiepileptics are particularly liable to displacement interactions. Another requirement is that the displacing drug should bind to the same sites on the plasma proteins with higher affinity. Displacement of bound drug will initially raise the concentration of the free and active form of the drug in plasma that may result in toxicity. However, such effects are usually brief, because the free form rapidly gets distributed, metabolized and excreted, so that steady-state levels are only marginally elevated. The clinical outcome of displacement interactions

is generally significant only when displacement extends to tissue binding sites as well, or is accompanied by inhibition of metabolism and/or excretion. Quinidine has been shown to reduce the binding of digoxin to tissue proteins as well as its renal and biliary clearance by inhibing the efflux transporter P-glycoprotein, resulting in nearly doubling of digoxin blood levels and toxicity.

Metabolism Certain drugs reduce or enhance the rate of metabolism of other drugs. They may thus affect the bioavailability (if the drug undergoes extensive first pass metabolism in liver) and the plasma half-life of the drug (if the drug is primarily eliminated by metabolism). Inhibition of drug metabolism may be due to competition for the same CYP450 isoenzyme or cofactor, and attains clinical significance mostly for drugs that are metabolized by saturation kinetics. Macrolide antibiotics, azole antifungals, chloramphenicol, omeprazole, SSRIs, HIV-protease inhibitors, cimetidine, ciprofloxacin and metronidazole are some important inhibitors of metabolism of multiple drugs. Risk of statin induced myopathy is increased by fibrates, niacin, erythromycin, azole antifungals and HIV-protease inhibitors, probably due to inhibition of statin metabolism. Because lidocaine metabolism is dependent on hepatic blood flow, propranolol has been found to prolong its t½ by reducing blood flow to the liver.

A number of drugs induce microsomal drug metabolizing enzymes and enhance biotransformation of several drugs (including their own in many cases). Induction involves gene mediated increased synthesis of certain CYP450 isoenzymes; takes 1–2 weeks of medication with the inducer to produce maximal effect (contrast inhibition of metabolism which develops quickly) and regresses gradually over 1–3 weeks after discontinuation of the inducer. Barbiturates, phenytoin, carbamazepine, rifampin, cigarette smoking, chronic alcoholism and certain pollutants are important microsomal enzyme inducers. Instances of failure of antimicrobial therapy with metronidazole, doxycycline or chloramphenicol have occurred in patients who are on long-term medication with an inducing drug. Contraceptive failure and loss of therapeutic effect of many other drugs have occurred due to enzyme induction. On the other hand, the toxic dose of paracetamol is lower in chronic alcoholics and in those on enzyme inducing medication, because one of the metabolites of paracetamol is responsible for its overdose hepatotoxicity.

Excretion Interaction involving excretion are important mostly in case of drugs actively secreted by tubular transport mechanisms, e.g. probenecid inhibits tubular secretion of penicillins and cephalosporins and prolongs their plasma t½. This is particularly utilized in the single dose treatment of gonorrhoea. Aspirin blocks the uricosuric action of probenecid and decreases tubular secretion of methotrexate. Change in the pH of urine can also affect excretion of weakly acidic or weakly basic drugs. This has been utilized in the treatment of poisonings. Diuretics and to some extent tetracyclines, ACE inhibitors and certain NSAIDs have been found to raise steady-state blood levels of lithium by promoting its tubular reabsorption.

Pharmacodynamic interactions

These interactions derive from modification of the action of one drug at the target site by another drug, independent of a change in its concentration. This may result in an enhanced response (synergism), an attenuated response (antagonism) or an abnormal response. The phenomena of synergism and antagonism are described in Chapter 4, and are deliberately utilized in therapeutics for various purposes. Of clinical significance are the inadvertent concurrent administration of synergistic or antagonistic pair of drugs with adverse consequences. Some examples are:

1. Excessive sedation, respiratory depression, motor incoordination due to concurrent administration of a benzodiazepine (diazepam), a sedating antihistaminic (promethazine), a neuroleptic (chlorpromazine), an opioid

TABLE 69.1 Selected clinically important drug interactions

	*Precipitant drug**	*Object drug£*	*Likely interaction and comments*
1.	Ampicillin, Amoxicillin	Oral contraceptives	Interruption of enterohepatic circulation of the estrogen → failure of contraception; Advise alternative contraception.
		Oral anticoagulants	Inhibition of gut flora → decreased vit K production in gut → risk of bleeding; Monitor INR and reduce anticoagulant dose if needed.
2.	Probenecid	Penicillin, Ampicillin, Cephalosporins	Inhibition of tubular secretion → prolongation of antibiotic action; Desirable interaction utilized for single dose therapy.
3.	Allopurinol	Ampicillin	Increased incidence of rashes; Avoid concurrent use.
		6-Mercaptopurine, Azathioprine	Inhibition of metabolism; Reduce dose of 6-MP/azathioprine to 1/3.
		Warfarin, Theophylline	Inhibition of metabolism; Monitor and reduce dose of object drug.
4.	Carbenicillin, Ticarcillin	Aspirin and other antiplatelet drugs	Perturbation of surface receptors on platelets → additive platelet inhibition → risk of bleeding; Avoid concurrent use.
5.	Ceftriaxone, Cefoperazone	Oral anticoagulants	Additive hypoprothrombinaemia → bleeding; Monitor INR and reduce dose of anticoagulant.
6.	Sulfonamides, Cotrimoxazole	Phenytoin	Displacement$ + inhibition of metabolism → phenytoin toxicity; Avoid concurrent use.
		Warfarin	Displacement + inhibition of metabolism + decreased production of vit K in gut → risk of bleeding; Monitor INR and reduce dose of warfarin.
		Sulfonylureas	Displacement + inhibition of metabolism → hypoglycaemia; Avoid concurrent use.
		Thiazide diuretics	Increased incidence of thrombocytopenia; Avoid concurrent use.
		Oral contraceptives	Interruption of enterohepatic circulation of the estrogen → failure of contraception; Advise alternative contraception.
7.	Metronidazole, Tinidazole, Cefoperazone	Alcohol	Possibly accumulation of acetaldehyde → disulfiram-like or bizarre reactions; Warn the patient not to drink alcohol.
8.	Metronidazole, Tinidazole	Lithium salts	Decreased excretion → Li^+ toxicity; Monitor Li^+ level and reduce lithium dose.
		Warfarin	Inhibition of metabolism → risk of bleeding; Avoid concurrent use.
9.	Ciprofloxacin, Norfloxacin, Pefloxacin	Theophylline, Warfarin	Inhibition of metabolism → toxicity of object drug; Monitor and reduce dose of object drug.
10.	Erythromycin, Clarithromycin, Ketoconazole, Itraconazole, Fluconazole, Protease inhibitors	Terfenadine, Astemizole, Cisapride	Inhibition of metabolism by CYP3A4 → rise in blood level of object drug → dangerous ventricular arrhythmia; Concurrent use contraindicated.
		Phenytoin, Carbamazepine, Warfarin, Sulfonylureas, Diazepam, Theophylline, Cyclosporine, HIV protease inhibitors	Inhibition of metabolism by CYP3A4 → toxicity of object drug; Avoid concurrent use or readjust dose of object drug.
		Statins	Inhibition of metabolism, higher risk of myopathy; Avoid concurrent use.

* Precipitant drug is the drug, which alters the action/pharmacokinetics of the other drug. *Contd...*

£ Object drug is the drug whose action/pharmacokinetics is altered.

$ Displacement of plasma protein bound drug.

TABLE 69.1 ***Contd...***

*Precipitant drug**	*Object drug£*	*Likely interaction and comments*
11. Gemfibrozil, Nicotinic acid	Statins	Increased risk of myopathy; Caution in concurrent use.
12. Tetracyclines	Oral contraceptives	Interruption of enterohepatic circulation of the estrogen → failure of contraception; Advise alternative contraception.
	Lithium salts	Rise in plasma Li^+ level due to decreased excretion; Avoid use of tetracycline or monitor and reduce dose of lithium.
13. Iron salts, Calcium salts, Antacids, Sucralfate	Tetracyclines, Fluoroquinolones	Decreased absorption due to formation of complexes in g.i.t. → failure of antibiotic therapy; Stager drug administration by 2–3 hours.
14. Furosemide	Minocycline	Enhanced vestibular toxicity; Avoid concurrent use.
	Aminoglycoside antibiotics	Additive ototoxicity and nephrotoxicity; Avoid concurrent use.
15. Diuretics	Tetracycline	Antianabolic effect of tetracycline increases urea production which is retained by the diuretic; Avoid concurrent use.
	Lithium	Decreased excretion—rise in Li^+ level—toxicity; Reduce dose of lithium and monitor level.
	Digoxin	Hypokalaemia caused by diuretic increases digoxin toxicity; Give K^+ sparing diuretic/K^+ supplements.
16. Tetracyclines, Chloramphenicol, Macrolide antibiotics, Clindamycin	Penicillins, Cephalosporins	Bactericidal action of penicillins and cephalosporins may be antagonized by the bacteriostatic antibiotics; Avoid concurrent use.
17. Clindamycin	Erythromycin, Clarithromycin, Azithromycin, Chloramphenicol	Mutual antagonism of antibacterial action due to proximal binding sites on bacterial ribosomes; Avoid concurrent use.
18. Phenobarbitone, Phenytoin, Carbamazepine, Rifampin	Metronidazole, Doxycycline, Chloramphenicol, Protease inhibitors, Warfarin, Corticosteroids, Oral contraceptives, Sulfonylureas, Antidepressants	Induction of metabolism → loss of efficacy of object drug; Avoid concurrent use or increase dose of object drug with monitoring.
19. Chloramphenicol	Warfarin, Phenytoin, Sulfonylureas	Inhibition of metabolism → toxicity of the object drug. Avoid concurrent use or monitor and reduce dose of object drug.
20. NSAIDs	Ciprofloxacin and other fluoroquinolones	Enhanced CNS toxicity, seizures; Avoid concurrent use.
21. Aspirin and other NSAIDs	Sulfonylureas, Phenytoin, Valproate, Methotrexate	Displacement and/or reduced elimination → toxicity of object drug; Avoid concurrent use/substitute NSAID with paracetamol.
	Warfarin, Heparin	Enhanced risk of bleeding due to antiplatelet action and gastric mucosal damage; Avoid concurrent use.
	ACE inhibitors, β blockers, Thiazide diuretics	Reduced antihypertensive effect due to inhibition of renal PG synthesis; Avoid concurrent use.
	Furosemide	Reduced diuretic action due to PG synthesis inhibition in kidney; Avoid concurrent use.

Contd...

TABLE 69.1 ***Contd...***

*Precipitant drug**	*Object drug£*	*Likely interaction and comments*
Aspirin and other NSAIDs	Alcohol Corticosteroids	Increased risk of gastric mucosal damage and gastric bleeding; Concurrent use contraindicated.
22. Aspirin	Spironolactone	Reduced K^+ conserving action due to decreased tubular secretion of canrenone (active metabolite of spironolactone); Avoid concurrent use.
23. Chronic alcoholism	Paracetamol	Hepatotoxic dose of paracetamol is reduced; doses ≤ 3 g/day are safe.
24. Chlorpromazine Imipramine and other TCAs	Morphine Pethidine Codeine	Enhanced CNS and respiratory depression; Avoid concurrent use.
25. Chlorpromazine Haloperidol Metoclopramide	Levodopa-carbidopa	Antagonism of antiparkinsonian effect; Concurrent use contraindicated.
26. Levodopa-carbidopa	ACE inhibitors Vasodilators Prazosin	Excessive postural hypotension; Reduce dose of antihypertensives.
27. TCAs	Adrenaline (added to local anaesthetic)	Potentiation due to neuronal uptake inhibition → rise in BP; Use plain local anaesthetic solution.
28. Promethazine Alcohol Opioids Antipsychotics	Diazepam and other benzodiazepines	Additive CNS and respiratory depression, motor impairment; Avoid concurrent use.
29. Cimetidine Isoniazid	Diazepam and other benzodiazepines	Inhibition of metabolism → exaggerated CNS depression; Avoid concurrent use or reduce benzodiazepine dose.
30. Sildenafil Tadalafil	Nitrates	Marked potentiation → precipitous fall in BP; Concurrent use contraindicated.
31. Propranolol	Adrenaline (injected with local anaesthetic)	Rise in BP due to blockade of vasodilator action of adrenaline that enters systemic circulation; Avoid adrenaline containing local anaesthetic.
	Lidocaine	Reduced hepatic clearance of lidocaine; Ceiling amount used in local anaesthesia is reduced.
32. Lidocaine	β-blockers	Enhanced bradycardia and hypotension; Avoid concurrent use.
	Quinidine and other antiarrhythmic drugs	Exaggerated cardiac depression, precipitation of arrhythmias; Avoid concurrent use.

NSAIDs: Nonsteroidal antiinflammatory drugs
TCAs: Tricyclic antidepressants

(morphine) or drinking alcoholic beverage while taking any of the above drugs.

2. Excessive fall in BP and fainting due to concurrent administration of α_1 adrenergic blockers, vasodilators, ACE inhibitors, high ceiling diuretics and cardiac depressants.
3. Pronounced and asymptomatic hypoglycaemia can occur when propranolol is administered to diabetics receiving insulin/sulfonylureas, due to blockade of β adrenoceptors which contribute to recovery from hypoglycaemia as well as some hypoglycaemic symptoms.
4. Additive prolongation of prothrombin time and bleeding by administration of ceftriaxone or cefoperazone to a patient on oral anticoagulants.
5. Excessive platelet inhibition resulting in bleeding due to simultaneous use of aspirin/ticlopidine/clopidogrel and carbenicillin.

6. Increased risk of bleeding due to concurrent use of antiplatelet drugs (aspirin, clopidogrel) with anticoagulants (warfarin).
7. Marked bradycardia due to administration of propranolol in digitalized patients.
8. Precipitous fall in BP and myocardial ischaemia due to use of sildenafil by patients receiving organic nitrates, because nitrates increase generation of cGMP, while sildenafil prevents its degradation by inhibiting PDE 5.
9. Severe hyperkalaemia by concurrent use of ACE inhibitors and K^+ sparing diuretics.
10. Additive ototoxicity due to use of an aminoglycoside antibiotic in a patient receiving furosemide.
11. Antagonism of bactericidal action of β-lactam antibiotic by combining it with a bacteriostatic drug like tetracycline, erythromycin or clindamycin.
12. Mutual antagonism of antibacterial action of macrolides, clindamycin and chloramphenicol due to interference with each other's binding to the bacterial 50S ribosome.
13. Reduction in antihypertensive action of clonidine by chlorpromazine and imipramine, possibly due to blockade of central action of clonidine.
14. Attenuation of antihypertensive effect of ACE inhibitors/β blockers/diuretics by NSAIDs due to inhibition of renal PG synthesis.
15. Blunting of K^+ conserving action of spironolactone by aspirin, because it inhibits the tubular secretion of canrenone (an active metabolite of spironolactone).
16. Blockade of antiparkinsonian action of levodopa by neuroleptics and metoclopramide having antidopaminergic action.

Abnormal responses sometimes result from pharmacodynamic interaction between certain drugs, e.g. bizarre somewhat disulfiram-like distressing symptoms are experienced by certain subjects when they drink alcoholic beverages while taking metronidazole or cefoperazone. It is not known whether this is due to inhibition of aldehyde dehydrogenase. The basis of certain interactions is not explained, e.g. ampicillin has produced high incidence of skin rashes in patients treated with allopurinol.

Drug interactions before administration

Certain drugs react with each other and get inactivated if their solutions are mixed before administration. In combined oral or parenteral formulations, the manufacturers take care that such incompatibilities do not take place. In practice situations, these *in vitro* interactions occur when injectable drugs are mixed in the same syringe or infusion bottle. Some examples are:

- Penicillin G or ampicillin mixed with gentamicin or another aminoglycoside antibiotic
- Thiopentone sodium when mixed with succinylcholine or morphine
- Heparin when mixed with penicillin/gentamicin/hydrocortisone
- Noradrenaline when added to sodium bicarbonate solution.

In general, it is advisable to avoid mixing of any two or more parenteral drugs before injecting.

Comment Not all patients taking interacting drugs experience adverse consequences, but it is advisable to take due precautions to avoid mishaps in all cases where interactions are possible. That two drugs have the potential to interact does not necessarily contraindicate their concurrent use. In many cases, knowledge of the nature and mechanism of the possible interaction may permit their concurrent use provided appropriate dose adjustments are made or other corrective measures are taken. A list of significant and common drug interactions that may be encountered in clinical practice is given in Table 69.1, along with the suggested corrective measure. However, it is prudent to consider the possibility of drug interaction whenever two or more drugs are prescribed to a patient, or any drug is added to what the patient is already taking.