Chapter 26 Local Anaesthetics

Local anaesthetics (LAs) are drugs which upon topical application or local injection cause reversible loss of sensory perception, especially of pain, in a restricted area of the body. They block generation and conduction of nerve impulse at any part of the neurone with which they come in contact, without causing any structural damage. Thus, not only sensory but also motor impulses are interrupted when a LA is applied to a mixed nerve, resulting in muscular paralysis and loss of autonomic control as well.

Important differences between general and local anaesthesia are tabulated in Table 26.1.

CLASSIFICATION

Injectable anaesthetic

Low potency, short duration

Procaine
Chloroprocaine

Intermediate potency and duration

Lidocaine (Lignocaine)
Prilocaine

High potency, long duration

Tetracaine (Amethocaine)
Bupivacaine
Ropivacaine
Dibucaine (Cinchocaine)

Surface anaesthetic

Soluble	*Insoluble*
Cocaine	Benzocaine
Lidocaine	Butylaminobenzoate
Tetracaine	(Butamben)
Benoxinate	Oxethazaine

Mepivacaine, Etidocaine, Articaine, Dyclonine, Proparacaine are other local anaesthetics, occasionally used in some countries.

Some other drugs, e.g. propranolol, chlorpromazine, H_1 antihistaminics, quinine have significant LA activity, but are not used for this purpose because of local irritancy or other prominent systemic activity. Local anaesthesia can be produced by cooling as well, e.g. application of ice, CO_2 snow, ethylchloride spray.

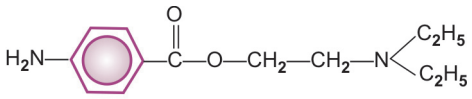
CHEMISTRY

The clinically useful LAs are weak bases with amphiphilic property. A hydrophilic secondary

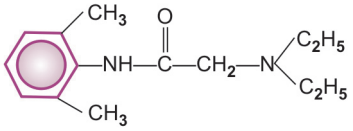
TABLE 26.1 **Comparative features of general and local anaesthesia**

	General anaesthesia	*Local anaesthesia*
1. Site of action	CNS	Peripheral nerves
2. Area of body involved	Whole body	Restricted area
3. Consciousness	Lost	Unaltered
4. Care of vital functions	Essential	Usually not needed
5. Physiological trespass	High	Low
6. Poor health patient	Risky	Safer
7. Use in non-cooperative patient	Possible	Not possible
8. Major surgery	Preferred	Cannot be used
9. Minor surgery	Not preferred	Preferred

or tertiary amine on one side and a lipophilic aromatic residue on the other are joined by an alkyl chain through an *ester* or *amide* linkage.



PROCAINE (ester)



LIDOCAINE (amide)

Ester-linked LAs Cocaine, procaine, chloroprocaine, tetracaine, benzocaine.

Amide-linked LAs Lidocaine, bupivacaine, dibucaine, prilocaine, ropivacaine.

Features of amide LAs
(compared to ester LAs)

- Produce more intense and longer lasting anaesthesia
- Bind to α_1 acid glycoprotein in plasma
- Not hydrolysed by plasma esterases
- Rarely cause hypersensitivity reactions; no cross sensitivity with ester LAs

Because of their short duration, less intense analgesia and higher risk of hypersensitivity, the ester-linked LAs are rarely used for infiltration or nerve block, but are still used topically on mucous membranes.

MECHANISM OF ACTION

The LAs block nerve conduction by decreasing the entry of Na^+ ions during upstroke of action potential (AP). As the concentration of the LA is increased, the rate of rise of AP and maximum depolarization decreases (Fig. 26.1) causing slowing of conduction. Finally, local depolarization fails to reach the threshold potential and conduction block ensues.

The LAs interact with a receptor situated within the voltage sensitive Na^+ channel and raise the threshold of channel opening: Na^+ permeability fails to increase in response to an impulse or stimulus. Impulse conduction is interrupted when the Na^+ channels over a critical length of the fibre (2–3 nodes of Ranvier in case of myelinated fibres) are blocked. The details are explained in Fig. 26.2. At physiological pH, the LA molecule is partly ionized. The equilibrium between the unionized base form (B) and the ionized cationic form (BH^+) depends on the pKa of the LA.

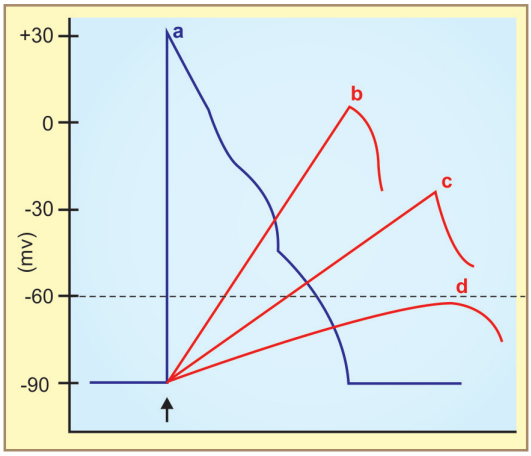


Fig. 26.1: Effect of progressively increasing concentrations (b,c,d) of a local anaesthetic on the generation of an action potential in a nerve fibre, (a) Untreated nerve fibre

Potency of a LA generally corresponds to the lipid solubility of its base form (B), because it is this form which penetrates the axon. However, the predominant active species is the cationic form of the LA which is able to approach its receptor only when the channel is open at the inner face, and it binds more avidly to the activated and inactivated states of the channel, than to the resting state. Binding of the LA prolongs the inactivated state. The channel takes longer to recover → refractory period of the fibre is increased. A resting nerve is rather resistant to blockade. Blockade develops rapidly when the nerve is stimulated repeatedly. The degree of blockade is frequency dependent: greater blockade occurs at higher frequency of stimulation. Moreover, exposure to higher concentration of Ca^{2+} reduces inactivation of Na^+

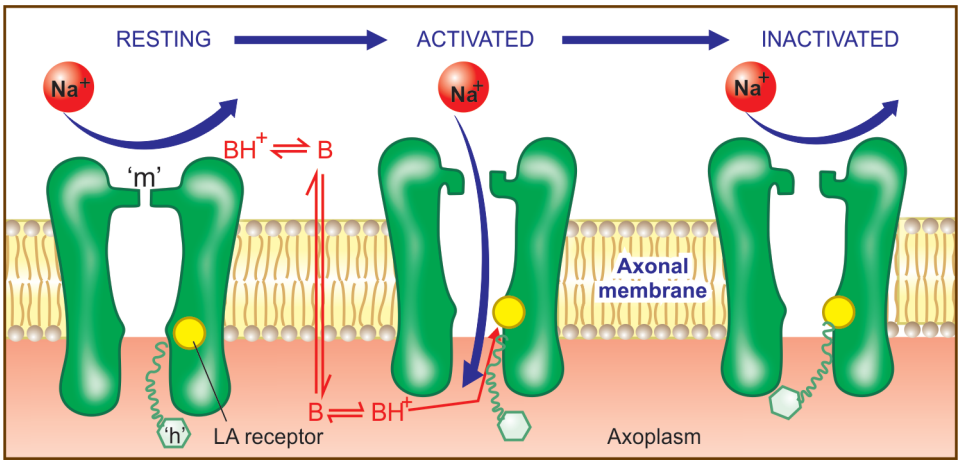


Fig. 26.2: A model of the axonal Na^+channel depicting the site and mechanism of action of local anaesthetics. The Na^+ channel has an activation gate (make or 'm' gate) near its extracellular mouth and an inactivation gate (halt or 'h' gate) at the intracellular mouth. In the resting state the activation gate is closed. Threshold depolarization of the membrane opens the activation gate allowing Na^+ ions to flow in along the concentration gradient. Within a few msec, the inactivation gate closes and ion flow ceases. The channel recovers to the resting state in a time-dependent manner.

The local anaesthetic (LA) receptor is located within the channel in its intracellular half. The LA traverses the membrane in its unionized lipophilic form (B), reionizes in the axoplasm and approaches the LA receptor through the intracellular mouth of the channel. It is the cationic form (BH^+) of the LA which primarily binds to the receptor. The receptor has higher affinity, or is more accessible to the LA in the activated as well as inactivated states compared to the resting state. Binding of LA to its receptor stabilizes the channel in the inactivated state and thus reduces the probability of channel opening.

The neuronal Na^+ channel is a 300 KD glycoprotein composed of a large (α) and two small (β_1, β_2) subunits. The α subunit encloses the Na^+ selective pore within its 4 homologous domains (I to IV), each domain has 6 membrane spanning helical segments (S1 to S6) connected alternately by intracellular and extracellular loops. The wall of the pore is formed by all four S5-S6 segments, while the short nonhelical loops connecting S5-S6 on the extracellular surface fold into the pore and serve as the activation gate. Voltage sensors located in the S4 segments move vertically on depolarization and open the activation gate by allosteric conformational change. A few msec later, the short intracellular loop connecting domains III and IV folds into the inner mouth of the pore inactivating the channel. The LA receptor is located in the S6 segment of domain IV. Channel activation either transforms the LA receptor to a higher affinity conformation or exposes it on the wall of the pore, and this persists during the subsequent inactivation phase.

channels and lessens the degree of block. Blockade of conduction by LA is not due to hyperpolarization; in fact, resting membrane potential is unaltered because K^+ channels are blocked only at higher concentrations of LA.

The onset time of blockade is related primarily to the pKa of the LA. Those with lower pKa (7.6–7.8), e.g. lidocaine, mepivacaine are fast acting, because 30–40% LA is in the undissociated base form at pH 7.4 and it is this form which penetrates the axon. Procaine, tetracaine, bupivacaine have higher pKa (8.1–8.9), only 15% or less is unionized at pH 7.4; these are slow acting. Chloroprocaine is an exception, having rapid onset despite high pKa (9.1).

LOCAL ACTIONS

The clinically used LAs have no/minimal local irritant action and block sensory nerve endings, nerve trunks, neuromuscular junction, ganglionic synapse and receptors (non-selectively), i.e. those structures which function through increased Na^+ permeability. They also reduce release

of acetylcholine from motor nerve endings. Injected around a mixed nerve they cause anaesthesia of skin and paralysis of the voluntary muscle supplied by that nerve.

Sensory and motor fibres are inherently equally sensitive, but some LAs do exhibit unequal ability to block them, e.g. bupivacaine produces sensory block at much lower concentration than that needed for motor block. The sensitivity to LA is determined by diameter of the fibres as well as by fibre type. Diameter remaining the same, myelinated nerves are blocked earlier than nonmyelinated. In general, smaller fibres are more sensitive than larger fibres. Fibres differ in the critical length of the axon that must be exposed to the LA for effective blockade. Smaller fibres tend to have shorter critical lengths, because in them voltage changes propagate passively for shorter distances. Also, more slender axons have shorter internodal distances and LAs easily enter the axon at the nodes of Ranvier. The density of Na^+ channel is much higher at these nodes. Moreover, frequency dependence of blockade makes smaller sensory fibres more vulnerable since they generate high frequency longer lasting action potentials than the motor fibres. Thus, fibre diameter itself may not govern sensitivity to LA.

Autonomic fibres are generally more susceptible than somatic fibres. Among the somatic afferents order of blockade is: pain—temperature sense—touch—deep pressure sense. Since pain is generally carried by smaller diameter fibres than those carrying other sensations or motor impulses, pain in the first modality to be affected. Applied to the tongue, bitter taste is lost first followed by sweet and sour, and salty taste last of all.

In general, fibres that are more susceptible to LA are the first to be blocked and the last to recover. Also, location of the fibre within a nerve trunk determines the latency, duration and often the depth of local anaesthesia. Nerve sheaths restrict diffusion of the LA into the nerve trunk so that fibres in the outer layers are blocked earlier than the inner or core fibres. As a result, the more proximal areas supplied by a nerve are affected earlier because axons supplying them are located more peripherally in the nerve than those supplying distal areas. The differential arrangement of various types of sensory and motor fibres in a mixed nerve may partly account for the differential blockade. Motor fibres are usually present circumferentially; may be blocked earlier than the sensory fibres in the core of the nerve.

The LA often fails to afford adequate pain control in inflamed tissues (like infected tooth). The likely reasons are:

a. Inflammation lowers pH of the tissue—greater fraction of the LA is in the ionized form hindering diffusion into the axolemma.
b. Blood flow to the inflamed area is increased—the LA is removed more rapidly from the site.
c. Effectiveness of Adr injected with the LA is reduced at the inflamed site.
d. Inflammatory products may oppose LA action.

Addition of a vasoconstrictor, e.g. adrenaline (1:50,000 to 1:200,000):

- Prolongs duration of action of LAs by decreasing their rate of removal from the local site into the circulation: contact time of the LA with the nerve fibre is prolonged.
- Enhances the intensity of nerve block.
- Reduces systemic toxicity of LAs: rate of absorption is reduced and metabolism keeps the plasma concentration lower.
- Provides a more bloodless field for surgery.
- Increases the chances of subsequent local tissue edema and necrosis as well as delays wound healing by reducing oxygen supply and enhancing oxygen consumption in the affected area.
- May raise BP and promote arrhythmia in susceptible individuals.

SYSTEMIC ACTIONS

Any LA injected or applied locally is ultimately absorbed and can produce systemic effects

depending on the concentration attained in the plasma and tissues.

C.N.S.

All LAs are capable of producing a sequence of stimulation followed by depression. *Cocaine* is a powerful CNS stimulant causing in sequence euphoria—excitement—mental confusion—restlessness—tremor and twitching of muscles—convulsions—unconsciousness—respiratory depression—death, in a dose-dependent manner.

Procaine and other synthetic LAs are much less potent in this regard. At safe clinical doses, they produce little apparent CNS effects. Higher dose or accidental i.v. injection produces CNS stimulation followed by depression.

The early neurological symptoms of overdose with *lidocaine* and other clinically used LAs are—circumoral numbness, abnormal sensation in the tongue, dizziness, blurred vision, tinnitus followed by drowsiness, dysphoria and lethargy. Still higher doses produce excitation, restlessness, agitation, muscle twitching, seizures and finally unconsciousness.

The basic action of all LAs is neuronal inhibition; the apparent stimulation seen initially is due to inhibition of inhibitory neurones. At high doses, all neurones are inhibited and flattening of waves in the EEG is seen.

C.V.S.

Heart LAs are cardiac depressants, but no significant effects are observed at conventional doses. At high doses (2–3 times the doses producing CNS effects) or on inadvertent i.v. injection, they decrease automaticity, excitability, contractility, conductivity and prolong effective refractory period (ERP). They have a quinidine-like antiarrhythmic action. *Procaine* is not used as antiarrhythmic because of short duration of action and propensity to produce CNS effects, but its amide derivative *procainamide* is a class IA antiarrhythmic (*see* Ch. 38). Electrophysiological properties of heart may be markedly altered at high plasma concentrations of LAs : QTc interval is prolonged and LAs can themselves induce cardiac arrhythmias. *Bupivacaine* is relatively more cardiotoxic and has produced ventricular tachycardia or fibrillation. *Lidocaine* has little effect on contractility and conductivity; it abbreviates ERP and has minimal proarrhythmic potential. It is used as an antiarrhythmic (*see* Ch. 38).

Blood vessels LAs tend to produce fall in BP. This is primarily due to sympathetic blockade, but high concentrations, as obtained locally at the site of injection, do cause direct relaxation of arteriolar smooth muscle. Bupivacaine is more vasodilatory than lidocaine, while prilocaine is the least vasodilatory. Toxic doses of LAs produce cardiovascular collapse. *Cocaine* has sympathomimetic property; increases sympathetic tone, causes local vasoconstriction, marked rise in BP and tachycardia.

Procaine and related drugs have weak anticholinergic, antihistaminic, ganglion blocking, neuromuscular blocking and smooth muscle relaxant properties, but these are clinically insignificant.

PHARMACOKINETICS

Because LAs act near their site of administration, pharmacokinetic characteristics are not important determinants of their efficacy, but markedly influence their systemic effects and toxicity.

Soluble surface anaesthetics (lidocaine, tetracaine) are rapidly absorbed from mucous membranes and abraded areas, but absorption from intact skin is minimal. Procaine does not significantly penetrate mucous membranes. Rate of absorption depends on the blood flow to the area of application or injection. The absorbed LA being lipophilic is widely distributed; rapidly enters highly perfused brain, heart, liver, and kidney, followed by muscle and other viscera.

Procaine is negligibly bound to plasma proteins, but amide LAs are bound to plasma α_1 acid glycoprotein. LAs are rapidly but temporarily bound to tissues, especially nerves, at the site of injection. Ester-linked LAs (procaine, etc.) are rapidly hydrolysed by plasma pseudocholinesterase and the remaining by esterases in the

liver. Amide-linked LAs (lidocaine, etc.) are degraded only in the liver microsomes by dealkylation and hydrolysis. Metabolism of lidocaine is hepatic blood-flow dependent. The maximal safe dose of LAs is lower in patients with hepatic disease and in the elderly who have decreased liver function.

After oral ingestion both procaine and lidocaine have high first pass metabolism in the liver. Thus, they are not active orally for anti-arrhythmic purposes.

ADVERSE EFFECTS

Systemic toxicity on rapid i.v. injection is related to the intrinsic anaesthetic potency of the LA. However, toxicity after topical application or regional injection is influenced by the relative rates of absorption and metabolism. Those rapidly absorbed but slowly metabolized are more toxic.

(1) CNS effects are light-headedness, dizziness, auditory and visual disturbances, mental confusion, disorientation, shivering, twitchings, involuntary movements, finally convulsions and respiratory arrest. This can be prevented and treated by diazepam.

(2) Cardiovascular toxicity of LAs is manifested as bradycardia, hypotension, cardiac arrhythmias and vascular collapse.

(3) Injection of LAs may be painful, but local tissue toxicity of LAs is low. However, wound healing may be sometimes delayed. Addition of vasoconstrictors enhances the local tissue damage; rarely necrosis results. Vasoconstrictors should not be added for ring block of hands, feet, fingers, toes, penis and in pinna. Bupivacaine has the highest local tissue irritancy.

(4) Hypersensitivity reactions like rashes, angioedema, dermatitis, contact sensitization, asthma and rarely anaphylaxis occur. These are more common with ester-linked LAs, but rare with lidocaine or its congeners. Cross reactivity is frequent among ester compounds, but not with amide-linked LAs.

Often methylparaben added as preservative in certain LA solutions is responsible for the allergic reaction.

Precautions and interactions

1. Before injecting the LA, aspirate lightly to avoid intravascular injection.
2. Inject the LA slowly and take care not to exceed the maximum safe dose, especially in children.
3. Propranolol (probably other β blockers also) may reduce metabolism of lidocaine and other amide LAs by reducing hepatic blood flow.
4. Vasoconstrictor (adrenaline) containing LA should be avoided for patients with ischaemic heart disease, cardiac arrhythmia, thyrotoxicosis, uncontrolled hypertension, and those receiving β blockers (rise in BP can occur due to unopposed α action) or tricyclic antidepressants (uptake blockade and potentiation of Adr).

INDIVIDUAL COMPOUNDS

Important properties of local anaesthetics are compared in Table 26.2.

Cocaine It is a natural alkaloid from leaves of *Erythroxylon coca*, a south American plant growing on the foothills of the Andes. The natives of Peru and Bolivia habitually chew these leaves. Cocaine is a good surface anaesthetic and is rapidly absorbed from buccal mucous membrane. It was first used for ocular anaesthesia in 1884. Cocaine should never be injected; it is a protoplasmic poison and causes tissue necrosis. Cocaine produces prominent CNS stimulation with marked effect on mood and behaviour. It induces a sense of wellbeing, delays fatigue and increases power of endurance. In susceptible individuals it produces a state referred to as 'high' leadting to strong psychological but little physical dependence. Cocaine is unique among drugs of abuse in not producing significant tolerance on repeated use; sometimes reverse tolerance is seen (behavioural effects are experienced at lower doses).

Cocaine also stimulates vagal centre→bradycardia; vasomotor centre→rise in BP; vomiting centre→nausea and vomiting; temperature regulating centre→pyrexia (also due to increased heat production as a result of enhanced muscular activity).

In the periphery, it blocks uptake of NA and Adr into adrenergic nerve endings, (*see* Fig. 9.4) resulting in higher concentration of the transmitter around the receptors→ sympathomimetic effect, potentiation of directly acting sympathomimetics and suppression of indirectly acting sympathomimetics. Local vasoconstriction, tachycardia, rise in BP and mydriasis are the manifestations of its sympathomimetic action.

TABLE 26.2 Comparative properties of important local anaesthetics

	Potency			Concn. used	Safe max* dose (inj.)	Onset of action	Metabolism in		Duration of nerve block (min.)
	surface	injection	toxic		Total (mg) (mg/kg)		plasma	liver	
Cocaine	1	1	1	–	not injected	fast	–	+	–
Procaine	1/10	1/2	1/6	1–2%	400 (6)	slow	+	+	30–60
Lidocaine	1	2	1/6	0.5–2%	300 (4.5)	fast	–	+	60–120
Tetracaine	4	10	2	0.25–0.5%	80 (1.2)	slow	+	+	180–480
Bupivacaine	–	10	2	0.25–0.5%	100 (1.5)	interm.	–	+	120–360
Dibucaine	6	15	3	0.25–0.5%	50	slow	–	+	180–600

* Without adrenaline; addition of adrenaline may increase safe limit by upto 40%

The only indication for cocaine is in ocular anaesthesia. However, it causes constriction of conjunctival vessels, clouding and rarely sloughing of cornea (due to drying and local tissue toxicity). Its use, therefore, is not warranted.

Procaine It is the first synthetic local anaesthetic introduced in 1905. Its popularity declined after the introduction of lidocaine, and it is not used now. It is not a surface anaesthetic.

Procaine forms poorly soluble salt with benzyl penicillin; *procaine penicillin* injected i.m. acts for 24 hours due to slow absorption from the site of injection.

Lidocaine (Lignocaine) Introduced in 1948, it is currently the most widely used LA. It is a versatile LA, good both for surface application as well as injection and is available in a variety of forms. Injected around a nerve it blocks conduction within 3 min, whereas procaine may take 15 min; also anaesthesia is more intense and longer lasting. Vasodilatation occurs in the injected area. It is used for surface application, infiltration, nerve block, epidural, spinal and intravenous regional block anaesthesia. Cross sensitivity with ester LAs is not seen. In contrast to other LAs, early central effects of lidocaine are depressant, i.e. drowsiness, mental clouding, dysphoria, altered taste and tinnitus. Overdose causes muscle twitching, convulsions, cardiac arrhythmias, fall in BP, coma and respiratory arrest like other LAs. Lidocaine is a popular antiarrhythmic (*see* Ch. 38)

XYLOCAINE, GESICAIN 4% topical solution, 2% jelly, 2% viscous, 5% ointment, 1% and 2% injection (with or without adrenaline), 5% heavy (for spinal anaesthesia); 100 mg/ml spray (10 mg per actuation).

A transdermal patch of lidocaine has been produced for application over the affected skin for relief of burning pain due to postherpetic neuralgia.

Prilocaine It is similar to lidocaine but does not cause vasodilatation at the site of infiltration and has lower CNS toxicity due to larger volume of distribution. One of its metabolites has potential to cause methaemoglobinaemia. It has been used mainly for infiltration, nerve block and intravenous regional anaesthesia.

Eutectic lidocaine/prilocaine This is a unique preparation which can anaesthetise intact skin after surface application. *Eutectic mixture* refers to lowering of melting point of two solids when they are mixed. This happens when lidocaine and prilocaine are mixed in equal proportion at 25°C. The resulting oil is emulsified into water to form a cream that is applied under occlusive dressing for 1 hr before i.v. cannulation, split skin graft harvesting and other superficial procedures. Anaesthesia up to a depth of 5 mm lasts for 1–2 hr after removal. It has been used as an alternative to lidocaine infiltration.

PRILOX 5% cream.

Tetracaine (Amethocaine) A highly lipid-soluble PABA ester, more potent and more toxic due to slow hydrolysis by plasma pseudocholinesterase. It is both surface and conduction block anaesthetic, but its use is restricted to topical application to the eye, nose, throat, tracheobronchial tree and rarely for spinal or caudal anaesthesia of long duration. Though it is slow acting, absorption from tracheobronchial

spray is very fast and blood concentrations approach those attained after i.v. injection.
ANETHANE powder for solution, 1% ointment.

Bupivacaine A potent and long-acting amide-linked LA: used for infiltration, nerve block, epidural and spinal anaesthesia of long duration. A 0.25–0.5% solution injected epidurally produces adequate analgesia without significant motor blockade. As a result, it has become very popular in obstetrics (mother can actively cooperate in vaginal delivery) and for postoperative pain relief by continuous epidural infusion. It has high lipid-solubility; distributes more in tissues than in blood after spinal/epidural injection. Therefore, it is less likely to reach the foetus (when used during labour) to produce neonatal depression. Bupivacaine is more prone to prolong QTc interval and induce ventricular tachycardia or cardiac depression—should not be used for intravenous regional analgesia. Epidural anaesthesia with 0.75% bupivacaine during labour has caused few fatalities due to cardiac arrest; use of this concentration is contraindicated.
MARCAIN 0.5%, 1% (hyperbaric for spinal anaesthesia). SENSORCAINE 0.25%, 0.5% inj, 0.5% heavy inj.
The S(–) enantiomer *Levobupivacaine* is equally potent but less cardiotoxic and less prone to cause seizures (after inadvertant intravascular injection) than racemic bupivacaine. It has been introduced in some countries as a single enantiomer preparation.

Ropivacaine A newer bupivacaine congener, equally long acting but less cardiotoxic. It blocks Aδ and C fibres (involved in pain transmission) more completely than Aβ fibres which control motor function. Though equieffective concentrations of ropivacaine are higher than those of bupivacaine, a greater degree of separation between sensory and motor block has been obtained with epidural ropivacaine. Continuous epidural ropivacaine is being used for relief of postoperative and labour pain. It can also be employed for nerve blocks. Recently, it has been approved for use in India.

Dibucaine (Cinchocaine) It is the most potent, most toxic and longest acting LA. It is used as a surface anaesthetic on less delicate mucous membranes (anal canal). Use for spinal anaesthesia of long duration has declined after the availability of bupivacaine.
NUPERCAINE 0.5% inj., NUPERCAINAL 1% ointment, in OTOGESIC 1% ear drops.

Benoxinate It is a good surface anaesthetic for the eye; has little irritancy. A 0.4% solution rapidly produces corneal anaesthesia sufficient for tonometry without causing mydriasis or corneal damage.
BENDZON 0.4% eyedrops.

Benzocaine and Butylaminobenzoate (Butamben) Because of very low aqueous solubility, these LAs are not significantly absorbed from mucous membranes or abraded skin. They produce long-lasting anaesthesia without systemic toxicity. They are used as lozenges for stomatitis, sore throat; as dusting powder/ointment on wounds/ulcerated surfaces and as suppository for anorectal lesions. Both are PABA derivative—can antagonize sulfonamides locally.
PROCTOSEDYL-M: Butylaminobenzoate 1% oint with framycetin and hydrocortisone acetate: for piles.
PROCTOQUINOL 5% ointment of benzocaine. ZOKEN 20% gel.

Oxethazaine A potent topical anaesthetic, unique in ionizing to a very small extent even at low pH values. It is, therefore, effective in anaesthetising gastric mucosa despite acidity of the medium. Swallowed along with antacids it affords symptomatic relief in gastritis, drug induced gastric irritation, gastroesophageal reflux and heartburn of pregnancy. Doses exceeding 100 mg/day may produce dizziness and drowsiness.
MUCAINE 0.2% in alumina gel + magnesium hydroxide suspension; 5–10 ml orally.
TRICAINE-MPS: Oxethazaine 10 mg with methyl polysiloxane 125 mg, alum. hydroxide gel 300 mg, mag. hydroxide 150 mg per 5 ml gel.

USES AND TECHNIQUES OF LOCAL ANAESTHESIA

1. Surface anaesthesia It is produced by topical application of a surface anaesthetic to mucous membranes and abraded skin. Only the superficial layer is anaesthetised and there is no loss of motor function. Onset and duration depends on the site, the drug, its concentration and form, e.g. lidocaine (10%) sprayed in the throat acts in 2–5 min and produces anaesthesia for 30–45 min. Addition of Adr does not affect duration of topical anaesthesia, but phenylephrine can cause mucosal vasoconstriction and prolong topical anaesthesia. Absorption of soluble LAs from mucous membranes is rapid; blood concentrations of lidocaine and tetracaine

sprayed in throat/tracheobronchial tree approach those attained on i.v. injection—toxicity can occur. Except for eutectic lidocaine/prilocaine, no other LA is capable of anaesthetizing intact skin. The sites and purposes for which surface anaesthesia is used are given in Table 26.3.

2. Infiltration anaesthesia Dilute solution of LA is infiltrated under the skin in the area of operation—blocks sensory nerve endings. Onset of action is almost immediate and duration is shorter than that after nerve block, e.g. lidocaine 30–60 min, bupivacaine 90–180 min. Infiltration is used for minor operations, e.g. incisions, excisions, hydrocele, herniorrhaphy, etc. when the area to be anaesthetised is small. Relatively larger amount of LA is required compared to the area anaesthetized, but motor function is not affected.

3. Conduction block The LA is injected around nerve trunks so that the area distal to injection is anaesthetised and paralysed. Choice of the LA and its concentration is mainly dictated by the required duration of action; lidocaine (1–2%) with intermediate duration of action is most commonly used, but for longer lasting anaesthesia bupivacaine may be selected.

(a) *Field block* It is produced by injecting the LA subcutaneously in a manner that all nerves coming to a particular field are blocked—as is done for herniorrhaphy, appendicectomy, dental procedures, scalp stitching, operations on forearms and legs, etc. Larger area beginning 2–3 cm distal to the line of injection can be anaesthetised with lesser drug compared to infiltration. The same concentration of LA as for infiltration is used for field block.

(b) *Nerve block* It is produced by injecting the LA around the appropriate nerve trunks or plexuses. The area of resulting anaesthesia is still larger compared to the amount of drug used. Muscles supplied by the injected nerve/plexus are paralysed. The latency of anaesthesia depends on the drug and the area to be covered by diffusion, e.g. lidocaine anaesthetises intercostal nerves within 3 min, but brachial plexus block may take 15 min. For plexus block a 'flooding'

TABLE 26.3 Sites and uses of surface anaesthesia

Site	*Drugs*		*Form*	*Purpose*
1. Eye	Tetracaine Benoxinate	1–2% 0.4%	ointment, drops drops	tonometry, surgery tonometry
2. Nose, ear	Lidocaine Tetracaine	2–4% 1–2%	drops	painful lesions, polyps
3. Mouth, throat	Benzocaine Lidocaine	 2%	lozenges rinse solution	stomatitis, sore throat painful ulcers
4. Pharynx, larynx, trachea, bronchi	Lidocaine Tetracaine	4–10% 1–2%	spray	tonsillectomy, endotracheal intubation, endoscopies
5. Esophagus, stomach	Oxethazaine	0.2%	suspension heartburn	gastritis, esophagitis,
6. Abraded skin	Tetracaine Benzocaine Butamben	1% 1–2% 1–2%	cream, ointment, dusting powder	ulcers, burns, itching dermatoses
7. Intact skin	Eutectic lidocaine/ prilocaine	5%	cream under occlusion	i.v. cannulation, skin surgery
8. Urethra	Lidocaine	2%	jelly	for dilatation, catheterisation
9. Anal canal, rectum	Lidocaine Dibucaine Benzocaine	4% 1% 5%	ointment, cream, suppository	fissure, painful piles, surgery, proctoscopy

technique is used and larger volumes are needed. Nerve block lasts longer than field block or infiltration anaesthesia. Frequently performed nerve blocks are—lingual, intercostal, ulnar, sciatic, femoral, brachial plexus, trigeminal, facial, phrenic, etc.—used for tooth extraction, operations on eye, limbs, abdominal wall, fracture setting, trauma to ribs, neuralgias, persistent hiccup, etc.

The primary purpose of nerve block anaesthesia is to abolish pain and other sensations. The accompanying motor paralysis may be advantageous by providing muscle relaxation during surgery, as well as disadvantageous if it interferes with breathing, ability to walk after the operation, or participation of the patient in labour or produces postural hypotension.

4. Spinal anaesthesia The LA is injected in the subarachnoid space between L2–3 or L3–4 i.e. below the lower end of spinal cord. The primary site of action is the nerve roots in the cauda equina rather than the spinal cord. Lower abdomen and hind limbs are anaesthetised and paralysed. The level of anaesthesia depends on the volume and speed of injection, specific gravity of drug solution and posture of the patient. The drug solution could be hyperbaric (in 10% glucose) or isobaric with CSF.

Nerve roots rapidly take up and retain the LA, therefore, its concentration in CSF falls quickly after injection. The level of anaesthesia does not change with change of posture (becomes fixed) after 10 min. Also, higher segments are exposed to progressively lower concentrations of the LA. Since autonomic preganglionic fibres are more sensitive and somatic motor fibres less sensitive than somatic sensory fibres, the level of sympathetic block is about 2 segments higher and the level of motor paralysis about 2 segments lower than the level of cutaneous analgesia.

The duration of spinal anaesthesia depends on the drug used and its concentration. Addition of 0.2–0.4 mg of adrenaline to the LA prolongs spinal anaesthesia by about 1/3rd when measured by the time taken for the level of sensory block to recede to L1. Adr may be enhancing spinal anaesthesia by reducing spinal cord blood flow or by its own analgesic effect exerted through spinal α_2 adrenoceptors (intrathecal clonidine, an α_2 agonist, produces spinal analgesia by itself).

TABLE 26.4 Drugs used for spinal anaesthesia and their duration of action

Drug	*Concentration (%)*	*Volume (ml)*	*Total dose (mg)*	*Duration of action (min)*
Lidocaine	1.5–5	1–2	25–100	60–90
Bupivacaine	0.5–0.75	2–3	10–25	90–150
Tetracaine	0.25–0.5	1–3	5–15	90–180

Women during late pregnancy require less drug for spinal anaesthesia, because inferior vena cava compression leads to engorgement of the vertebral system and a decrease in the capacity of subarachnoid space.

Spinal anaesthesia is used for operations on the lower limbs, pelvis, lower abdomen, e.g. prostatectomy, fracture setting, obstetric procedures, caesarean section, etc. Choice of the LA for spinal anaesthesia primarily depends on the nature and duration of the operative procedure. The LAs employed with their doses and duration of anaesthesia are given in Table 26.4.

Advantages of spinal anaesthesia over general anaesthesia are:

(i) It is safer.
(ii) Produces good analgesia and muscle relaxation without loss of consciousness.
(iii) Cardiac, pulmonary, renal disease and diabetes pose less problem.

Complications of spinal anaesthesia

1. *Respiratory paralysis* with proper care, this is rare; intercostal muscles may be paralysed, but diaphragm (supplied by phrenic nerve) maintains breathing. Hypotension and ischaemia of respiratory centre is more frequently the cause of respiratory failure than diffusion of the anaesthetic to higher centres. Due to paralysis of external abdominal and intercostal muscles, coughing and expectoration becomes less effective. This may lead to pulmonary complications.

2. *Hypotension* It is due to blockade of sympathetic vasoconstrictor outflow to blood vessels; venous pooling and decreased return to the heart contributes more to the fall in BP than arteriolar dilatation. Paralysis of skeletal muscles of lower limb is another factor reducing venous return. Decreased sympathetic flow to heart and low venous return produce bradycardia. Raising the foot end overcomes the hypotension by promoting venous drainage. Sympathomimetics, especially those with prominent constrictor effect on veins (ephedrine, mephentermine) effectively prevent and counteract hypotension.

3. *Headache* is due to seepage of CSF; can be minimised by using smaller bore needle.

4. *Cauda equina syndrome* is a rare neurological complication resulting in prolonged loss of control over bladder and bowel sphincters. It may be due to traumatic damage to nerve roots or chronic arachnoiditis caused by inadvertent introduction of the antiseptic or particulate matter in the subarachnoid space.

5. *Septic meningitis* This may occur due to infection introduced during lumbar puncture. Actual incidence is very low in majority of hospitals.

6. *Nausea and vomiting* after abdominal operations is due to reflexes triggered by traction on abdominal viscera. Premedication with opioid analgesics prevents it.

5. Epidural anaesthesia The spinal dural space is filled with semiliquid fat through which nerve roots travel. The LA injected in this space—acts primarily on nerve roots (in the epidural as well as subarachnoid spaces to which it diffuses) and small amount permeates through intervertebral foramina to produce multiple paravertebral blocks. Epidural anaesthesia can be divided into 3 categories depending on the site of injection.

(i) *Thoracic* Injection is made in the midthoracic region. The epidural space in this region is relatively narrow, smaller volume of drug is needed and a wide segmental band of analgesia involving the middle and lower thoracic dermatomes is produced. It is used generally for pain relief following thoracic/upper abdominal surgery. Specially designed catheters are available which can be placed for repeated injections or continuous infusion of the LA to achieve epidural analgesia lasting few days.

Contraindications to spinal anaesthesia

- Hypotension and hypovolemia.
- Uncooperative or mentally ill patients.
- Infants and children—control of level is difficult.
- Bleeding diathesis.
- Raised intracranial pressure.
- Vertebral abnormalities e.g. kyphosis, lordosis, etc.
- Sepsis at injection site.

(ii) *Lumbar* Relatively large volume of drug is needed because epidural space is wide. It produces anaesthesia of lower abdomen, pelvis and hind limbs. Use of lumbar epidural anaesthesia is similar to that of spinal anaesthesia.

(iii) *Caudal* Injection is given in the sacral canal through the sacral hiatus—produces anaesthesia of pelvic and perineal region. It is used mostly for vaginal delivery, anorectal and genitourinary operations.

Lidocaine (1–2%) and bupivacaine (0.25–0.5%) are popular drugs for epidural anaesthesia. Onset is slower and duration of anaesthesia is longer with bupivacaine and action of both the drugs is prolonged by addition of adrenaline. Technically epidural anaesthesia is more difficult than spinal anaesthesia and relatively larger volumes of drug are needed. Consequently, blood concentrations of the LA are higher. Cardiovascular complications are similar to that after spinal anaesthesia, but headache and neurological complications are less likely, because intrathecal space is not entered. Spread of the LA in the epidural space is governed by the volume injected: larger volume anaesthetizes more extensive area. Zone of differential sympathetic blockade is not evident after epidural

injection but motor paralysis is 4–5 segments caudal, especially with lower concentrations of the drug. Greatest separation between sensory and motor block is obtained by use of 0.25% bupivacaine. This is especially valuable for obstetric purposes (mother can participate in labour without feeling pain) and for postoperative pain relief.

6. Intravenous regional anaesthesia (Intravascular infiltration anaesthesia) It consists of injection of LA in a vein of a tourniquet occluded limb such that the drug diffuses retrograde from the peripheral vascular bed to nonvascular tissues including nerve endings. The limb is first elevated to ensure venous drainage by gravity and then tightly wrapped in an elastic bandage for maximal exsanguination. Tourniquet is then applied proximally and inflated to above arterial BP. Elastic bandage is now removed and 20–40 ml of 0.5% lidocaine is injected i.v. under pressure distal to the tourniquet. Regional analgesia is produced within 2–5 min and lasts till 5–10 min after deflating the tourniquet which is kept inflated for not more than 15–60 min to avoid ischaemic injury. Deflation in < 15 min may allow toxic amounts of the LA to enter systemic circulation. The safety of the procedure depends on the rapid uptake of LA by peripheral tissues; only 1/4 of the injected drug enters systemic circulation when the tourniquet is released. Bradycardia can occur.

It is mainly used for the upper limb and for orthopedic procedures. Obstructing the blood supply of lower limb is more difficult and larger volume of anaesthetic is needed. Therefore, it is rarely used for lower limb, except the foot. Bupivacaine should not be employed because of its higher cardiotoxicity.

☞ PROBLEM DIRECTED STUDY

26.1 A healthy full-term primigravida aged 26 years who has gone into labour presents for delivery. There is no cephalopelvic disproportion or any other contraindication to normal vaginal delivery. However, she demands relief of pain associated with labour and delivery.

(a) Can some form of regional anaesthesia be used to relieve her pain? If so, which type of regional anaesthesia with which drug would be most suitable for her?

(see Appendix-1 for solution)

SECTION 7

Drugs Acting on Central Nervous System

Chapter 27 General Anaesthetics

General anaesthetics (GAs) are drugs which produce reversible loss of all sensation and consciousness. The cardinal features of general anaesthesia are:

- Loss of all sensation, especially pain
- Sleep (unconsciousness) and amnesia
- Immobility and muscle relaxation
- Abolition of somatic and autonomic reflexes.

In the modern practice of balanced anaesthesia, these modalities are achieved by using combination of inhaled and i.v. drugs, each drug for a specific purpose. Anaesthesia has developed as a highly specialized science in itself.

History Before the middle of 19th century a number of agents like alcohol, opium, cannabis, or even concussion and asphyxia were used to obtund surgical pain, but operations were horrible ordeals. Horace Wells, a dentist, picked up the idea of using *nitrous oxide* (N_2O) from a demonstration of laughing gas in 1844. However, he often failed to relieve dental pain completely and the use of N_2O had to wait till other advances were made. Morton, a dentist and medical student at Boston, after experimenting on animals, gave a demonstration of *ether* anaesthesia in 1846, and it soon became very popular. *Chloroform* was used by Simpson in Britain for obstetrical purpose in 1847, and despite its toxic potential, it became a very popular surgical anaesthetic. *Cyclopropane* was introduced in 1929, but the new generation of anaesthetics was heralded by *halothane* in 1956. The first i.v. anaesthetic *thiopentone* was introduced in 1935.

MECHANISM OF GENERAL ANAESTHESIA

The mechanism of action of GAs is not precisely known. A wide variety of chemical agents produce general anaesthesia. Therefore, GA action had been related to some common physicochemical property of the drugs. Mayer and Overton (1901) pointed out a direct parallelism between lipid/water partition coefficient of the GAs and their anaesthetic potency.

Minimal alveolar concentration (MAC) is the lowest concentration of the anaesthetic in pulmonary alveoli needed to produce immobility in response to a painful stimulus (surgical incision) in 50% individuals. It is accepted as a valid measure of potency of inhalational GAs, because it remains fairly constant for most young adults. The MAC of all inhalational anaesthetics declines progressively as age advances beyond 50 years.

The MAC of a number of GAs shows excellent correlation with their oil/gas partition coefficient. However, this only reflects capacity of the anaesthetic to enter into CNS and attain sufficient concentration in the neuronal membrane, but not the mechanism by which

anaesthesia is produced. The *'unitary hypothesis'* that some single common molecular mechanism (like membrane expansion/perturbation/fluidization) is responsible for the action of all inhalational anaesthetics has now been replaced by the *'agent specific theory'* according to which different GAs produce anaesthesia by different mechanisms.

Recent evidence favours a direct interaction of the GA molecules with hydrophobic domains of membrane proteins or the lipid-protein interface.

Not only different anaesthetics appear to act by different molecular mechanisms, they also may exhibit stereospecific effects, and that various components of the anaesthetic state may involve action at discrete loci in the cerebrospinal axis. The principal locus of causation of unconsciousness appears to be in the thalamus or reticular activating system, amnesia may result from action in cerebral cortex and hippocampus, while spinal cord is the likely seat of immobility on surgical stimulation.

Recent findings show that ligand gated ion channels (but not voltage sensitive ion channels) are the major targets of anaesthetic action. The $GABA_A$ receptor gated Cl^- channel is the most important of these. Many inhalational anaesthetics, barbiturates, benzodiazepines and propofol potentiate the action of inhibitory transmitter GABA to open Cl^- channels. Each of the above anaesthetics appears to interact with its own specific binding site on the $GABA_A$ receptor-Cl^- channel complex, but none binds to the GABA binding site as such; though some inhaled anaesthetics and barbiturates (but not benzodiazepines) can directly activate Cl^- channels. Action of glycine (another inhibitory transmitter which also activates Cl^- channels) in the spinal cord and medulla is augmented by barbiturates, propofol and many inhalational anaesthetics. This action may block responsiveness to painful stimuli resulting in immobility of the anaesthetic state. Certain fluorinated anaesthetics and barbiturates, in addition, inhibit the neuronal cation channel gated by nicotinic cholinergic receptor which may mediate analgesia and amnesia.

On the other hand, N_2O and ketamine do not affect GABA or glycine gated Cl^- channels. Rather they selectively inhibit the excitatory NMDA type of glutamate receptor. This receptor gates mainly Ca^{2+} selective cation channels in the neurones, inhibition of which appears to be the primary mechanism of anaesthetic action of ketamine as well as N_2O. The volatile anaesthetics have little action on this receptor.

Neuronal hyperpolarization caused by GAs has been ascribed to activation of a specific type of K^+ channels called 'two-pore domain' channels. This may cause inhibition of presynaptic transmitter release as well as postsynaptic activation. Inhibition of transmitter release from presynaptic neurones has also been related to interaction with certain critical synaptic proteins. Thus, different facets of anaesthetic action may have distinct neuronal basis, as opposed to the earlier belief of a global neuronal depression.

Unlike local anaesthetics which act primarily by blocking axonal conduction, the GAs appear to act by depressing synaptic transmission.

STAGES OF ANAESTHESIA

GAs cause an irregularly descending depression of the CNS, i.e. the higher functions are lost first and progressively lower areas of the brain are involved, but in the spinal cord lower segments are affected somewhat earlier than the higher segments. The vital centres located in the medulla are paralysed the last as the depth of anaesthesia increases. Guedel (1920) described four stages with *ether* anaesthesia, dividing the III stage into 4 planes. These clear-cut stages are not seen now-a-days with the use of faster acting GAs, premedication and employment of many drugs together. The precise sequence of events differs somewhat with anaesthetics other than ether. However, ether continues to be used in resource poor remote areas, and description of these stages still serves to define the effects of light and deep anaesthesia. Important features of different stages are depicted in Fig. 27.1.

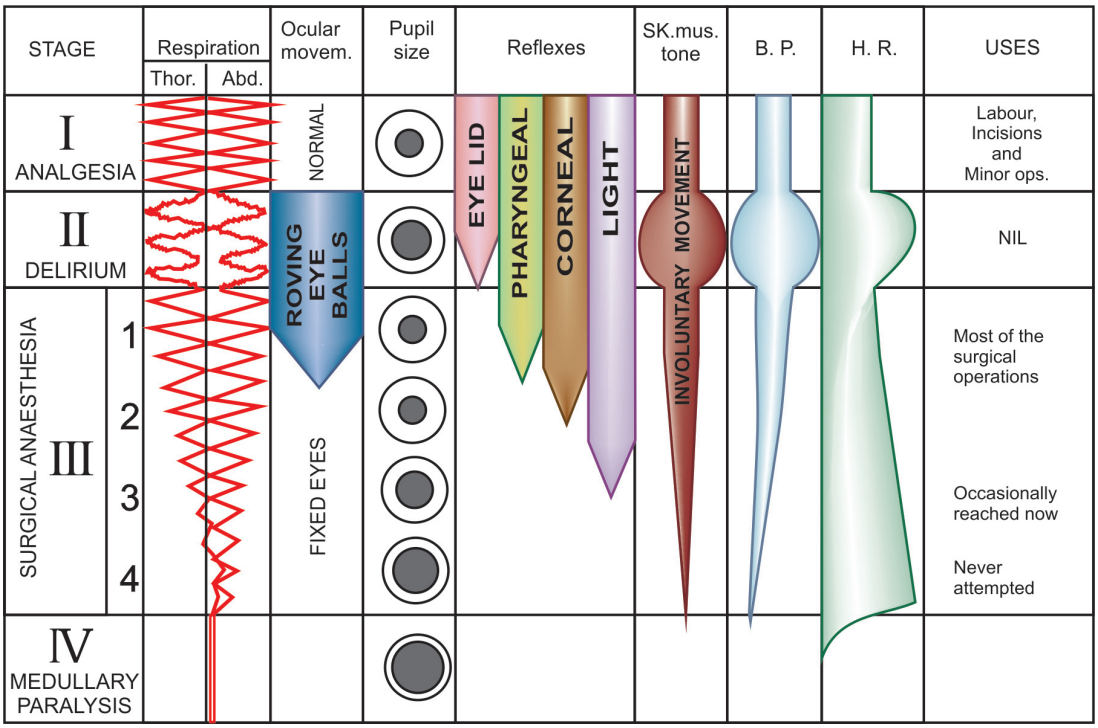


Fig. 27.1: Physiological changes during stages of general anaesthesia (with ether)

I. Stage of analgesia Starts from beginning of anaesthetic inhalation and lasts upto the loss of consciousness. Pain is progressively abolished. Patient remains conscious, can hear and see, and feels a dream like state; amnesia develops by the end of this stage. Reflexes and respiration remain normal.

Though some minor operations can be carried out during this stage, it is rather difficult to maintain—use is limited to short procedures.

II. Stage of delirium From loss of consciousness to beginning of regular respiration. Apparent excitement is seen—patient may shout, struggle and hold his breath; muscle tone increases, jaws are tightly closed, breathing is jerky; vomiting, involuntary micturition or defecation may occur. Heart rate and BP may rise and pupils dilate due to sympathetic stimulation.

No stimulus should be applied or operative procedure carried out during this stage. This stage is inconspicuous in modern anaesthesia.

III. Surgical anaesthesia Extends from onset of regular respiration to cessation of spontaneous breathing. This has been divided into 4 planes which may be distinguished as:

Plane 1 Roving eyeballs. This plane ends when eyes become fixed.

Plane 2 Loss of corneal and laryngeal reflexes.

Plane 3 Pupil starts dilating and light reflex is lost.

Plane 4 Intercostal paralysis, shallow abdominal respiration, dilated pupil.

As anaesthesia passes to deeper planes, progressively—muscle tone decreases, BP falls, HR increases with weak pulse, respiration decreases in depth and later in frequency also. Thoracic respiration lags behind abdominal respiration.

IV. Medullary paralysis Cessation of breathing to failure of circulation and death. Pupil is widely dilated, muscles are totally flabby, pulse is thready or imperceptible and BP is very low.

Many of the above indices of anaesthesia have been robbed by the use of atropine (pupillary, heart rate), morphine (respiration, pupillary), muscle relaxants (muscle tone, respiration, eye movements, reflexes), etc. and the modern anaesthetist has to depend on several other observations to gauge the depth of anaesthesia.

- If eyelash reflex is present and patient is making swallowing movements—stage II has not been reached.
- Loss of response to painful stimulus (e.g. pressure on the upper nasal border of orbit) — stage III has been reached.

- Incision of the skin causes reflex increase in respiration, BP rise or other effects; insertion of endotracheal tube is resisted and induces coughing, vomiting, laryngospasm; tears appear in eye; passive inflation of lungs is resisted—anaesthesia is light.
- Fall in BP, cardiac and respiratory depression are signs of deep anaesthesia.

In the present day practice, anaesthesia is generally kept light; adequate analgesia, amnesia and muscle relaxation are produced by the use of intravenous drugs. Premedication with CNS depressants and opioids or their concurrent use lowers MAC of the inhaled anaesthetic. When a combination of two inhalational anaesthetics (e.g. N_2O + isoflurane) is used, their MACs are additive: lower concentration of each is required, e.g. 0.5 MAC of N_2O (53%) and 0.5 MAC of isoflurane (0.6%) produce CNS depression equivalent to 1 MAC of isoflurane alone. The dose-response relationship of inhaled anaesthetics is very steep; just 30% higher concentration (1.3 MAC) immobilizes 95% subjects. Concentrations of inhalational anaesthetics exceeding 1.5 MAC are rarely used, and 2–3 MAC is often lethal. Anaesthetized subjects generally wake up when anaesthetic concentration falls to 0.4 MAC.

PHARMACOKINETICS OF INHALATIONAL ANAESTHETICS

Inhalational anaesthetics are gases or vapours that diffuse rapidly across pulmonary alveoli and tissue barriers. The depth of anaesthesia depends on the potency of the agent (MAC is an index of potency) and its partial pressure (PP) in the brain, while induction and recovery depend on the rate of change of PP in the brain. Transfer of the anaesthetic between lung and brain depends on a series of tension gradients which may be summarized as—

$$\text{Alveoli} \rightleftharpoons \text{Blood} \rightleftharpoons \text{Brain}$$

Factors affecting the PP of anaesthetic attained in the brain are—

1. *PP of anaesthetic in the inspired gas* This is proportional to its concentration in the inspired gas mixture. Higher the inspired tension more anaesthetic will be transferred to the blood. Thus, induction can be hastened by administering the GA at high concentration in the beginning.

2. *Pulmonary ventilation* It governs delivery of the GA to the alveoli. Hyperventilation will bring in more anaesthetic per minute and respiratory depression will have the opposite effect. Influence of minute volume on the rate of induction is greatest in the case of agents which have high blood solubility because their PP in blood takes a long time to approach the PP in alveoli. However, it does not affect the terminal depth of anaesthesia attained at any given concentration of a GA.

3. *Alveolar exchange* The GAs diffuse freely across alveoli, but if alveolar ventilation and perfusion are mismatched (as occurs in emphysema and other lung diseases) the attainment of equilibrium between alveoli and blood is delayed: well perfused alveoli may not be well ventilated—blood draining these alveoli carries less anaesthetic and dilutes the blood coming from well ventilated alveoli. Induction and recovery both are slowed.

4. *Solubility of anaesthetic in blood* This is the most important property determining induction and recovery. Large amount of an anaesthetic that is highly soluble in blood (ether) must dissolve before its PP is raised. The rise as well as fall of PP in blood and consequently induction as well as recovery are slow. Drugs with low blood solubility, e.g. N_2O, sevoflurane, desflurane induce quickly.

Blood: gas partition coefficient (λ) given by the ratio of the concentration of the anaesthetic in blood to that in the gas phase at equilibrium is the index of solubility of the GA in blood.

5. *Solubility of anaesthetic in tissues* Relative solubility of the anaesthetic in blood and tissue determines its concentration in that tissue at equilibrium. Most of the GAs are

equally soluble in lean tissues as in blood, but more soluble in fatty tissue. Anaesthetics with higher lipid solubility (halothane) continue to enter adipose tissue for hours and also leave it slowly. The concentration of these agents is much higher in white matter than in grey matter.

6. *Cerebral blood flow* Brain is a highly perfused organ; as such GAs are quickly delivered to it. This can be hastened by CO_2 inhalation which causes cerebral vasodilatation—induction and recovery are accelerated. Carbon dioxide stimulates respiration and this also speeds up the transport.

Elimination When anaesthetic inhalation is discontinued, gradients are reversed and the channel of absorption (pulmonary epithelium) becomes the channel of elimination. All inhaled anaesthetics are eliminated mainly through lungs. The same factors which govern induction also govern recovery. Anaesthetics, in general, continue to enter and persist for long periods in adipose tissue because of their high lipid solubility and low blood flow to fatty tissues. Muscles occupy an intermediate position between brain and adipose tissue. Most GAs are eliminated unchanged. Metabolism is significant only for halothane which is >20% metabolized in liver. Others are practically not metabolized. Recovery may be delayed after prolonged anaesthesia, especially in case of more lipid-soluble anaesthetics (halothane, isoflurane), because large quantities of the anaesthetic have entered the muscle and fat, from which it is released slowly into blood.

Second gas effect and diffusion hypoxia

In the initial part of induction, diffusion gradient from alveoli to blood is high and larger quantity of anaesthetic is entering blood. If the inhaled concentration of anaesthetic is high, substantial loss of alveolar gas volume will occur and the gas mixture will be sucked in, independent of ventilatory exchange—gas flow will be higher than tidal volume. This is significant only with N_2O, since it is given at 70–80% concentration; though it has low solubility in blood, about 1 litre/min of N_2O enters blood in the first few minutes. As such, gas flow is 1 litre/min higher than minute volume. If another potent anaesthetic, e.g. halothane (1–2%) is being given at the same time, it also will be delivered to blood at a rate 1 litre/min higher than minute volume and induction will be faster. This is called *'second gas effect'*.

The reverse occurs when N_2O is discontinued after prolonged anaesthesia; N_2O having low blood solubility rapidly diffuses into alveoli and dilutes the alveolar air, and PP of oxygen in alveoli is reduced. The resulting hypoxia, called *diffusion hypoxia*, is not of much consequence if cardiopulmonary reserve is normal, but may be dangerous if it is low. Diffusion hypoxia can be prevented by continuing 100% O_2 inhalation for a few minutes after discontinuing N_2O, instead of straight away switching over to air. Diffusion hypoxia is not significant with other anaesthetics, because they are administered at low concentrations (0.2–4%) and cannot dilute alveolar air by more than 1–2% in any case.

TECHNIQUES OF INHALATION OF ANAESTHETICS

Different techniques are used according to facility available, agent used, condition of the patient, type and duration of operation.

1. Open drop method Liquid anaesthetic is poured over a mask with gauze and its vapour is inhaled with air. A lot of anaesthetic vapour escapes in the surroundings and the concentration of anaesthetic breathed by the patient cannot be determined. It is wasteful—can be used only for a cheap anaesthetic. However, it is simple and requires no special apparatus. Use now is limited to peripheral areas. Either is the only agent administered by this method, especially in children.

2. Through anaesthetic machines Use is made of gas cylinders, specialized graduated vaporisers, flow meters, unidirectional valves, corrugated rubber tubing and reservoir bag.

The gases are delivered to the patient through a tightly fitting face mask or endotracheal tube. Administration of the anaesthetic can be more precisely controlled and in many situations its concentration estimated. Respiration can be controlled and assisted by the anaesthetist.

(a) *Open system* The exhaled gases are allowed to escape through a valve and fresh anaesthetic mixture is drawn in each time. No rebreathing is allowed—flow rates are high—more drug is consumed. However, predetermined O_2 and anaesthetic concentration can be accurately delivered.

(b) *Closed system* The patient rebreaths the exhaled gas mixture after it has circulated through sodalime which absorbs CO_2. Only as much O_2 and anaesthetic as have been taken up by the patient are added to the circuit. Flow rates are low. This is especially useful for expensive and explosive agents (little anaesthetic escapes in the surrounding air). Halothane, isoflurane, desflurane can be used through closed system. However, control of inhaled anaesthetic concentration is imprecise.

(c) *Semiclosed system* Partial rebreathing is allowed through a partially closed valve. Conditions are intermediate with moderate flow rates.

Properties of an ideal anaesthetic

A. *For the patient* It should be pleasant, non-irritating, should not cause nausea or vomiting. Induction and recovery should be fast with no after effects.

B. *For the surgeon* It should provide adequate analgesia, immobility and muscle relaxation. It should be noninflammable and nonexplosive so that cautery may be used.

C. *For the anaesthetist* Its administration should be easy, controllable and versatile.

- Margin of safety should be wide—no fall in BP.
- Heart, liver and other organs should not be affected.
- It should be potent so that low concentrations are needed and oxygenation of the patient does not suffer.
- Rapid adjustments in depth of anaesthesia should be possible.
- It should be cheap, stable and easily stored.
- It should not react with rubber tubing or soda lime.

The important physical and anaesthetic properties of inhalational anaesthetics are presented in Table 27.1.

CLASSIFICATION

Inhalational

Gas	*Volatile liquids*
Nitrous oxide	Ether
	Halothane
	Isoflurane
	Desflurane
	Sevoflurane

TABLE 27.1 Physical and anaesthetic properties of inhalational anaesthetics

Anaesthetic	*Boiling point (°C)*	*Inflammability*	*Irritancy (odour)*	*Oil: Gas partition coefficient**	*Blood: Gas partition coefficient**	*MAC (%)*	*Induction*	*Muscle relaxation*
1. Ether	35	Infl. + Explo.	+++ (Pungent)	65	12.1	1.9	Slow	V. good
2. Halothane	50	Noninfl.	– (Pleasant)	224	2.3	0.75	Interm.	Fair
3. Isoflurane	48	Noninfl.	± (Unpleasant)	99	1.4	1.2	Interm.	Good
4. Desflurane	24	Noninfl.	+ (Unpleasant)	19	0.42	6.0	Fast	Good
5. Sevoflurane	59	Noninfl.	– (Pleasant)	50	0.68	2.0	Fast	Good
6. Nitrous oxide	Gas	Noninfl.	–	1.4	0.47	105	Fast	Poor

*At 37°C; Oil: gas and blood: gas partition coefficients are measures of solubility of the anaesthetic in lipid and blood respectively.
MAC—Minimal alveolar concentration; Infl.—Inflammable; Explo.—Explosive; Interm.—Intermediate

Intravenous

Fast acting drugs	*Slower acting drugs*
Thiopentone sod.	*Benzodiazepines*
Methohexitone sod.	Diazepam
Propofol	Lorazepam
Etomidate	Midazolam
	Dissociative anaesthesia
	Ketamine
	Opioid analgesia
	Fentanyl

Cyclopropane, trichloroethylene, methoxyflurane and enflurane are no longer used.

INHALATIONAL ANAESTHETICS

1. Nitrous oxide (N_2O) It is a colourless, odourless, heavier than air, noninflammable gas supplied under pressure in steel cylinders. It is nonirritating, but low potency anaesthetic; unconsciousness cannot be produced in all individuals without concomitant hypoxia; MAC is 105% implying that even pure N_2O cannot produce adequate anaesthesia at 1 atmosphere pressure. Patients maintained on 70% N_2O + 30% O_2 along with muscle relaxants often recall the events during anaesthesia, but some lose awareness completely.

Nitrous oxide is a good analgesic; even 20% produces analgesia equivalent to that produced by conventional doses of morphine. Muscle relaxation is minimal. Neuromuscular blockers are mostly required. Onset of N_2O action is quick and smooth (but thiopentone is often used for induction), recovery is rapid, because of its low blood solubility. Second gas effect and diffusion hypoxia occur with N_2O only. Post-anaesthetic nausea is not marked. It tends to increase sympathetic tone which counteracts weak direct depressant action on heart and circulation.

Nitrous oxide is generally used as a carrier and adjuvant to other anaesthetics. A mixture of 70% N_2O + 25–30% O_2 + 0.2–2% another potent anaesthetic is employed for most surgical procedures. In this way concentration of the other anaesthetic can be reduced to 1/3 for the same level of anaesthesia. Because N_2O has little effect on respiration, heart and BP: breathing and circulation are better maintained with the mixture than with the potent anaesthetic given alone in full doses. However, N_2O can expand pneumothorax and other abnormal air pockets in the body. It increases cerebral blood flow and tends to elevate intracranial pressure.

As the sole agent, N_2O (50%) has been used with O_2 for dental and obstetric analgesia. It is nontoxic to liver, kidney and brain. However, prolonged N_2O anaesthesia has the potential to depress bone marrow and cause peripheral neuropathy. Metabolism of N_2O does not occur; it is quickly removed from the body by lungs. It is cheap and commonly used.

2. Ether (Diethyl ether) It is a highly volatile liquid, produces irritating vapours which are inflammable and explosive.

$$(C_2H_5 — O — C_2H_5)$$

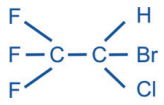
Ether is a potent anaesthetic, produces good analgesia and marked muscle relaxation by reducing ACh output from motor nerve endings. The dose of competitive neuromuscular blockers should be reduced to about 1/3.

It is highly soluble in blood. Induction is prolonged and unpleasant with struggling, breath-holding, salivation and marked respiratory secretions (atropine must be given as premedication to prevent the patient from drowning in his own secretions). Recovery is slow; post-anaesthetic nausea, vomiting and retching are marked.

Respiration and BP are generally well maintained because of reflex stimulation and high sympathetic tone. It does not sensitize the heart to Adr, and is not hepatotoxic.

Ether is not used now in developed countries because of its unpleasant and inflammable properties. However, it is still used in developing countries, particularly in peripheral areas because it is—cheap, can be given by open drop method (though congestion of eye, soreness of trachea and ether burns on face can occur) without the need for any equipment, and is relatively safe even in inexperienced hands.

3. Halothane (FLUOTHANE) It is a volatile liquid with sweet odour, nonirritant and noninflammable. Solubility in blood is intermediate—induction is reasonably quick and pleasant.



HALOTHANE

It is a potent anaesthetic—precise control of administered concentration is essential. For induction 2–4% and for maintenance 0.5–1% is delivered by the use of a special vaporizer. It is not a good analgesic or muscle relaxant, but it potentiates competitive neuromuscular blockers.

Halothane causes direct depression of myocardial contractility by reducing intracellular Ca^{2+} concentration. Moreover, sympathetic activity fails to increase reflexly. Cardiac output is reduced with deepening anaesthesia. BP starts falling early and parallels the depth. A 20–30 mm Hg drop in BP is common. Many vascular beds dilate but total peripheral resistance is not significantly reduced. Heart rate is reduced by vagal stimulation, direct depression of SA nodal automaticity and absence of baroreceptor activation even when BP falls. It tends to sensitize the heart to the arrhythmogenic action of Adr. The electrophysiological effects are conducive to reentry—tachyarrhythmias occur occasionally.

Halothane causes relatively greater depression of respiration; breathing is shallow and rapid—PP of CO_2 in blood rises if respiration is not assisted. Cerebral blood flow increases. Ventilatory support with added oxygen is frequently required. It tends to accentuate perfusion-ventilation mismatch in the lungs by causing vasodilatation in hypoxic alveoli.

Pharyngeal and laryngeal reflexes are abolished early and coughing is suppressed while bronchi dilate. As such, halothane is preferred for asthmatics. It inhibits intestinal and uterine contractions. This property is utilized for facilitating external or internal version during late pregnancy. However, its use during labour can prolong delivery and increase postpartal blood loss.

Urine formation is decreased during halothane anaesthesia—primarily due to low g.f.r. as a result of fall in BP.

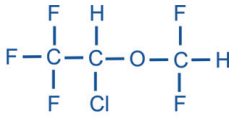
Hepatitis occurs in rare susceptible individuals (1 in 35000 to 1 in 10,000) especially after repeated use and in those with familial predisposition. A metabolite of halothane is probably involved—causes chemical or immunological injury.

A genetically determined reaction *malignant hyperthermia* occurs rarely. Many susceptible subjects have an abnormal RyR1 (Ryanodine receptor) calcium channel at the sarcoplasmic reticulum of skeletal muscles. This channel is triggered by halothane to release massive amounts of Ca^{2+} intracellularly causing persistent muscle contraction and increased heat production. Succinylcholine accentuates the condition (*see* Ch. 25). Rapid external cooling, bicarbonate infusion, 100% O_2 inhalation and i.v. dantrolene (*see* p. 356) are used to treat malignant hyperthermia.

About 20% of halothane that enters blood is metabolized in the liver, the rest is exhaled out. Elimination may continue for 24–48 hours after prolonged administration due to accumulation in fatty and other tissues. Recovery from halothane anaesthesia is smooth and reasonably quick; shivering may occur but nausea and vomiting are rare. Psychomotor performance and mental ability remain depressed for several hours after regaining consciousness.

Halothane is a popular anaesthetic in developing countries, because it is relatively cheap and nonirritant, noninflammable, pleasant with relatively rapid action. It is particularly suitable for use in children, both for induction as well as maintenance. In adults, it is mainly used as a maintenance anaesthetic after i.v. induction. Halothane toxicity is less frequent in children. However, in affluent countries it has been largely replaced by the newer agents which are costlier. Its deficiencies in terms of poor analgesia and muscle relaxation are compensated by concomitant use of N_2O or opioids and neuromuscular blockers.

4. Isoflurane (SOFANE, FORANE, ISORANE) This fluorinated anaesthetic introduced in 1981 is currently the routinely used anaesthetic all over. It has totally replaced its earlier introduced isomer enflurane. Isoflurane is somewhat less potent and less soluble in blood as well as in fat than halothane, but equally volatile. Compared to halothane, it produces relatively rapid induction and recovery, and is administered through a special vaporizer; 1.5–3% induces anaesthesia in 7–10 min, and 1–2% is used for maintenance.



ISOFLURANE

Magnitude of fall in BP is similar to halothane, but unlike halothane, this is primarily due to vasodilatation, while cardiac output is well maintained. Heart rate is increased. These cardiovascular effects probably result from stimulation of β adrenergic receptors, but it does not sensitize the heart to adrenergic arrhythmias. Isoflurane dilates coronaries. Though not encountered clinically, possibility of 'coronary steal' has been apprehended in coronary artery disease patients on theoretical grounds. Respiratory depression is prominent and assistance is usually needed to avoid hypercarbia. Secretions are slightly increased.

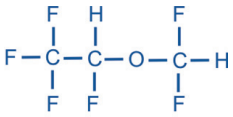
Uterine and skeletal muscle relaxation is similar to halothane. Potentiation of neuromuscular blockers is greater than that with halothane.

Metabolism of isoflurane is negligible. Renal and hepatic toxicity has not been encountered. Postanaesthetic nausea and vomiting is low.

Pupils do not dilate and light reflex is not lost even at deeper levels.

Though mildly pungent, isoflurane has many advantages, i.e. better adjustment of depth of anaesthesia and low toxicity. It is a good maintenance anaesthetic, but not preferred for induction because of ether like odour which is not liked by conscious patients, especially children. In contrast to enflurane, it does not provoke seizures and is particularly suitable for neurosurgery.

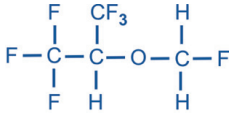
5. Desflurane It is a newer all fluorinated congener of isoflurane which has gained popularity as an anaesthetic for out patient surgery. Though it is highly volatile, a thermostatically heated special vapourizer is used to deliver a precise concentration of pure desflurane vapour in the carrier gas ($N_2O + O_2$) mixture. Its distinctive properties are lower lipid solubility as well as very low solubility in blood and tissues, because of which induction and recovery are very fast. Depth of anaesthesia changes rapidly with change in inhaled concentration giving the anaesthetist better control. Postanaesthetic cognitive and motor impairment is shortlived, so that patient can be discharged a few hours after surgery.



DESFLURANE

Desflurane is 5 times less potent than isoflurane; higher concentration has to be used for induction which irritates air passage and may induce coughing, breath-holding and laryngospasm. A somewhat pungent odour makes it unsuitable for induction. Rapid induction sometimes causes brief sympathetic stimulation and tachycardia which may be risky in those with cardiovascular disease. Degree of respiratory depression, muscle relaxation, vasodilatation and fall in BP are similar to isoflurane. Cardiac contractility and coronary blood flow are maintained. Lack of seizure provoking potential arrhythmogenicity and absence of liver as well as kidney toxicity are also similar to isoflurane. It is rapidly exhaled unchanged. As such, desflurane can serve as a good alternative to isoflurane for routine surgery as well, especially prolonged operations. If closed circuit is used, soda lime should be fresh and well hydrated.

6. Sevoflurane (SEVORANE) This new polyfluorinated anaesthetic has properties intermediate between isoflurane and desflurane. Solubility in blood and tissues as well as potency are less than isoflurane but more than desflurane.



SEVOFLURANE

Induction and emergence from anaesthesia are fast so that rapid changes in depth can be achieved. Absence of pungency makes it pleasant and administrable through a face mask. Unlike desflurane, it poses no problem in induction and is frequently selected for this purpose. Acceptability is good even by pediatric patients. Recovery is smooth; orientation, cognitive and motor functions are regained almost as quickly as with desflurane. Sevoflurane is suitable both for outpatient as well as inpatient surgery, induction as well as maintenance, but its high cost and need for high-flow open or semiclosed system makes it very expensive to use. In India, only high-end hospitals are using it.

Sevoflurane does not cause sympathetic stimulation and airway irritation even during rapid induction. Fall in BP is due to vasodilatation as well as modest cardiac depression. Respiratory depression, and absence of seizure or arrhythmia precipitating propensity are similar to isoflurane. About 3% of absorbed sevoflurane is metabolized, but the amount of fluoride liberated is safe for kidney and liver. However, it reacts with sodalime—not recommended for use in fully closed circuit.

INTRAVENOUS ANAESTHETICS

FAST ACTING DRUGS

These are drugs which on i.v. injection produce loss of consciousness in one arm-brain circulation time (~11 sec). They are generally used for induction because of rapidity of onset of action. Anaesthesia is then usually maintained by an inhalational agent. They also serve to reduce the amount of maintenance anaesthetic. Supplemented with analgesics and muscle relaxants, they can also be used as the sole anaesthetic.

1. Thiopentone sod. It is an ultrashort acting thiobarbiturate, highly soluble in water yielding a very alkaline solution, which must be prepared freshly before injection. Extravasation of the solution or inadvertent intraarterial injection produces intense pain; necrosis and gangrene can occur.

Injected i.v. (3–5 mg/kg) as a 2.5% solution, it produces unconsciousness in 15–20 sec. Its undissociated form has high lipid solubility—enters brain almost instantaneously. Initial distribution depends on organ blood flow—brain gets large amounts. However, as other less vascular tissues (muscle, fat) gradually take up the drug, blood concentration falls and it back diffuses from the brain: consciousness is regained in 6–10 min (t½ of distribution phase is 3 min).

On repeated injection, the extracerebral sites are gradually filled up—lower doses produce anaesthesia which lasts longer. Its ultimate disposal occurs mainly by hepatic metabolism (elimination t½ is 8–12 hr), but this is irrelevant for termination of action of a single dose. Residual CNS depression may persist for > 12 hr. The patient should not be allowed to leave the hospital without an attendant before this time.

Thiopentone is a poor analgesic. Painful procedures should not be carried out under its influence unless an opioid or N_2O has been given; otherwise, the patient may struggle, shout and show reflex changes in BP and respiration.

It is a weak muscle relaxant; does not irritate air passages. Respiratory depression with inducing doses of thiopentone is generally marked but transient. With large doses it can be severe. BP falls immediately after injection mainly due to vasodilatation, but recovers rapidly. Cardiovascular collapse may occur if hypovolemia, shock or sepsis are present. Reflex tachycardia occurs, but thiopentone does not sensitize the heart to Adr, arrhythmias are rare.

TABLE 27.2 Effects of intravenous anaesthetics on vital functions

Anaesthetic drug	*HR*	*BP*	*Resp.*	*CBF*
1. Thiopentone	↑↑	↓↓	↓↓	↓↓↓
2. Propofol	–, ↓	↓↓↓	↓↓↓	↓↓↓
3. Etomidate	–	↓	↓	↓↓↓
4. Diazepan	–, ↑	↓	↓↓	↓↓
5. Ketamine	↑↑	↑↑	↓, –	↑↑↑
6. Fentanyl	↓	↓	↓↓↓	↓

HR—Heart rate; BP—Systemic arterial blood pressure; Resp.—Respiratory drive; CBF—Cerebral blood flow. (Changes in intracranial pressure parallel CBF).

Cerebral blood flow is reduced, both due to fall in BP as well as constriction of cerebral vessels. However, cerebral oxygenation does not suffer, because there is greater decrease in cerebral O_2 consumption and cerebral perfusion is maintained. A comparative summary of effects of i.v. anaesthetics is presented in Table 27.2.

Thiopentone is a commonly used inducing agent. It can be employed as the sole anaesthetic for short operations that are not painful.

Adverse effects Laryngospasm occurs generally when respiratory secretions or other irritants are present, or when intubation is attempted while anaesthesia is light. This can be prevented by atropine premedication and administration of succinylcholine immediately after thiopentone. Succinylcholine and thiopentone react chemically—should not be mixed in the same syringe.

Shivering and delirium may occur during recovery. Pain in the postoperative period is likely to induce restlessness; adequate analgesia should be provided. Postanaesthetic nausea and vomiting are uncommon.

It can precipitate acute intermittent porphyria in susceptible individuals, therefore contraindicated.

Other uses Occasionally used for rapid control of convulsions.

Gradual i.v. infusion of subanaesthetic doses can be used to facilitate verbal communication with psychiatric patients and for 'narcoanalysis' of criminals; acts by knocking off guarding.

PENTOTHAL, INTRAVAL SODIUM 0.5, 1 g powder for making fresh injectable solution.

2. Methohexitone sod. It is similar to thiopentone, 3 times more potent, has a quicker and briefer (5–8 min) action. Excitement during induction and recovery is more common. It is more rapidly metabolized (t½ 4 hr) than thiopentone: patient may be roadworthy more quickly.

3. Propofol Currently, propofol has superseded thiopentone as an i.v. anaesthetic, both for induction as well as maintenance. It is an oily liquid employed as a 1% emulsion. Unconsciousness after propofol injection occurs in 15–45 sec and lasts 5–10 min. Propofol distributes rapidly (distribution t½ 2–4 min). Elimination t½ (100 min) is much shorter than that of thiopentone due to rapid metabolism.

Intermittent injection or continuous infusion of propofol is frequently used for total i.v. anaesthesia when supplemented by fentanyl. It lacks airway irritancy and is not likely to induce bronchospasm: preferred in asthmatics. It is particularly suited for outpatient surgery, because residual impairment is less marked and shorter-lasting. Incidence of postoperative nausea and vomiting is low; patient acceptability is very good. Excitatory effects and involuntary movements are noted in few patients. Induction apnoea lasting ~1 min is common. Fall in BP due primarily to vasodilatation with less marked cardiac depression occurs consistently, and is occasionally severe, but short lasting. Baroreflex is suppressed; heart rate remains unchanged or may decrease. Maintenance anaesthesia with

propofol produces dose-dependent respiratory depression which is more marked than with thiopentone. Effect of cerebral blood flow and O_2 consumption is similar to thiopentone. Pain during injection is frequent; can be minimized by combining with lidocaine.

Dose: 2 mg/kg bolus i.v. for induction; 100–200 µg/kg/min for maintenance.

PROPOVAN 10 mg/ml and 20 mg/ml in 10, 20 ml vials.

In subanaesthetic doses (25–50 µg/kg/min) it is the drug of choice for sedating intubated patients in intensive care units. However, it is not approved for such use in children; prolonged sedation with higher doses has caused severe metabolic acidosis, lipaemia and heart failure even in adults.

4. Etomidate It is another induction anaesthetic (0.2–0.5 mg/kg) which has a briefer duration of action (4–8 min) than thiopentone; produces little cardiovascular and respiratory depression, but motor restlessness and rigidity is more prominent as are pain on injection or nausea and vomiting on recovery. It is a poor analgesic and has not found much favour.

SLOWER ACTING DRUGS

1. Benzodiazepines (BZDs) In addition to preanaesthetic medication, BZDs are now frequently used for inducing, maintaining and supplementing anaesthesia as well as for 'conscious sedation'. Relatively large doses (diazepam 0.2–0.3 mg/kg or equivalent) injected i.v. produce sedation, amnesia and then unconsciousness in 5–10 min. If no other anaesthetic or opioid is given, the patient becomes responsive in 1 hr or so due to redistribution of the drug (distribution t½ of diazepam is 15 min), but amnesia persists for 2–3 hr and sedation for 6 hr or more. Recovery is further delayed if larger doses are given. BZDs are poor analgesics : an opioid or N_2O is usually added if the procedure is painful.

By themselves, BZDs donot markedly depress respiration, cardiac contractility or BP, but when opioids are also given these functions are considerably compromised. BZDs decrease muscle tone by central action, but require neuromuscular blocking drugs for muscle relaxation of surgical grade. They do not provoke postoperative nausea or vomiting. Involuntary movements are not stimulated.

BZDs are now the preferred drugs for endoscopies, cardiac catheterization, angiographies, conscious sedation during local/regional anaesthesia, fracture setting, ECT, etc. They are a frequent component of balanced anaesthesia employing several drugs. The anaesthetic action of BZDs can be rapidly reversed by flumazenil 0.5–2 mg i.v.

Diazepam 0.2–0.5 mg/kg by slow undiluted injection in a running i.v. drip: this technique reduces the burning sensation in the vein and incidence of thrombophlebitis.

VALIUM, CALMPOSE 10 mg/2 ml inj.

Lorazepam Three times more potent, slower acting and less irritating than diazepam. It distributes more gradually—awakening may be delayed. Amnesia is more profound.

Dose: 2–4 mg (0.04 mg/kg) i.v. CALMESE 4 mg/2 ml inj.

Midazolam This BZD is water soluble, non-irritating to veins, faster and shorter acting (t½ 2 hours) and 3 times more potent than diazepam. Fall in BP is somewhat greater than with diazepam. It is being preferred over diazepam for anaesthetic use: 1–2.5 mg i.v. followed by 1/4th supplemental doses. Also used for sedation of intubated and mechanically ventilated patients and in other critical care anaesthesia as 0.02–0.1 mg/kg/hr continuous i.v. infusion.

FULSED, MEZOLAM, SHORTAL 1 mg/ml, 5 mg/ml inj.

2. Ketamine This unique anaesthetic is pharmacologically related to the hallucinogen phencyclidine. It induces a so called '*dissociative anaesthesia*' characterized by profound analgesia, immobility, amnesia with light sleep. The patient appears to be conscious, i.e. opens his eyes, makes swallowing movements and his muscles are stift, but he is unable to process sensory stimuli and does not reeact to them. Thus, the patient appears to be dissociated from his body and surroundings. The primary site of action is in the cortex and

subcortical areas; not in the reticular activating system, which is the site of action of barbiturates.

Respiration is not depressed, bronchi dilate, airway reflexes are maintained, muscle tone increases. Non-purposive limb movements occur. Heart rate, cardiac output and BP are elevated due to sympathetic stimulation. A dose of 1–2 (average 1.5) mg/kg i.v. or 3–5 mg/kg i.m. produces the above effects within a minute, and recovery starts after 10–15 min, but patient remains amnesic for 1–2 hr. Emergence delirium, hallucinations and involuntary movements occur in upto 50% patients during recovery; but the injection is not painful. Children tolerate the drug better. Ketamine is rapidly metabolized in the liver and has an elimination t½ of 2–4 hr.

Ketamine has been used for operations on the head and neck, in patients who have bled, in asthmatics (relieves bronchospasm), in those who do not want to lose consciousness and for short operations. It is good for repeated use; particularly suitable for burn dressing. Combined with diazepam, it has found use in angiographies, cardiac catheterization and trauma surgery. It may be dangerous for hypertensives, in ischaemic heart disease (increases cardiac work), in congestive heart failure and in those with raised intracranial pressure (ketamine increases cerebral blood flow and O_2 consumption), but is good for hypovolemic patients.

KETMIN, KETAMAX, ANEKET 50 mg/ml in 2 ml amp, 10 ml vial.

Clandestinely mixed in drinks, ketamine has been misused as rape drug.

3. Fentanyl This highly lipophilic, short acting (30–50 min) potent opioid analgesic related to pethidine (*see* Ch. 34) is generally given i.v. at the beginning of painful surgical procedures. Reflex effects of painful stimuli are abolished. It is frequently used to supplement anaesthetics in balanced anaesthesia. This permits use of lower anaesthetic concentrations with better haemodynamic stability. Combined with BZDs, it can obviate the need for inhaled anaesthetics for diagnostic, endoscopic, angiographic and other minor procedures in poor risk patients, as well as for burn dressing. Anaesthetic awareness with dreadful recall is a risk.

After i.v. fentanyl (2–4 µg/kg) the patient remains drowsy but conscious and his co-operation can be commanded. Respiratory depression is marked, but predictable; the patient may be encouraged to breathe and assistance may be provided. Tone of chest muscles and masseters may increase with rapid fentanyl injection: a muscle relaxant is then required to facilitate mechanical ventilation. Heart rate decreases, because fentanyl stimulates vagus. Fall in BP is slight and heart is not sensitized to Adr. Cerebral blood flow and O_2 consumption are slightly decreased. Supplemental doses of fentanyl are needed every 30 min or so, but recovery is prolonged after repeated doses.

Nausea, vomiting and itching often occurs during recovery. The opioid antagonist naloxone can be used to counteract persisting respiratory depression and mental clouding. Fentanyl is also employed as adjunct to spinal and nerve block anaesthesia, and to relieve postoperative pain.

TROFENTYL, FENDOP, FENT 50 µg/ml in 2 ml amp, 10 ml vial.

Alfentanil, *Sufentanil* and *remifentanil* are still shorter acting analogues which can be used in place of fentanyl.

4. Dexmedetomidine Activation of central α_2 adrenergic receptors has been known to cause sedation and analgesia. Clonidine (a selective α_2 agonist antihypertensive) given before surgery reduces anaesthetic requirement. Dexmedetomidine is a centrally active selective α_{2A} agonist that has been introduced for sedating critically ill/ventilated patients in intensive care units. It is also being used as an adjunct to anaesthesia.Analgesia and sedation are produced with little respiratory depression, amnesia or anaesthesia. Sympathetic response to stress and noxious stimulus is blunted. It is administered by i.v. infusion. Side effects are similar to those with clonidine, *viz.* hypotension, bradycardia and dry mouth. It has been recently approved for use in India as well.

CONSCIOUS SEDATION

'Conscious sedation' is a monitored state of altered consciousness that can be employed (supplemented with local/regional anaesthesia), to carryout diagnostic/short therapeutic/dental procedures in apprehensive subjects or medically compromised patients, in place of general anaesthesia. It allows the operative procedure to be performed with minimal physiologic and psychologic stress. In conscious

sedation, drugs are used to produce a state of CNS depression (but not unconsciousness), sufficient to withstand the trespass of the procedure, while maintaining communication with the patient, who at the same time responds to commands and is able to maintain a patent airway. The difference between conscious sedation and anaesthesia is one of degree. The protective airway and other reflexes are not lost, making it safer. Drugs used for conscious sedation are:

1. *Diazepam* It is injected i.v. in small (1–2 mg) repeated doses or by slow infusion until the desired level of sedation is produced indicated by relaxation, indifference, slurring of speech, ptosis, etc. Further injection is stopped, after which this state lasts for about 1 hour and psychomotor impairment persists for 6–24 hours; an escort is needed to take the patient back to home. Flumazenil can be used to reverse the sedation, but repeated doses are needed.

   Midazolam (i.v.) is a shorter acting alternative to diazepam. Oral diazepam administered 1 hr before is also used with the limitation that level of sedation cannot be titrated. The patient remains sedated (not roadworthy) for several hours.

2. *Propofol* Because of brief action, it has to be administered as continuous i.v. infusion throughout the procedure by using a regulated infusion pump. Advantage is that level of sedation can be altered during the procedure and recovery is relatively quick, permitting early discharge of the patient.

3. *Nitrous oxide* The patient is made to breathe 100% oxygen through a nose piece or hood and N_2O is added in 10% increments (to a maximum of 50%, rarely 70%) till the desired level of sedation assessed by constant verbal contact is obtained. This is maintained till the procedure is performed. Thereafter, N_2O is switched off, but 100% O_2 is continued for next 5 min. The patient is generally roadworthy in 30–60 min.

4. *Fentanyl* Injected i.v. (1–2 µg/kg every 15–30 min), it can be used alone or in combination with midazolam/propofol.

COMPLICATIONS OF GENERAL ANAESTHESIA

A. *During anaesthesia*

1. Respiratory depression and hypercarbia.
2. Salivation, respiratory secretions. This is less problematic now as nonirritant anaesthetics are mostly used.
3. Cardiac arrhythmias, asystole.
4. Fall in BP.
5. Aspiration of gastric contents: acid pneumonitis.
6. Laryngospasm and asphyxia.
7. Awareness: dreadful perception and recall of events during surgery. This may occur due to use of light anaesthesia + analgesics and muscle relaxants.
8. Delirium, convulsions and other excitatory effects are generally seen with i.v. anaesthetics; especially if phenothiazines or hyoscine have been given in premedication. These are suppressed by opioids.
9. Fire and explosion. This is rare now due to use of non-inflammable anaesthetics.

B. *After anaesthesia*

1. Nausea and vomiting.
2. Persisting sedation: impaired psychomotor function.
3. Pneumonia, atelectasis.
4. Organ toxicities: liver, kidney damage.
5. Nerve palsies—due to faulty positioning.
6. Emergence delirium.
7. Cognitive defects: prolonged excess cognitive decline has been observed in some patients, especially the elderly, who have undergone general anaesthesia, particularly of long duration.

DRUG INTERACTIONS

1. Patients on antihypertensives given general anaesthetics—BP may fall markedly.
2. Neuroleptics, opioids, clonidine and monoamine oxidase inhibitors potentiate anaesthetics.
3. Halothane sensitizes the heart to Adr.
4. If a patient on corticosteroids is to be anaesthetized, give 100 mg hydrocortisone intraoperatively because anaesthesia is a stressful state—can precipitate adrenal insufficiency and cardiovascular collapse.
5. Insulin need of a diabetic is increased during GA: switch over to plain insulin even if the patient is on oral hypoglycaemics.

PREANAESTHETIC MEDICATION

Preanaesthetic medication refers to the use of drugs before anaesthesia to make it more pleasant and safe. The aims are:

1. Relief of anxiety and apprehension preoperatively and to facilitate smooth induction.
2. Amnesia for pre- and postoperative events.
3. Supplement analgesic action of anaesthetics and potentiate them so that less anaesthetic is needed.
4. Decrease secretions and vagal stimulation that may be caused by the anaesthetic.
5. Antiemetic effect extending to the postoperative period.
6. Decrease acidity and volume of gastric juice so that it is less damaging if aspirated.

Different drugs achieve different purposes. One or more drugs may be used in a patient depending on the needs.

1. Sedative-antianxiety drugs Benzodiazepines like diazepam (5–10 mg oral) or lorazepam (2 mg oral or 0.05 mg/kg i.m. 1 hour before) have become popular drugs for preanaesthetic medication because they produce tranquility and smoothen induction; there is loss of recall of perioperative events (especially with lorazepam) with little respiratory depression or accentuation of postoperative vomiting. They counteract CNS toxicity of local anaesthetics and are being used along with pethidine/fentanyl for a variety of minor surgical and endoscopic procedures.

Midazolam is a good amnesic with potent and shorter lasting action; it is also better suited for i.v. injection, due to water solubility.

Promethazine (50 mg i.m.) is an antihistaminic with sedative, antiemetic and anticholinergic properties. It causes little respiratory depression.

2. Opioids Morphine (10 mg) or pethidine (50–100 mg), i.m. allay anxiety and apprehension of the operation, produce pre- and postoperative analgesia, smoothen induction, reduce the dose of anaesthetic required and supplement poor analgesics (thiopentone, halothane) or weak anaesthetics (N_2O). Postoperative restlessness is also reduced.

Disadvantages They depress respiration, interfere with pupillary signs of anaesthesia, may cause fall in BP during anaesthesia, can precipitate asthma and tend to delay recovery. Other disadvantages are lack of amnesia, flushing, delayed gastric emptying and biliary spasm. Some patients experience dysphoria. Morphine particularly contributes to postoperative constipation, vomiting and urinary retention. Tachycardia sometimes occurs when pethidine has been used.

Use of opioids is now mostly restricted to those having preoperative pain. When indicated, fentanyl is mostly injected i.v. just before induction.

3. Anticholinergics (*see* Ch. 8) Atropine or hyoscine (0.6 mg or 10–20 µg/kg i.m./i.v.) or glycopyrrolate (0.2–0.3 mg or 5–10 µg/kg i.m./i.v.) have been used, primarily to reduce salivary and bronchial secretions. This need is infrequent now due to use of non-irritant anaesthetics. However, they must be given beforehand when ether is used. The main aim of their use now is to prevent vagal bradycardia and hypotension (which occur reflexly due to certain surgical procedures), and prophylaxis of laryngospasm which is precipitated by respiratory secretions.

Hyoscine, in addition, produces amnesia and antiemetic effect, but tends to delay recovery. Some patients get disoriented; emergence delirium is more common. Moreover, antibradycardiac effect of hyoscine is less marked. Therefore, it is infrequently selected for use during anaesthesia.

Glycopyrrolate is twice as potent and longer acting quaternary antimuscarinic which does not produce central effects. Antisecretory action is more marked than atropine, while tachycardia is less marked, especially after i.m. injection. It acts rapidly when given i.v. and is the preferred antimuscarinic in anaesthetic practice.

Action	*Atropine*	*Glycopyrrolate*
1. Antisecretory	++	+++
2. Tachycardia	+++	++
3. CNS effects	+	–
4. Bronchodilatation	++	++

Antimuscarinics facilitate assisted ventilation by reducing airway resistance, but tend to increase the anatomic dead space. They dilate pupils, abolish the pupillary signs and increase chances of gastric reflux by decreasing tone of lower esophageal sphincter (LES). They should not be used in febrile patients. Dryness of mouth

in the pre- and postoperative period may be distressing. As such, they are now mostly used i.v. intraoperatively when need arises.

4. Neuroleptics Chlorpromazine (25 mg), triflupromazine (10 mg) or haloperidol (2–4 mg) i.m. are infrequently used in premedication. They allay anxiety, smoothen induction and have antiemetic action. However, they potentiate respiratory depression and hypotension caused by the anaesthetics and delay recovery.

Involuntary movements and muscle dystonias can occur, especially in children.

5. H_2 blockers/proton pump inhibitors Patients undergoing prolonged operations, caesarian section and obese patients are at increased risk of gastric regurgitation and aspiration pneumonia. Ranitidine (150 mg)/famotidine (20 mg) or omeprazole (20 mg)/pantoprazole (40 mg) given night before and in the morning benefit by raising pH of gastric juice and may also reduce its volume and thus chances of regurgitation. The chances of reflux and damage to lungs on aspiration is minimal if volume of gastric juice is <25 ml and pH is >3.5. Prevention of stress ulcers is another advantage. They are now routinely used before prolonged surgery.

6. Antiemetics *Metoclopramide* 10–20 mg i.m. preoperatively is effective in reducing postoperative vomiting. By enhancing gastric emptying and tone of LES, it reduces the chances of reflux and its aspiration. Extrapyramidal effects and motor restlessness can occur. Combined use of metoclopramide and H_2 blockers is more effective.

Domperidone is nearly as effective and does not produce extrapyramidal side effects.

Ondansetron (4–8 mg i.v.) the selective 5-HT_3 blocker has been found highly effective in reducing the incidence of post-anaesthetic nausea and vomiting (*see* Ch. 47). It is practically devoid of side effects and has become the antiemetic of choice in anaesthetic practice.

Chapter 28 Ethyl and Methyl Alcohols

ETHYL ALCOHOL (Ethanol)

Alcohols are hydroxy derivatives of aliphatic hydrocarbons. When unqualified, 'alcohol' refers to *ethyl alcohol* or *ethanol*. Pharmacology of alcohol is important for its presence in beverages (which have been used since recorded history), alcoholism and for alcohol intoxication, rather than as a medicinal substance.

Alcohol is manufactured by fermentation of sugars:

$$C_6H_{12}O_6 \xrightarrow[(in\ yeast)]{Zymase} 2CO_2 + 2C_2H_5OH$$

Fermentation proceeds till alcohol content reaches ~ 15%. Then the reaction is inhibited by alcohol itself. Starchy cereals, e.g. barley, when soaked produce malt:

$$STARCH \xrightarrow{Convertase} MALTOSE$$

which can then be fermented by yeast to produce alcohol. The major source of commercial alcohol is *mollases*, a byproduct of sugar industry.

ALCOHOLIC BEVERAGES

There are a large variety of alcoholic beverages.

A. Malted liquors Obtained by fermentation of germinating cereals; are undistilled—alcohol content is low (3–6%) e.g. Beers, Stout. Now strong beers (upto 10%) are also available.

B. Wines Produced by fermentation of natural sugars as present in grapes and other fruits. These are also undistilled.

Light wines Claret, Cider; alcohol content 9–12%, cannot exceed 15%.

Fortified wines Port, Sherry (alcohol 16–22%): distilled beverages are added from outside.

Effervescent wines Champagne (12–16% alcohol): bottled before fermentation is complete.

Wines are called 'dry' when all sugar present has been fermented and 'sweet' when some is left.

C. Spirits These are distilled after fermentation; e.g. Rum, Gin, Whiskey, Brandy, Vodka, etc. Though the alcohol content of these can vary from 40–55%, in India (and almost internationally) for all licenced brands it is standardized to 42.8% v/v or 37% w/w.

The taste, flavour and value of alcoholic beverages depends not only on alcohol content but on the presence of higher ethers, higher alcohols, aldehydes, esters, polymers, and volatile oils; many of these are formed during 'maturation' of the beverage.

Other forms of alcohol

1. *Absolute alcohol* 99% w/w ethanol (dehydrated alcohol).
2. *Rectified spirit* 90% w/w ethyl alcohol produced from fermented mollases, by distillation.
3. *Proof spirit* It is an old term. If whiskey is poured on gun powder and ignited and it explodes, then it was labelled to be of 'proof strength'. If water is mixed to it, gun powder will not ignite. 100% proof spirit is 49.29% w/w or 57.1% v/v alcohol.
4. *Methylated spirit (industrial)* Also called 'denatured spirit' is produced by adding 5 parts of wood naphtha (methyl alcohol) to 95 parts of rectified spirit so as to render it unfit for drinking. It is tinted blue by methylene blue dye for distinction. It can be applied on the skin for antiseptic, cleaning and astringent purposes.

PHARMACOLOGICAL ACTIONS

1. Local actions Ethanol is a mild rubefacient and counterirritant when rubbed on the skin. By evaporation it produces cooling. Applied to delicate skin (scrotum) or mucous membranes it produces irritation and burning sensation. Concentrated alcohol (spirit) should not be applied in the mouth, nose, etc. Injected s.c. it causes intense pain, inflammation and necrosis followed by fibrosis. Injected around a nerve it produces permanent damage.

Applied to the surface, alcohol is an astringent—precipitates surface proteins and hardens the skin. By precipitating bacterial proteins it acts as an antiseptic. The antiseptic

action increases with concentration from 20 to 70%, remains constant from 70 to 90% and decreases above that. That 100% ethanol is more dehydrating but poorer antiseptic than 90% ethanol, shows that antibacterial action is not due to dehydration of bacterial protoplasm. Alcohol does not kill bacterial spores.

2. CNS Alcohol is a neuronal depressant. Since the highest areas are most easily deranged and these are primarily inhibitory—apparent excitation and euphoria are experienced at lower plasma concentrations (30–60 mg/dl). Hesitation, caution, self-criticism and restraint are lost first. Mood and feelings are altered; anxiety may be allayed. With increasing concentration (80–150 mg/dl) mental clouding, disorganization of thought, impairment of attention, memory and other faculties, alteration of gait and perception and drowsiness supervene. At 150–200 mg/dl the person is sloppy, ataxic and drunk, 'blackouts' occur; 200–300 mg/dl result in stupor and above this unconsciousness prevails, medullary centres are paralysed and death may occur. Though, alcohol can produce anaesthesia, margin of safety is narrow.

Any measurable concentration of alcohol produces a measurable slowing of reflexes: driving is dangerous. Performance is impaired, fine discrimination and precise movements are obliterated; errors increase, except if fear of punishment and anxiety of failure has already impaired it. Under such situation performance may be improved by allaying of anxiety and fear.

At any given blood alcohol level, central effects are more marked when the concentration is rising than when it is falling. This is considered to be a manifestation of acute tolerance.

Alcohol can induce sleep but is not a dependable hypnotic. Some individuals report poor quality of sleep and repeated or early morning awakening. Sleep architecture may be disorganized and sleep apnoea aggravated. 'Hangover' (headache, dry mouth, laziness, disturbed mood, impaired performance) may occur the next morning. Alcohol raises pain threshold and also alters reaction to it, but is not a dependable analgesic—severe pain can precipitate confusion and convulsions. During the time alcohol is acting on brain, it exerts anticonvulsant action, but this is followed by lowering of threshold: seizures may be precipitated in epileptics. Chronic alcohol abuse damages brain neurones, causes shrinkage of brain.

The cortex and the reticular activating system are most sensitive to alcohol; other areas get depressed as concentration rises.

Mechanism of action Alcohol was believed to produce CNS depression by a generalized membrane action altering the state of membrane lipids. However, lately specific effect on multiple receptor operated and voltage gated ion channels/other critical proteins has been demonstrated at concentrations attained during moderate drinking. Thus, several neurohumoral systems are concurrently affected producing a complex pattern of action quite different from that produced by other depressants like barbiturates and benzodiazepines, which predominantly facilitate $GABA_A$ receptor mediated Cl^- channel opening. Alcohol has been shown to enhance GABA release at $GABA_A$ sites in the brain. It also inhibits NMDA and kainate type of excitatory amino acid receptors (operating through cation channels). Action of 5-HT on $5\text{-}HT_3$ inhibitory autoreceptor (having an intrinsic ion channel) is augmented. Some studies suggest that cerebral nicotinic cholinergic receptor (operating through Na^+ channel) may also be one of the targets of alcohol action. Ethanol can indirectly reduce neurotransmitter release by inhibiting voltage sensitive neuronal Ca^{2+} channels. It also activates specific type of K^+ channels in certain brain areas. Release and turnover of DA in brain is enhanced through β endorphin release in nucleus accumbens and an opioid receptor dependent mechanism. This is probably important in the pleasurable reinforcing effects of alcohol and in the genesis of alcohol dependence. Activity of membrane bound enzymes like Na^+ K^+ ATPase and adenylyl cyclase is also altered. The activity and translocation of channel/enzyme proteins in the membrane could be affected by alcohol through protein kinase C (PKC) and protein kinase A (PKA) mediated alteration in the state of their phosphorylation.

Alcohol : conscious → anaesthesia → death.

Ether : conscious → anaesthesia → death.

3. CVS The effects are dependent on dose.

Small doses: produce only cutaneous (especially on the face) and gastric vasodilatation. Skin is warm and flushed and there may be conjunctival injection; BP is not affected.

Moderate doses: cause tachycardia and a mild rise in BP due to increased muscular activity and sympathetic stimulation.

Large doses: cause direct myocardial as well as vasomotor centre depression and there is fall in BP.

Epidemiological studies have confirmed that chronic alcoholism contributes to hypertension and can lead to cardiomyopathy. Atrial fibrillation and other cardiac arrhythmias may occur due to conduction defects and Q-T prolongation.

4. Blood Regular intake of small to moderate amounts of alcohol (1–2 drinks) has been found to raise HDL-cholesterol levels and decrease LDL oxidation. This may be responsible for the 15–35% lower incidence of coronary artery disease in such individuals. Risk reduction is greatest in high risk subjects and protection is lost if ≥ 3 drinks are consumed daily. However, it is considered inapproptiate to advise nondrinkers to start drinking on this account, since other adverse consequences may more than nullify this benefit. Mild anaemia is common in chronic alcoholics. Megaloblastic anaemia occurring in chronic alcoholism is due to interference with folate metabolism.

5. Body temperature Alcohol is reputed to combat cold. It does produce a sense of warmth due to cutaneous and gastric vasodilatation, but heat loss is actually increased in cold surroundings. High doses depress temperature regulating centre.

6. Respiration Brandy or whiskey are reputed as respiratory stimulants in collapse. They irritate buccal and pharyngeal mucosa which may transiently stimulate respiration reflexly. However, it is better not to depend on this, because the direct action of alcohol on respiratory centre is only a depressant one.

7. GIT Alcoholic beverages have variable effect on gastric secretion depending on the beverage itself and whether the individual likes it. However, dilute alcohol (optimum 10%) put in the stomach by Ryle's tube is a strong stimulant of gastric secretion (especially of acid). It acts directly as well as reflexly. Higher concentrations (above 20%) inhibit gastric secretion, cause vomiting, mucosal congestion and gastritis. Alcoholism is an important cause of chronic gastritis. Lower esophageal sphincter (LES) tone is reduced by alcohol. Drinking may accentuate gastric reflux. Bowel movements may be altered in either direction. Acute pancreatitis is a complication of heavy drinking.

8. Liver Neither brief alcohol intoxication nor chronic intake of small-to-moderate amounts cause significant liver damage, provided adequate nutrition is maintained. However, it does mobilize peripheral fat and increases fat synthesis in liver in a dose-dependent manner. Proteins may also accumulate in liver because their secretion is decreased. Chronic alcoholism exposes liver to oxidative stress and causes cellular necrosis followed by fibrosis. Acetaldehyde produced during metabolism of alcohol appears to damage the hepatocytes and induce inflammation, especially on chronic ingestion of large amounts. Increased lipid peroxidation and glutathione depletion occurs. These combined with vitamin and other nutritional deficiencies may be responsible for the so called *alcoholic cirrhosis*.

Regular alcohol intake induces microsomal enzymes.

9. Skeletal muscle Alcohol produces little direct effect. Fatigue is allayed by small doses, but muscle work is increased or decreased depending on the predominating central effect. Weakness and myopathy occurs in chronic alcoholism.

10. Kidney Diuresis is often noticed after alcohol intake. This is due to water ingested along with drinks as well as alcohol induced inhibition of ADH secretion. It does not impair renal function.

11. Sex Alcohol is reputed as an aphrodisiac. Aggressive sexual behaviour is due to loss of restraint and inhibition. However, performance of the sexual act is often impaired. Chronic alcoholism can produce impotence, testicular atrophy, gynaecomastia and infertility in both men and women.

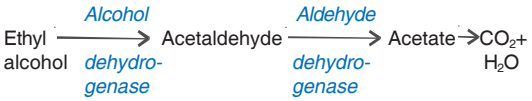
12. Endocrine effects Moderate amounts of alcohol increase Adr release which can cause hyperglycaemia and other sympathetic effects. However, acute intoxication is often associated with hypoglycaemia and depletion of hepatic glycogen, because gluconeogenesis is inhibited. Glucagon, thus fails to reverse it and glucose must be given to counteract hypoglycaemia.

13. Uterine contractions are suppressed at moderate blood levels.

PHARMACOKINETICS

Rate of alcohol absorption from the stomach is dependent on its concentration, presence of food, and other factors, but is generally quite slow. Absorption from intestines is very fast; peak levels are attained after ~30 min. Thus, gastric emptying determines rate of absorption. Limited first pass metabolism occurs in stomach and liver. Absorption of alcohol from skin of adults is minimal but may be significant in infants given alcohol sponges.

Alcohol gets distributed widely in the body (vol of distribution 0.7 L/kg), crosses blood brain barrier efficiently: concentration in brain is very near blood concentration. It also crosses placenta freely. Alcohol is oxidized in liver to the extent of 98%. Even with high doses, not more than 10% escapes metabolism.



In addition to alcohol dehydrogenase, small amounts of alcohol are oxidized by hepatic microsomal enzymes (mainly CYP2E1) as well. Metabolism of alcohol follows *zero order* kinetics, i.e. a constant amount (8–12 ml of absolute alcohol/ hour) is degraded in unit time, irrespective of blood concentration. Thus, rate of consuming drinks governs whether a person will get drunk.

Excretion of alcohol occurs through kidney and lungs, but neither is quantitatively significant. Concentration in exhaled air is about 0.05% of blood concentration: this is utilized for medico-legal determination of drunken state. The subject blows in a balloon and alcohol is measured by portable breath analyser.

INTERACTIONS

1. Alcohol synergises with anxiolytics, antidepressants, antihistaminics, hypnotics, opioids → marked CNS depression with motor impairment can occur: Chances of accidents increase.
2. Individuals taking a sulfonylurea, cefoperazone, or metronidazole have experienced bizarre, somewhat disulfiram-like reactions when they consume alcohol. This reaction occurs only in some individuals and its basis is unclear. It passes off with time as alcohol is metabolized. Only reassurance and supportive treatment is needed.
3. Acute alcohol ingestion inhibits, while chronic intake induces CYP enzymes (especially CYP2E1). Formation of toxic metabolite of paracetamol (NAPQI) is increased in chronic alcoholics (*see* p. 207). Safe dose limit of paracetamol is lower in them. Metabolism of tolbutamide, phenytoin and some other drugs is similarly affected by acute and chronic alcohol intake.
4. Hypoglycaemic action of insulin and sulfonylureas is enhanced by alcohol ingestion.
5. Aspirin and other NSAIDs cause more gastric bleeding when taken with alcohol.

Food value

Alcohol requires no digestion and is metabolized rapidly. It is an energy yielding substrate: 7 Cal/g, but these cannot be stored. However, it spares carbohydrates and fats as energy source, so that regular intake can contribute to obesity.

Alcohol does not supply body building and other essential constituents of food. Those who consume substantial part of their caloric intake as alcohol, often suffer from nutritional deficiencies. Thus, alcohol is an imperfect and expensive food.

CONTRAINDICATIONS

Alcohol is seldom prescribed medically. However, it is rampently consumed. Intake of alcohol should be avoided by—

1. Peptic ulcer, hyperacidity and gastroesophageal reflux patients (alcohol increases gastric secretion and relaxes LES).
2. Epileptics: seizures may be precipitated.
3. Severe liver disease patients.
4. Unstable personalities: they are likely to abuse it and become excessive drinkers.
5. Pregnant women: Even moderate drinking during pregnancy can produce *foetal alcohol syndrome* resulting in intrauterine and postnatal growth retardation, low IQ, microcephaly, cranio-facial and other abnormalities, and immunological impairment→increased susceptibility to infections. Heavy drinking during pregnancy, in addition, increases the incidence of miscarriage, stillbirths and low birth-weight babies.

Guidelines for safe drinking Physicians are often asked to advise on safe ways of drinking. Various official agencies, physician organizations and alcoholism experts have putforth guidelines in this regard, but they are not uniform. The following may be concluded:

- On an average 1–2 drinks per day is usually safe.
- Not more than 3 drinks on any one occasion.
- Consumption of >3 drinks per day is associated with documented adverse health effects.
- Do not drive or engage in hazardous activities after drinking.
- Do not drink if an interacting drug has been taken.
- Subjects with any contraindication should not drink.
- Safe limits are somewhat lower for women than for men, because metabolism of alcohol is slower and its bioavailability higher (due to less first pass metabolism in stomach) in women than in men.

[Note: 1 drink = 50 ml of spirits = 150 ml of wines = 400 ml of beer; all have roughly 16 g alcohol, which taken in empty stomach produces a peak alcohol blood level of ~ 30 mg/dl in an adult male of average built.]

TOXICITY

A. *Side effects of moderate drinking* Nausea, vomiting, flushing, hangover, traffic accidents.

B. *Acute alcoholic intoxication* Unawareness, unresponsiveness, stupor, hypotension, gastritis, hypoglycaemia, respiratory depression, collapse, coma and death.

Treatment: Gastric lavage is helpful only when the patient is brought soon after ingesting alcohol, which is rare. Since most patients are disoriented or comatose, the first priority is to maintain patent airway and prevent aspiration of vomitus. Tracheal intubation and positive pressure respiration may be needed if it is markedly depressed. Analeptics should not be given. They may precipitate convulsions. Most patients will recover with supportive treatment, maintenance of fluid and electrolyte balance and correction of hypoglycaemia by glucose infusion till alcohol is metabolized. Thiamine (100 mg in 500 ml glucose solution infused i.v.) should be added. Recovery can be hastened by haemodialysis. Insulin + fructose drip has been found to accelerate alcohol metabolism. However, its clinical impact is not remarkable.

C. *Chronic alcoholism* On chronic intake, tolerance develops to subjective and behavioral effects of alcohol, but is generally of a low degree. It is both pharmacokinetic (reduced rate of absorption due to gastritis and faster metabolism due to enzyme induction) and cellular tolerance. Psychic dependence often occurs even with moderate drinking; depends a lot on

individual's likings and attitudes. It is manifested in alcohol-seeking behaviour, and the priority that the subject accords to obtaining and consuming alcohol over other needs, or the extent to which he will go for maintaining alcohol intake.

Recent studies have confirmed that a genetic basis contributes to progression from social drinking to alcoholism in about 50% individuals. Alcoholism is often a familial trait. Some differences in sensitivity of various neuronal systems to alcohol among 'predisposed' and 'not predisposed' individuals have been demonstrated.

There is no single explanation for why people drink. Diverse feelings and behaviours are provoked by alcohol in different individuals and in the same individual on different occasions. Alcohol can make people happy as well as sad, curtious as well as mean, talkative as well as silent, friendly as well as hostile. All this cannot be explained on the basis of pharmacological actions of alcohol alone. Attitudes, beliefs, peer groups, social setting and learned experiences all have a bearing. Alcohol is said to produce good mood, sense of wellbeing, self confidence, sociability, etc. But these infact are learned behaviours. In some societies, alcoholic beverages have become an acceptable form of extending courtesy and of entertainment. Drinking is often related to 'celebration' and 'high living'. There is 'wine snobbery' in high social groups.

To some, excess drinking provides the excitement of risk taking. People often boast of their capacity to drink. To the young, drinking may be a symbol of rebellion against the oppressive older generation and rejection of the values of the establishment. 'Binge drinking' is a specific behavioural pattern of bouts of excessive drinking. Alcohol is often an excuse for bad behaviour. Society's view that intoxicated person is unaware of his actions (therefore not responsible) makes intoxication an attractive state, because there is increased freedom of what one can say or do after drinking. Thus, there are a variety of motivations for drinking.

Physical dependence occurs only on heavy and round-the-clock drinking (if alcohol is present in the body continuously). Heavy drinking is often associated with nutritional deficiencies, because food is neglected and malabsorption may occur. In addition to impaired mental and physical performance, neurological afflictions are common—polyneuritis, pellagra, tremors, seizures, loss of brain mass, Wernicke's encephalopathy, Korsakoff's psychosis and megaloblastic anaemia. Alcoholic cirrhosis of liver, hypertension, cardiomyopathy, CHF, arrhythmias, stroke, acute pancreatitis, impotence, gynaecomastia, infertility and skeletal myopathy are other complications. Incidence of oropharyngeal, esophageal and hepatic malignancy and respiratory infections is high; immune function is depressed.

Withdrawal syndrome When a physically dependent subject stops drinking, withdrawal syndrome appears within a day. Its severity depends on the duration and quantity of alcohol consumed by the subject. It consists of anxiety, sweating, techycardia, tremor, impairment of sleep, confusion, hallucinations, delirium tremens, convulsions and collapse.

Treatment Psychological and medical supportive measures are needed during withdrawal. Many CNS depressants like barbiturates, phenothiazines, chloral hydrate have been used as substitution therapy in the past (to suppress withdrawal syndrome) but benzodiazepines (chordiazepoxide, diazepam) are the preferred drugs now. These have a long duration of action and can be gradually withdrawn later.

Naltrexone: Several studies have demonstrated involvement of opioid system in the pleasurable reinforcing effects of alcohol through dopamine mediated reward function. The post-addict treated with the long-acting opioid antagonist naltrexone (*see* Ch. 34) does not experience the same pleasurable effect on taking alcohol; reinforcement is weakened. Trials have shown that it helps prevent relapse of alcoholism. It reduced alcohol craving, number of drinking days and chances of resumed heavy drinking. Naltrexone is approved for use as adjuvant in comprehensive treatment programmes for alcohol dependent subjects and is being used in India at most deaddiction centres, after the individual has undergone withdrawal and is motivated.

Acamprosate It is a weak NMDA-receptor antagonist with modest $GABA_A$ receptor agonistic activity that is being used in USA, UK and Europe for maintenance therapy of alcohol abstinence. In conjunction with social and motivational therapy, it has been found to reduce relapse of the drinking behaviour. The efficacy of acamprosate in this regard is rated comparable to naltrexone. It should be started soon after withdrawing alcohol and then given continuously at a dose

of 666 mg 2–3 times a day. Loose motion is a common side effect. Others are nausea, abdominal pain and itching.

The 5-HT_3 antagonist *ondansetron* and the antiepileptic *topiramate* have also shown some promise in treating alcoholism.

CLINICAL USES

Medicinal uses of ethanol are primarily restricted to external application and as a vehicle for liquid preparations used internally.

1. As antiseptic (*see* Ch. 65).
2. Rubefacient and counterirritant for sprains, joint pains, etc. Spirit is generally used as vehicle for other ingredients.
3. Rubbed into the skin to prevent bedsores. It should not be applied on already formed sores. Astringent action of alcohol is utilized in antiperspirant and aftershave lotions.
4. Alcoholic sponges to reduce body temperature in fever. However, cold water/ice may be better.
5. Intractable neuralgias (trigeminal and others), severe cancer pain. Injection of alcohol round the nerve causes permanent loss of transmission.
6. To ward off cold. Alcohol in the form of whiskey or brandy may benefit by causing vasodilatation of blanched mucosae; but further exposure after taking alcohol may be deleterious because alcohol increases heat loss due to cutaneous vasodilatation.
7. As appetite stimulant and carminative: 30–50 ml of 7–10% alcohol may be taken as beverages or tinctures (of ginger/cardemom, etc.) before meal.
8. Reflex stimulation in fainting/hysteria: 1 drop in nose.
9. To treat methanol poisoning (*see* below).

Aldehyde dehydrogenase inhibitor

Disulfiram It inhibits the enzyme aldehyde dehydrogenase (Fig. 28.1) probably after conversion into active metabolites. When alcohol is ingested after taking disulfiram, the concentration of acetaldehyde in tissues and blood rises and a number of highly distressing symptoms (aldehyde syndrome) are produced promptly. These are—flushing, burning sensation, throbbing headache, perspiration, uneasiness, tightness in chest, dizziness, vomiting, visual disturbances, mental confusion, postural fainting and circulatory collapse. Duration of the syndrome (1–4 hours) depends on the amount of alcohol consumed. Because of risk of severe reaction, disulfiram is to be used with great caution, only in well-motivated subjects.

Disulfiram aversion therapy is indicated in abstinent subjects who sincerely desire to leave the habit. After making sure that the subject has not taken alcohol in the past 12 hours, disufiram is given at a dose of 500 mg/day for one week followed by 250 mg daily. Sensitization to alcohol develops after 2–3 hours of first dose, reaches its peak at ~12 hours and lasts for 7–14 days after stopping it, because inhibition of aldehyde dehydrogenase with disulfiram is irreversible: synthesis of fresh enzyme is required for return of activity. The subject's resolve not to drink is reinforced by the distressing symptoms that occur if he drinks a little bit. The subject should be cautioned to avoid alcohol altogether. Disulfiram should not be used in patients who are physically dependent on alcohol.

Side effects of disulfiram (as such) are infrequent, include rashes, metallic taste, nervousness, malaise and abdominal upset. It inhibits a number of other enzymes as well including alcohol dehydrogenase, dopamine β hydroxylase and several cytochrome P450 isoenzymes. Thus, it prolongs t½ of many drugs.

ESPERAL, ANTADICT, DEADICT 250 mg tab. (internationally marketed as ANTABUSE)

METHYL ALCOHOL (Methanol, Wood alcohol)

Methyl alcohol is added to industrial rectified spirit to render it unfit for drinking. It is only of toxicological importance. Mixing of methylated spirit with alcoholic beverages by bootlegers or its inadvertent ingestion results in methanol poisoning.

Methanol is metabolized to formaldehyde and formic acid by alcohol and aldehyde dehydro-

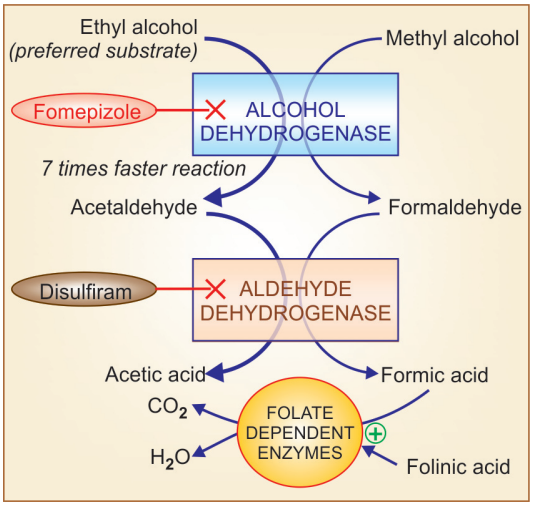


Fig. 28.1: Shared metabolic pathway of ethyl and methyl alcohols

genases respectively (Fig. 28.1), but the rate is 1/7th that of ethanol. Like ethanol, metabolism of methanol also follows *zero order* kinetics and t½ of 20–60 hours has been measured.

Methanol also is a CNS depressant, but less inebriating than ethanol. Toxic effects of methanol are largely due to formic acid, since its further metabolism is slow and folate dependent. A blood level of >50 mg/dl methanol is associated with severe poisoning. Even 15 ml of methanol has caused blindness and 30 ml has caused death; fatal dose is regarded to be 75–100 ml.

Manifestations of methanol poisoning are vomiting, headache, epigastric pain, uneasiness, drunkenness, disorientation, tachypnoea, dyspnoea, bradycardia and hypotension. Delirium and seizures may occur and the patient may suddenly pass into coma. *Acidosis* is prominent and entirely due to production of formic acid. The specific toxicity of formic acid is *retinal damage*. Blurring of vision, congestion of optic disc followed by blindness always precede death which is due to respiratory failure.

Treatment

1. Keep the patient in a quiet, dark room; protect the eyes from light.
2. Gastric lavage with sod. bicarbonate if the patient is brought within 2 hours of ingesting methanol. Supportive measures to maintain ventilation and BP should be instituted.
3. Combat acidosis by i.v. *Sod. bicarbonate* infusion. This is the most important measure; prevents retinal damage and other symptoms; large quantities may be needed.
4. Pot. chloride infusion is needed only when hypokalemia occurs due to alkali therapy.
5. *Ethanol* is preferentially metabolized by alcohol dehydrogenase over methanol. At a concentration of 100 mg/dl in blood it saturates alcohol dehydrogenase and retards methanol metabolism. This helps by reducing the rate of generation of formaldehyde and formic acid. Ethanol (10% in water) is administered through a nasogastric tube; loading dose of 0.7 ml/kg is followed by 0.15 ml/kg/hour. Because pharmacokinetics of alcohol changes over time and no i.v. formulation is available, maintenance of a fixed concentration is difficult. Alcohol blood level needs to be repeatedly measured. Moreover, the enzyme saturating concentration of ethanol itself produces intoxication and can cause hypoglycaemia. Use of ethanol for this purpose is tricky. Treatment has to be continued for several days because the sojourn of methanol in body is long.
6. Haemodialysis: clears methanol as well as formate and hastens recovery.
7. *Fomepizole* (4-methylpyrazole) is a specific inhibitor of alcohol dehydrogenase and the drug of choice for methanol poisoning by retarding its metabolism. A loading dose of 15 mg/kg i.v. followed by 10 mg/kg every 12 hours till serum methanol falls below 20 mg/dl, has been found effective and safe. It has several advantages over ethanol, *viz.* longer t½ and lack of inebriating action, but is not available commercially in India.
8. Folate therapy: Calcium leucovorin 50 mg injected 6 hourly has been shown to reduce blood formate levels by enhancing its oxidation. This is a promising adjuvant approach.

Ethylene glycol poisoning Ethylene glycol poisoning has occurred sporadically, especially among children. It is an industrial solvent, coolant and antifreeze. Ethylene glycol is oxidized in the body by alcohol dehydrogenase to glycoaldehyde and then to glycolic acid—glyoxylic acid—oxalic acid in steps. Ethylene glycol itself can cause intoxication similar to ethanol, but generation of metabolites results in acidosis, cardiopulmonary complications and renal tubular necrosis.

Fomepizole used in the same manner as for methanol poisoning is the drug of choice. It is approved by US-FDA for this indication and has 'orphan drug status'. Ethanol is employed as an alternative.

☞ PROBLEM DIRECTED STUDY

28.1 A school boy aged 16 years developed tonic-clonic epilepsy and was maintained on carbamazepine 200 mg 3 times a day. He was seizure free for the last one year, but reported back one afternoon with the complaint of recurrence of two seizure episodes since morning. On questioning, he revealed that last evening he attended a party with his friends and consumed 4 drinks of whiskey, and was awake till late night. This was the first time that he had taken an alcoholic drink.

(a) Could the recurrence of seizures be related to the intake of alcohol previous night? If so, what could be the mechanism?

(b) Does his antiepileptic therapy need any change or adjustment of doses due to this recurrence of seizures. What further advise will you give to this patient?

(see Appendix-1 for solution)

Chapter 29 Sedative-Hypnotics

Sedative A drug that subdues excitement and calms the subject without inducing sleep, though drowsiness may be produced. Sedation refers to decreased responsiveness to any level of stimulation; is associated with some decrease in motor activity and ideation.

Hypnotic A drug that induces and/or maintains sleep, similar to normal arousable sleep. This is not to be confused with 'hypnosis' meaning a trans-like state in which the subject becomes passive and highly suggestible.

The sedatives and hypnotics are more or less global CNS depressants with somewhat differing time-action and dose-action relationships. Those with quicker onset, shorter duration and steeper dose-response curves are preferred as *hypnotics* while more slowly acting drugs with flatter dose-response curves are employed as *sedatives*. However, there is considerable overlap; a hypnotic at lower dose may act as sedative. Thus, sedation—hypnosis—general anaesthesia may be regarded as increasing grades of CNS depression. Hypnotics given in high doses can produce general anaesthesia. However, benzodiazepines (BZDs) cannot be considered nonselective or global CNS depressants like barbiturates and others.

Treatment of insomnia is the most important use of this class of drugs.

Alcohol and opium have been the oldest hypnotics and continue to be used for this purpose as self-medication by people. Bromides introduced in 1857 are now obsolete, so are chloral hydrate (1869) and paraldehyde (1882). Fischer and von Mering introduced barbitone in 1903 and phenobarbitone in 1912. Barbiturates reigned supreme till 1960s when benzodiazepines started eroding their position and have now totally replaced them. In the mean time, a number of other sedative-hypnotics (glutethimide, methyprilon, methaqualone) were introduced but none was significantly different from barbiturates; all are redundant now. Some non-BZD hypnotics have become available over the past two decades, and a novel melatonin receptor agonist ramelteon has been introduced.

Sleep

The duration and pattern of sleep varies considerably among individuals. Age has an important effect on quantity and depth of sleep. It has been recognized that sleep is an architectured cyclic process (Fig. 29.1). The different phases of sleep and their characteristics are—

Stage 0 (awake) From lying down to falling asleep and occasional nocturnal awakenings; constitutes 1–2% of sleep time. EEG shows α activity when eyes are closed and β activity when eyes are open. Eye movements are irregular or slowly rolling.

Stage 1 (dozing) α activity is interspersed with θ waves. Eye movements are reduced but there may be bursts of rolling. Neck muscles relax. Occupies 3–6% of sleep time.

Stage 2 (unequivocal sleep) θ waves with interspersed spindles, K complexes can be evoked on sensory stimulation; little eye movement; subjects are easily arousable. This comprises 40–50% of sleep time.

Stage 3 (deep sleep transition) EEG shows θ, δ and spindle activity, K complexes can be evoked with strong stimuli only. Eye movements are few; subjects are not easily arousable; comprises 5–8% of sleep time.

Stage 4 (cerebral sleep) δ activity predominates in EEG, K complexes cannot be evoked. Eyes are practically fixed; subjects are difficult to arouse. Night terror may occur at this time. It comprises 10–20% of sleep time.

During stage 2, 3 and 4 heart rate, BP and respiration are steady and muscles are relaxed. Stages 3 and 4 together are called slow wave sleep (SWS).

REM sleep (paradoxical sleep) EEG has waves of all frequency, K complexes cannot be elicited. There are marked, irregular and darting eye movements; dreams and nightmares

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The EEG waves have been divided into—
α: high amplitude, 8–14 c.p.s. (cycles per second)
β: low amplitude, 15–35 c.p.s.
θ: low amplitude, 4–7 c.p.s.
δ: high amplitude, 0.5–3 c.p.s.
K complex: deep negative wave followed by positive wave and a few spindles.

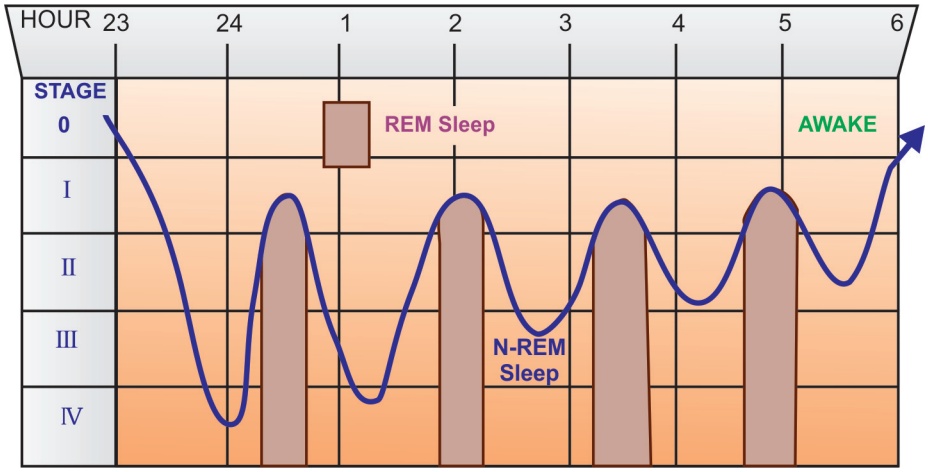


Fig. 29.1: A normal sleep cycle

occur, which may be recalled if the subject is aroused. Heart rate and BP fluctuate; respiration is irregular. Muscles are fully relaxed, but irregular body movements occur occasionally. Erection occurs in males. About 20–30% of sleep time is spent in REM.

Normally stages 0 to 4 and REM occur in succession over a period of 80–100 min. Then stages 1–4–REM are repeated cyclically.

CLASSIFICATION

1. *Barbiturates*

Long acting	*Short acting*	*Ultra-short acting*
Phenobarbitone	Butobarbitone	Thiopentone
	Pentobarbitone	Methohexitone

2. *Benzodiazepines*

Hypnotic	*Antianxiety*	*Anticonvulsant*
Diazepam	Diazepam	Diazepam
Flurazepam	Chlordiazepoxide	Lorazepam
Nitrazepam	Oxazepam	Clonazepam
Alprazolam	Lorazepam	Clobazam
Temazepam	Alprazolam	
Triazolam		

3. *Newer nonbenzodiazepine hypnotics*

Zopiclone Zolpidem Zaleplon

Chloral hydrate, Triclophos, Paraldehyde, Glutethimide, Methyprylon, Methaqualone and Meprobamate are historical sedative-hypnotics no longer used. They are described in earlier editions of this book.

In addition some antihistaminics (promethazine, diphenhydramine), some neuroleptic/antidepressants (chlorpromazine, amitriptyline), some anticholinergic (hyoscine) and opioids (morphine, pethidine) have significant sedative action, but are not reliable for treatment of insomnia.

BARBITURATES

Barbiturates have been popular hypnotics and sedatives of the last century upto 1960s, but are not used now to promote sleep or to calm patients. However, they are described first because they are the prototype of CNS depressants.

Barbiturates are substituted derivatives of barbituric acid (malonyl urea). Barbituric acid as such is not a hypnotic but compounds with alkyl or aryl substitution on C5 are. Replacement of O with S at C2 yields *thiobarbiturates* which are more lipid-soluble and more potent. Barbiturates have variable lipid solubility, the more soluble ones are more potent and shorter acting. They are insoluble in water but their sodium salts dissolve yielding highly alkaline solution.

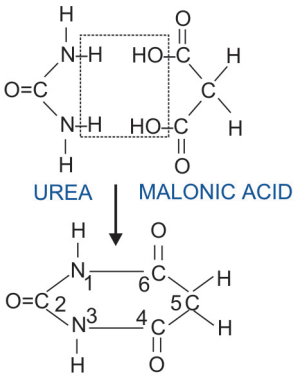
PHARMACOLOGICAL ACTIONS

Barbiturates are general depressants for all excitable cells, the CNS is most sensitive where the effect is almost global, but certain areas are more susceptible.

1. CNS Barbiturates produce dose-dependent effects:

sedation → sleep → anaesthesia → coma.

Hypnotic dose shortens the time taken to fall asleep and increases sleep duration. The sleep is arousable, but the subject may feel confused and unsteady if waken early. Night awakenings are reduced. REM and stage 3, 4 sleep are decreased; REM-NREM sleep cycle is disrupted. The effects on sleep become progressively less marked if the drug is taken every night consecutively. A rebound increase in REM sleep and nightmares is often noted when the drug is discontinued after a few nights of use and it takes several nights for normal pattern to be restored (Fig. 29.2). Hangover (dizziness, distortions of mood, irritability and lethargy) may occur in the morning after a nightly dose.



Condensation of malonic acid and urea to produce barbituric acid

Sedative dose (smaller dose of a longer acting barbiturate) given at daytime can produce drowsiness, reduction in anxiety and excitability. However, they do not have selective antianxiety action. Barbiturates can impair learning, short-term memory and judgement. They have no analgesic action; small doses may even cause hyperalgesia. Euphoria may be experienced by addicts.

Barbiturates have anticonvulsant property. The 5-phenyl substituted compounds (phenobarbitone) have higher anticonvulsant : sedative ratio, i.e. they have specific anticonvulsant action independent of general CNS depression.

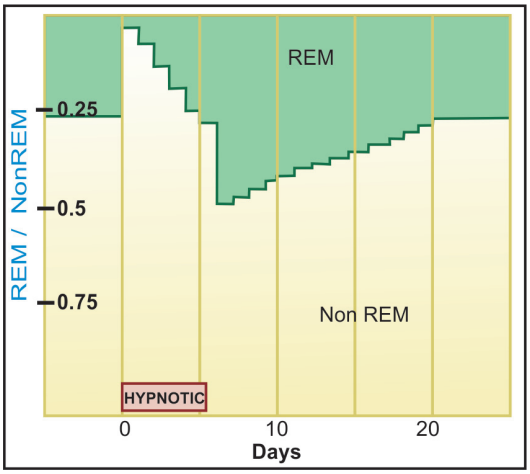


Fig. 29.2: Effect of hypnotic use for 6 consecutive nights on the ratio of REM / Non-REM sleep duration

Higher dose of a barbiturate induces a predominance of slow, high voltage EEG activity. Progressive burst suppression occurs if dose is increased further. Barbiturates depress all areas of the CNS, but reticular activating system is the most sensitive; its depression is primarily responsible for inability to maintain wakefulness.

Mechanism of action Barbiturates appear to act primarily at the GABA : BZD receptor–Cl^- channel complex (*see* Fig. 29.3) and potentiate GABAergic inhibition by increasing the lifetime of Cl^- channel opening induced by GABA (contrast BZDs which enhance frequency of Cl^- channel opening). They do not bind to the BZD receptor, but bind to another site on the same macromolecular complex to exert the GABA-facilitatory action. The barbiturate site appears to be located on α or β subunit, because presence of only these subunits is sufficient for their response. Presence of γ subunit is not necessary as is the case with BZDs. They also enhance BZD binding to its receptor. At high concentrations, barbiturates directly increase Cl^- conductance (GABA-mimetic action; contrast BZDs which have only GABA-facilitatory action) and inhibit Ca^{2+} dependent release of neurotransmitters. In addition they depress glutamate induced neuronal depolarization through AMPA

receptors (a type of excitatory amino acid receptors). At very high concentrations, barbiturates depress voltage sensitive Na^+ and K^+ channels as well. A dose-dependent effect on multiple neuronal targets appears to confer the ability to produce any grade of CNS depression.

2. Other systems

Respiration is depressed by relatively higher doses. Neurogenic, hypercapneic and hypoxic drives to respiratory centre are depressed in succession. Barbiturates donot have selective antitussive action.

CVS Hypnotic doses of barbiturates produce a slight decrease in BP and heart rate. Toxic doses produce marked fall in BP due to vasomotor centre depression, ganglionic blockade and direct decrease in cardiac contractility. Reflex tachycardia can occur, though pressor reflexes are depressed. However, the dose producing cardiac arrest is about 3 times larger than that causing respiratory failure.

Skeletal muscle Hypnotic doses have little effect but anaesthetic doses reduce muscle contraction by action on neuromuscular junction.

Smooth muscles Tone and motility of bowel is decreased slightly by hypnotic doses; more profoundly during intoxication. Action on bronchial, ureteric, vesical and uterine muscles is not significant.

Kidney Barbiturates tend to reduce urine flow by decreasing BP and increasing ADH release. Oliguria attends barbiturate intoxication.

PHARMACOKINETICS

Barbiturates are well absorbed from the g.i. tract. They are widely distributed in the body. The rate of entry into CNS is dependent on lipid solubility. Highly-lipid soluble thiopentone has practically instantaneous entry, while less lipid-soluble ones (pentobarbitone) take longer; phenobarbitone enters very slowly. Plasma protein binding varies with the compound, e.g. thiopentone 75%, phenobarbitone 20%. Barbiturates cross placenta and are secreted in milk; can produce effects on the foetus and suckling infant.

Three processes are involved in termination of action of barbiturates: the relative importance of each varies with the compound.

(a) *Redistribution* It is important in the case of highly lipid-soluble thiopentone. After i.v. injection, consciousness is regained in 6–10 min due to redistribution (*see* Ch. 2) while the ultimate disposal occurs by metabolism (t½ of elimination phase is 9 hours).

(b) *Metabolism* Drugs with intermediate lipid-solubility (short-acting barbiturates) are primarily metabolized in liver by oxidation, dealkylation and conjugation. Their plasma t½ ranges from 12–40 hours.

(c) *Excretion* Barbiturates with low lipid-solubility (long-acting agents) are significantly excreted unchanged in urine. The t½ of phenobarbitone is 80–120 hours. Alkalinization of urine increases ionization and excretion. This is most significant in the case of long-acting agents.

Barbiturates induce several hepatic microsomal enzymes and increase the rate of their own metabolism as well as that of many other drugs.

USES

Except for phenobarbitone in epilepsy (Ch. 30) and thiopentone in anaesthesia (Ch. 27) no other barbiturate is used now. As hypnotic and anxiolytic they have been superseded by BZDs. They are occasionally employed as adjuvants in psychosomatic disorders.

Phenobarbitone 30–60 mg oral OD–TDS; 100–200 mg i.m./i.v.
GARDENAL 30, 60 mg tab, 20 mg/5 ml syr; LUMINAL 30 mg tab; PHENOBARBITONE SOD 200 mg /ml inj.

ADVERSE EFFECTS

Side effects Hangover was common after the use of barbiturates as hypnotic. On repeated use they accumulate in the body—produce tolerance and dependence. Mental confusion, impaired performance and traffic accidents may occur (also *see* Ch. 30).

Idiosyncrasy In an occasional patient barbiturates produce excitement. This is more common in the elderly.
Precipitation of porphyria in susceptible individuals is another idiosyncratic reaction.

Hypersensitivity Rashes, swelling of eyelids, lips, etc.—more common in atopic individuals.

Tolerance and dependence Both cellular and pharmacokinetic (due to enzyme induction) tolerance develops on repeated use. However, fatal dose is not markedly increased: addicts may present with acute barbiturate intoxication. There is partial cross tolerance with other CNS depressants.

Psychological as well as physical dependence occurs and barbiturates have considerable abuse liability. This is one of the major disadvantages. Withdrawal symptoms are—excitement, hallucinations, delirium, convulsions; deaths have occurred.

Acute barbiturate poisoning Mostly suicidal, sometimes accidental. It is infrequently encountered now due to inavailability of barbiturates. However, the principles of treatment apply to any CNS depressant poisoning.

Manifestations are due to excessive CNS depression—patient is flabby and comatose with shallow and failing respiration, fall in BP and cardiovascular collapse, renal shut down, pulmonary complications, bullous eruptions.

Lethal dose depends on lipid solubility. It is 2–3 g for the more lipid-soluble agents (short-acting barbiturates) and 5–10 g for less lipid-soluble phenobarbitone.

Treatment

1. Gastric lavage; leave a suspension of activated charcoal in the stomach to prevent absorption of the drug from intestines.
2. Supportive measures: such as, patent airway, assisted respiration, oxygen, maintenance of blood volume by fluid infusion and use of vasopressors—dopamine may be preferred for its renal vasodilating action.
3. Alkaline diuresis: with sodium bicarbonate 1 mEq/kg i.v. with or without mannitol is helpful only in the case of long-acting barbiturates which are eliminated primarily by renal excretion.
4. Haemodialysis and haemoperfusion (through a column of activated charcoal or other adsorbants) is highly effective in removing long-acting as well as short-acting barbiturates.

There is no specific antidote for barbiturates. In the past, analeptics like metrazol, bemegride, etc. have been used in an attempt to awaken the patient. This is dangerous, may precipitate convulsions while the patient is still comatose—mortality is increased. The emphasis now is on keeping the patient alive till the poison has been eliminated.

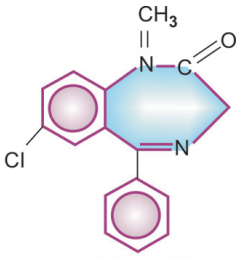
Interactions

1. Barbiturates induce several CYP isoenzymes, including glucuronyl transferase, and increase the metabolism of many drugs and reduce their effectiveness—warfarin, steroids (including contraceptives), tolbutamide, griseofulvin, chloramphenicol, theophylline.
2. Additive action with other CNS depressants—alcohol, antihistamines, opioids, etc.
3. Sodium valproate increases plasma concentration of phenobarbitone.
4. Phenobarbitone competitively inhibits as well as induces phenytoin and imipramine metabolism: complex interaction.
5. Phenobarbitone decreases absorption of griseofulvin from the g.i.t.

BENZODIAZEPINES (BZDs)

Chlordiazepoxide and diazepam were introduced around 1960 as antianxiety drugs. Since then this class has proliferated and has replaced barbiturates as hypnotic and sedative as well, because—

1. BZDs produce a lower degree of neuronal depression than barbiturates. They have a high therapeutic index. Ingestion of even 20 hypnotic doses does not usually endanger life—there is no loss of consciousness (though amnesia occurs) and patient can be aroused; respiration is mostly not so depressed as to need assistance.



DIAZEPAM

2. Hypnotic doses do not affect respiration or cardiovascular functions. Higher doses produce mild respiratory depression and hypotension which is problematic only in patients with respiratory insufficiency or cardiac/haemodynamic abnormality.
3. BZDs have practically no action on other body systems. Only on i.v. injection the BP falls (may be marked in an occasional patient) and cardiac contractility decreases. Fall in BP in case of diazepam and lorazepam is due to reduction in cardiac output while that due to midazolam is due to decrease in peripheral resistance. The coronary arteries dilate on i.v. injection of diazepam.
4. BZDs cause less distortion of sleep architecture; rebound phenomena on discontinuation of regular use are less marked.
5. BZDs do not alter disposition of other drugs by microsomal enzyme induction.
6. They have lower abuse liability: tolerance is mild, psychological and physical dependence, drug seeking and withdrawal syndrome are less marked.
7. A specific BZD antagonist *flumazenil* is available which can be used in case of poisoning.

CNS actions The overall action of all BZDs is qualitatively similar, but there are prominent differences in selectivity for different facets of action, and in their time-course of action. Different members are used for different purposes. In contrast to barbiturates, they are not general depressants, but exert relatively selective anxiolytic, hypnotic, muscle relaxant and anticonvulsant effects in different measures. Even when apparently anaesthetic dose of diazepam is administered i.v., some degree of awareness is maintained, though because of anterograde amnesia (interference with establishment of memory trace) the patient does not clearly recollect the events on recovery.

Antianxiety: Some BZDs exert relatively selective antianxiety action (*see* Ch. 33) which is probably not dependent on their sedative property. With chronic administration relief of anxiety is maintained, but drowsiness wanes off due to development of tolerance.

Sleep: While there are significant differences among different BZDs, in general, they hasten onset of sleep, reduce intermittent awakening and increase total sleep time (specially in those who have a short sleep span). Time spent in stage 2 is increased while that in stage 3 and 4 is decreased. They tend to shorten REM phase, but more REM cycles may occur, so that effect on total REM sleep is less marked than with barbiturates. Nitrazepam has been shown to actually increase REM sleep. Night terrors and body movements during sleep are reduced and stage shifts to stage 1 and 0 are lessened. Most subjects wake up with a feeling of refreshing sleep. Some degree of tolerance develops to the sleep promoting action of BZDs after repeated nightly use.

Muscle relaxant: BZDs produce centrally mediated skeletal muscle relaxation without impairing voluntary activity (*see* Ch. 25). Clonazepam and diazepam have more marked muscle relaxant property. Very high doses depress neuromuscular transmission.

Anticonvulsant: Clonazepam, diazepam, nitrazepam, lorazepam and flurazepam have more prominent anticonvulsant activity than other BZDs. Diazepan and lorazepam are highly effective for short-term use in status-epilepticus, but their utility in long-term treatment of epilepsy is limited by development of tolerance to the anticonvulsant action.

Given i.v., diazepam (but not others) causes analgesia. In contrast to barbiturates, BZDs do not produce hyperalgesia.

Other actions Diazepam decreases nocturnal gastric secretion and prevents stress ulcers. BZDs do not significantly affect bowel movement.

Short-lasting coronary dilatation is produced by i.v. diazepam.

Site and mechanism of action

Benzodiazepines act preferentially on midbrain ascending reticular formation (which maintains wakefulness) and on limbic system (thought and mental functions). Muscle relaxation is produced by a primary medullary site of action and ataxia is due to action on cerebellum.

BZDs act by enhancing presynaptic/postsynaptic inhibition through a specific BZD receptor which is an integral part of the $GABA_A$ receptor–Cl^- channel complex. The subunits of this complex form a pentameric transmembrane anion channel (Fig. 29.3) gated by the primary ligand (GABA), and modulated by secondary ligands which include BZDs. Only the α and β subunits are required for GABA action, and most likely the binding site for GABA is located on the β subunit, while the α/γ subunit interface carrys the BZD binding site. The modulatory BZD receptor increases the frequency of Cl^- channel opening induced by submaximal concentrations of GABA. The BZDs also enhance GABA binding to $GABA_A$ receptor. The $GABA_A$ antagonist bicuculline antagonizes BZD action in a noncompetitive manner. It is noteworthy that the BZDs do not themselves increase Cl^- conductance; have only GABA

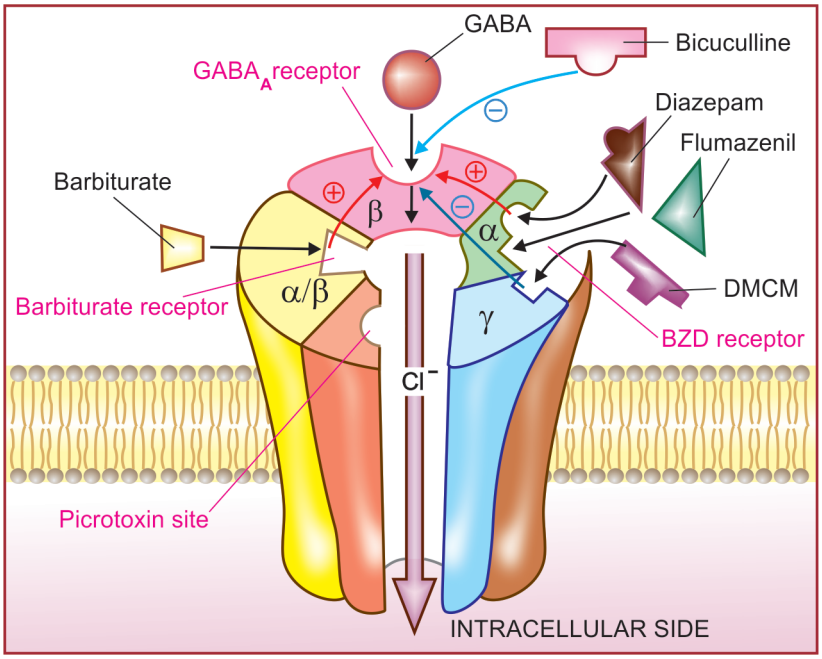


Fig. 29.3: Schematic depiction of $GABA_A$-benzodiazepine receptor-chloride channel complex
The chloride channel is gated by the primary ligand GABA acting on $GABA_A$ receptor located on the β subunit. The benzodiazepine (BZD) receptor located on the interface of α and γ subunits modulates $GABA_A$ receptor in either direction: agonists like diazepam facilitate, while inverse agonists like DMCM hinder GABA mediated Cl^- channel opening, and BZD antagonist flumazenil blocks the action of both. The barbiturate receptor, located either on α or β subunit also facilitates GABA and is capable of opening Cl^- channel directly as well. Bicuculline blocks $GABA_A$ receptor, while picrotoxin blocks the Cl^- channel directly

facilitatory but no GABA mimetic action. This probably explains the lower ceiling CNS depressant effect of BZDs.

The BZD receptor exhibits a considerable degree of constitutive activation. As such, it is capable of fine tuning GABA action in either direction. While the BZD-agonists enhance GABA induced hyperpolarization (due to influx of Cl^- ions), and decrease firing rate of neurones, other compounds called *BZD-inverse agonists* like dimethoxyethyl-carbomethoxy-β-carboline (DMCM) inhibit GABA action and are convulsants. The competitive BZD-antagonist flumazenil blocks the sedative action of BZDs as well as the convulsant action of DMCM.

The $GABA_A$-BZD receptor-Cl^- channel complex is composed of five α, β, γ, and in some cases δ, ε, θ or π subunits as well. Several isoforms of α, β and γ subunits have been cloned. The subunit composition of the complex differs at different sites, i.e. there are multiple subtypes of BZD receptor. The ($\alpha_1 2\ \beta_2\ 2\ \gamma_2$) pentamer appears to be the most commonly expressed BZD receptor isoform.

Based on studies conducted in genetically mutated mice, it has been suggested that BZD receptor isoforms containing the α_1 subunit are involved in mediating sedative, hypnotic, and amnesic actions of BZDs, while those containing α_2 subunits mediate anxiolytic and muscle relaxant actions. Diazepam has similar affinity for BZD receptor containing different (α_1 or α_2, or α_3 or α_5) subunits, and has broad spectrum action. Receptor inhomogeneity may provide an explanation for the pharmacological diversity of other BZDs. The newer non-BZD hypnotics zaleplon, Zolpidem, etc. have high affinity for α_1 subunit isoform of BZD receptor and exert selective hypnotic-amnesic effect, but have little antiseizure or muscle relaxant property.

At high concentrations BZDs also potentiate the depressant action of adenosine by blocking its uptake. Certain actions of BZDs are countered by the adenosine antagonist theophylline. Thus, BZDs could be acting through other mechanisms as well.

Drugs affecting $GABA_A$-receptor gated chloride channel		
• GABA	:	Endogenous agonist at $GABA_A$ receptor → promotes Cl^- influx
• Muscimol	:	Agonist at $GABA_A$ site
• Bicuculline	:	Competitive antagonist at $GABA_A$ receptor
• Picrotoxin	:	Blocks Cl^- channel noncompetitively; acts on picrotoxin sensitive site
• Barbiturates	:	Agonist at an allosteric site; prolong GABA action; and open Cl^- channel
• Alcohol, Inhalational anaesthetics, Propofol	:	Open Cl^- channel directly; allosteric facilitation of GABA
• Benzodiazepines	:	Agonist at an allosteric BZD site → facilitate GABA action
• β-Carboline (DMCM)	:	Inverse agonist at BZD site → impede GABA action
• Flumazenil	:	Competitive antagonist at BZD site

PHARMACOKINETICS

There are marked pharmacokinetic differences among BZDs because they differ in lipid-solubility by > 50 fold. These differences are important factors governing their choice for different uses. Oral absorption of some is rapid while that of others is slow. Absorption from i.m. sites is irregular except for lorazepam. Plasma protein binding also varies markedly (flurazepam 10% to diazepam 99%). BZDs are widely distributed in the body. The more lipid soluble members enter brain rapidly and have a two phase plasma concentration decay curve; first due to distribution to other tissues and later due to elimination. A relatively short duration of action is obtained with single dose of a drug that is rapidly redistributed, even though it may have a long elimination t½. Using the elimination t½ alone to predict duration of action may be misleading. However, elimination t½ determines duration of action in case of drugs whose elimination is by far the dominant feature or when the drug is given repeatedly.

Benzodiazepines are metabolized in liver mainly by CYP3A4 and CYP2C19 to dealkylated and hydroxylated metabolites, some of which may be active. The biological effect half-life of these drugs may be much longer than the plasma t½ of the administered compound. The phase I metabolites and certain BZDs themselves are conjugated with glucuronic acid. Some BZDs (e.g. diazepam) undergo enterohepatic circulation. BZDs and their phase I metabolites are excreted in urine as glucuronide conjugates. BZDs cross placenta and are secreted in milk.

Drugs with a long t½ or those which generate active metabolites cumulate on nightly use; their action may then extend into the next day. Some features of BZDs used as hypnotic are given in Table 29.1.

BZDs may be categorized according to their pharmacokinetic profile into:

I. *Slow elimination of parent drug or active metabolite*

Flurazepam Produces an active metabolite which has a long t½. Residual effects are likely next morning; cumulation occurs on daily ingestion peaking after 3–5 days. It is suitable for patients who have frequent nocturnal awakenings and in whom some day time sedation is acceptable.

NINDRAL, FLURAZ 15 mg cap.

II. *Relatively slow elimination but marked redistribution*

Diazepam It is the oldest and all purpose BZD, used as anxiolytic, hypnotic, muscle

TABLE 29.1 Some pharmacokinetic and clinical features of benzodiazepines used as hypnotics

Drug	t½ (hr)*	Redistribution$	Hypnotic dose (mg)	Clinical indications
I. LONG ACTING				
Flurazepam	50–100	–	15–30	Chronic insomnia, short-term insomnia with anxiety; Frequent nocturnal awakening; Night before operation
Diazepam	30–60	+	5–10	
Nitrazepam	30	±	5–10	
II. SHORT ACTING				
Alprazolam	12	+	0.25–0.5	Individuals who react unfavourably to unfamiliar surroundings or unusual timings of sleep. Sleep onset difficulties.
Temazepam	8–12	+	10–20	
Triazolam	2–3	±	0.125–0.25	

* t½ of elimination phase, including that of active metabolite
$ + indicates that redistribution contributes to termination of action of single dose

relaxant, premedicant, anaesthetic and for emergency control of seizures due to its broad spectrum activity. It generates active metabolites (desmethyl-diazepam, oxazepam). On occasional use it is free of residual effects. With regular use accumulation occurs and prolonged anxiolytic effect may be obtained. It is less likely to cause rebound insomnia on discontinuation of chronic use. Withdrawal phenomena are mild. VALIUM 2, 5, 10 mg tab., 10 mg/2 ml inj., CALMPOSE 2.5, 5, 10 mg tab, 2 mg/5 ml syr, 10 mg/2 ml inj, PLACIDOX 2, 5, 10 mg tab, 10 mg/2 ml inj.

Nitrazepam Dose to dose equipotent as diazepam. Accumulation and residual effects can be avoided only if ingestion is occasional. Good for patients with frequent nocturnal awakenings, when some day time sedation is acceptable. SEDAMON, HYPNOTEX, NITRAVET 5 mg tab., 5, 10 mg cap.

III. *Relatively rapid elimination and marked redistribution*

Alprazolam The primary indication of this potent and intermediate acting BZD is anxiety disorder (*see* Ch. 33), but it is also being employed as night-time hypnotic with few residual effects the next day. Discontinuation after regular use has produced relatively marked withdrawal phenomena.

Temazepam It is an intermediate acting BZD. Absorption is slow in case of tablet but fast when used in soft gelatin capsule. Good for sleep onset difficulty, free of residual effects. Accumulation can occur on daily ingestion. Does not produce active metabolites.

IV. *Ultrarapid elimination*

Triazolam Very potent, peak effect occurs in < 1 hour; good for sleep induction but poor for maintaining it. Patient may wake up early in the morning and feel anxious. This may be a withdrawal phenomenon. Rebound insomnia may occur when it is discontinued after a few nights of use. It does not accumulate on repeated nightly use and no residual effects are noted in the morning. However, higher doses can alter sleep architecture, produce anterograde amnesia and anxiety the following day. Some cases of paranoia and other psychiatric disturbances have been noted. For this reason, it has been withdrawn from U.K., but is employed in other countries for elderly patients, shift workers, travellers, etc.

Midazolam Extremely rapid absorption—peak in 20 min. It can cause problems in the elderly (ataxia, blackouts); more liable for abuse. Therefore, it is not available now for oral use as a hypnotic. It is mainly used as an i.m. premedicant or an i.v. anaesthetic (*see* p. 383).

ADVERSE EFFECTS

Benzodiazepines are relatively safe drugs. Side effects of hypnotic doses are dizziness, vertigo, ataxia, disorientation, amnesia, prolongation of reaction time—impairment of psychomotor skills (should not drive). Hangover is less common, but may be noted if larger doses are used, especially of longer acting drugs. Weakness, blurring of vision, dry mouth and urinary incontinence are sometimes complained. Older individuals are more susceptible to

psychomotor side effects. Like any hypnotic, BZDs can aggravate sleep apnoea.

Paradoxical stimulation, irritability and sweating may occur in an occasional patient, especially with flurazepam. Some patients experience increase in nightmares and behavioural alterations, especially with flurazepam and nitrazepam.

Tolerance to the sedative effects develops gradually, but there is little tendency to increase the dose. Cross tolerance to alcohol and other CNS depressants occurs.

The dependence producing liability of BZDs is low. They are weak reinforcers (less pleasurable) and seldom abused alone. Drug abusers find them rather bland and prefer other CNS depressants. Withdrawal syndrome is generally mild; may be more intense in case of ultrarapid elimination drugs. Anxiety, insomnia, restlessness, malaise, loss of appetite, bad dreams is all that occurs in most cases. Agitation, panic reaction, tremors and delirium are occasional; convulsions are rare. Drug seeking behaviour is not prominent.

An earlier report of increased birth defects on use of diazepam during pregnancy has been disputed. Administration during labour may cause flaccidity and respiratory depression in the neonate.

INTERACTIONS

BZDs synergise with alcohol and other CNS depressants leading to excessive impairment. Concurrent use with sod. valproate has provoked psychotic symptoms.

Drug interactions due to displacement from protein binding or microsomal enzyme induction are not significant.

Since CYP 3A4 isoenzyme plays important role in metabolism of several BZDs, their action can be prolonged by CYP 3A4 inhibitors like ketoconazole, erythromycin and others. Cimetidine, isoniazid and oral contraceptives also retard BZD metabolism.

NON-BENZODIAZEPINE HYPNOTICS

This lately developed group of hypnotics are chemically different from BZDs, but act as agonists on a specific subset of BZD receptors. Their action is competitively antagonized by the BZD antagonist flumazenil, which can be used to treat their overdose toxicity. The non-BZD hypnotics act selectively on α_1 subunit containing BZD receptors and produce hypnotic-amnesic action with only weak antianxiety, muscle relaxant and anticonvulsant effects. They have lower abuse potential than hypnotic BZDs. Given their shorter duration of action, they are being preferred over BZDs for the treatment of insomnia.

Zopiclone This is the first of the non-BZD hypnotics, which acts as an agonist at a subtype of BZD receptor involved in the hypnotic action. The effect on sleep resemble those of BZDs, but it does not alter REM sleep and tends to prolong stages 3 and 4. It is reported not to disturb sleep architecture, but some degree of next morning impairment can occur. Zopiclone has been used to wean off insomniacs taking regular BZD medication. Its t½ is 5–6 hours.

Zopiclone is indicated for short term (< 2 weeks) treatment of insomnia. Side effects are metallic or bitter after-taste, impaired judgement and alertness, psychological disturbances, dry mouth and milder dependence. Safety in overdose is similar to BZDs.

ZOPITRAN, ZOPICON, ZOLIUM, 7.5 mg tab, one tab at bedtime for not more than 2–4 weeks (elderly 3.75 mg).

Eszopiclone The active (S) enantiomer of zopiclone has recently been approved. It produces little tolerance and physical dependence, and is considered suitable for treatment of short-term as well as chronic insomnia.

Zolpidem This structurally non-BZD, but selective BZD receptor agonist has pronounced hypnotic effect. Sleep latency is shortened, sleep duration is prolonged in insomniacs, but anticonvulsant, muscle relaxant and antianxiety effects are not evident. Its advantages are: relative lack of effect on sleep stages (REM suppression is slight); minimal residual day time sedation

or fading of hypnotic action on repeated nightly use; no/little rebound insomnia on discontinuation; near absence of tolerance and low abuse potential combined with safety in overdose like BZDs.

Zolpidem is nearly completely metabolized in liver (t½ 2 hr), and has short duration of action. It is indicated for short-term (1–2 weeks) use in sleep onset insomnia as well as for intermittent awakenings. Because the plasma t½ is short, next day sedation is minimal, but morning sedation or prolongation of reaction-time can occur if it is taken late at night. Side effects are few. Even large doses do not markedly depress respiration. Currently, it is one of the most commonly prescribed hypnotics.
Dose: 5–10 mg (max 20 mg) at bedtime; ½ dose in elderly and liver disease patients.
NITREST, ZOLDEM, DEM 5, 10 mg tabs.

Zaleplon This is the shortest acting of the newer non-BZD hypnotics that selectively act on a subset of BZD receptors containing the α_1 subunit which appear to mediate the hypnotic action. It is rapidly absorbed; oral bioavailability is ~30% due to first pass metabolism; is rapidly cleared by hepatic metabolism with a t½ of 1 hour. No active metabolite is produced. As such it is effective only in sleep-onset insomnia; does not prolong total sleep time or reduce the number of awakenings. Because of brevity of action, it can be taken late at night (> 4 hour before waking time) without causing morning sedation. Surprisingly, despite very short action, no daytime anxiety or rebound insomnia has been observed, and hypnotic effect does not fade on nightly use. However, its use should be limited to 1–2 weeks. The hypnotic efficacy of zaleplon is rated similar to zolpidem. Like the latter, effect on sleep stages and REM sleep are less than that of BZDs. Tolerance and dependence is unusual.
Dose: 5–10 mg (max 20 mg) at bed time.
ZAPLON, ZALEP, ZASO 5, 10 mg tabs.

USES

Currently, BZDs are one of the most frequently prescribed drugs. They have also been combined with many other categories of drugs with a view to improve efficacy by relieving attendant anxiety.

1. As hypnotic A hypnotic should not be casually prescribed for every case of insomnia. Understanding the pattern and cause of insomnia in the specific patient is important, and use of a variety of other measures can avoid unnecessary hypnotic medication. When indicated, BZDs or the newer non-BZDs like zolpidem, zaleplon are the hypnotic of choice. A wide range of compounds have been developed to suit specific requirements. Some important points are outlined below:

- A hypnotic may be used to shorten sleep latency, to reduce nocturnal awakenings, or to provide anxiolytic effect the next day when insomnia is accompanied with marked element of anxiety.
- In the use of hypnotics, consideration must be given to onset and duration of action of the drug. The most suitable pharmacokinetic profile drug should be chosen for a given case.
- Next morning impairment is largely related to the dose and pharmacokinetic profile of the drug. The next day effects are either due to prolonged sedation (longer acting drugs) or rebound anxiety (shorter acting drugs).
- Any hypnotic (probably except zolpidem-like drugs) becomes ineffective after regular use for a few days; may actually be harmful.
- Though effect of the drug on EEG stages of sleep, including REM sleep, could be physiologically relevant, most important is the subject's own assessment of having slept restfully and waking up feeling fresh with no impairment the following day. The subjective impression that quality of sleep was poor is the major criterion of insomnia. This probably correlates more closely with effect of the hypnotic on the *cyclic alternating pattern (CAP)* of sleep.
- Insomnia arises under a variety of circumstances. It could be a long-term (months-years), short-term (weeks) or transient (a day or two, mostly situational) problem.

Chronic insomnia (> 3 weeks) Uncertainty exists about the use of hypnotics in this situation. The patient may have a personality disorder, but often there is no specific stress factor. He may have used hypnotics for long periods or may be alcoholic or have some somatic disease, e.g. gastroesophageal reflux, pain, COPD, etc. which interfere with sleep. Measures like aerobic exercise, training at mental relaxation, avoiding anxiety about past/future performance while in bed, attempting sleep when sleepiness is maximum, avoiding napping at daytime, maintaining regular sleep-wake timings and other sleep-hygiene measures, coffee/alcohol restriction, treatment of concurrent somatic illness, psychotherapy and controlled sleep curtailment may succeed. Good nightly sleep improves the quality of day-time wakefulness. Patients of obstructive sleep apnoea have poor sleep and feel sleepy during the day. All hypnotics aggravate sleep apnoea and are contraindicated.

Intermittent use of a hypnotic, say once every 3 days, may be tried. Risk of tolerance and abuse are maximum among chronic insomniacs. A slowly eliminated drug is preferable because rebound insomnia and withdrawal symptoms are least marked with such drugs.

Short-term insomnia (3–21 days) Emotional problem (occupational stress, bereavement) and physical illness are the usual causes. Patient may have induction difficulty or may be waking up early. Cautious use of low doses of an appropriate drug for the type of sleep disturbance may be made. Generally a hypnotic, free of residual effects should be selected, but when anxiety is a dominant feature, a BZD whose action extends into the next day may be better. Short acting drugs are preferable in the elderly. Intermittent hypnotic use should be limited to 2–3 weeks.

Transient insomnia (1–3 days) Due to alterations in the circumstances of sleep, e.g. unusual noise, on an overnight train, new place, unusual pattern of work, shift workers, intercontinental travel–jetlag, etc. A rapidly eliminated hypnotic or one with marked distribution is to be preferred to avoid residual effects the next morning. However, night before surgery—a long acting drug is better.

2. Other uses

(a) As anxiolytic and for day-time sedation (*see* Ch. 33).
(b) As anticonvulsant, especially emergency control of status epilepticus, febrile convulsions, tetanus, etc. (*see* Ch. 30).
(c) As centrally acting muscle relaxant (*see* Ch. 25).
(d) For preanaesthetic medication, i.v. anaesthesia and conscious sedation (*see* Ch. 27).
(e) Before ECT, electrical cardioversion of arrhythmias, cardiac catheterization, endoscopies, in obstetrics and many minor procedures—diazepam i.v. has gained popularity because of its calming-amnesic-analgesic and muscle relaxant properties and relative safety.
(f) Alcohol withdrawal in dependent subjects.
(g) Along with analgesics, NSAIDs, spasmolytics, antiulcer and as adjuvants to treat 'gas' or nonspecific dyspeptic symptoms.

Fixed dose combinations of sedative/hypnotic/anxiolytic drugs with analgesic-antipyretics has been banned in India.

BENZODIAZEPINE ANTAGONIST

Flumazenil It is a BZD analogue which has little intrinsic activity (practically no effect on normal subjects), but competes with BZD agonists as well as inverse agonists for the BZD receptor and reverses their depressant or stimulant effects respectively.

Flumazenil abolishes the hypnogenic, psychomotor, cognitive and EEG effects of BZDs. At higher doses it has some week BZD agonist-like as well as inverse agonist-like activity in animal models, but these are of no clinical significance.

Flumazenil is absorbed orally; oral bioavailability is ~16%, but it is not used orally. On i.v. injection, action of flumazenil starts in

seconds and lasts for 1–2 hr; elimination t½ is 1 hr, due to rapid metabolism.

Uses

1. *To reverse BZD anaesthesia* Patients anaesthetized/sedated with a BZD wakeup, get oriented and regain motor control within 1 min of an i.v. injection of 0.3–1 mg of flumazenil. Resedation generally occurs within 1 hour (more with diazepam than with midazolam): supplemental doses of flumazenil may be given. This may allow early discharge of patients after diagnostic procedures and facilitates postanaesthetic management.

2. *BZD overdose* Majority of patients of BZD overdose require only supportive measures like patent airway, maintenance of BP, cardiac and renal function (by fluid transfusion, etc.). In addition, flumazenil 0.2 mg/min may be injected i.v. till the patient regains consciousness. Practically all patients intoxicated with a BZD alone respond within 5 min. However, reversal of respiratory depression is incomplete. Flumazenil blocks the hypnotic effect of zolpidem-like non-BZDs as well. In mixed CNS depressant poisoning, whatever sedation is not abolished by 5 mg of flumazenil should be taken to be due to a non-BZD/non-Zolpidem-like depressant. It thus helps in differential diagnosis of such patients.

Adverse effects Flumazenil is safe and well tolerated.

Agitation, discomfort, tearfulness, anxiety, coldness and withdrawal seizures are the occasional side effects.

Melatonin It is the principal hormone of the pineal gland which is secreted at night and has been found to play an important role in entraining (synchronizing) the sleep-wakefulness cycle with the circadian rhythm. Two subtypes of melatonin receptor MT_1 and MT_2 have been identified in the brain. Both are GPCRs and are believed to carry out the function of facilitating sleep onset and fixing its timing in relation to the circadian clock. Though high doses (80 mg) of melatonin administered orally can induce sleep, low doses (2–10 mg) do not depress the CNS, but probably increase the propensity of falling asleep. Started before the flight it has been shown to reduce jet-lag symptoms and to hasten reentrainment with day-night cycle of the new place in intercontinental travellers. Beneficial effects in shift workers and in individuals with delayed sleep phase syndrome have also been reported. Elderly insomniacs have reported subjective improvement in sleep quality. However, melatonin is not a dependable hypnotic; has little effect on latency and duration of sleep, especially in non-elderly insomniacs. A meta-analysis has concluded that it is no more effective than placebo in the short-term for sleep disorders. Though it does not have the disadvantages of conventional hypnotics, its long-term safety is not known. Use may therefore be restricted to treatment of jet-lag, shift workers and elderly insomniacs.

Since melatonin secretion declines with age, it has been argued that melatonin supplementation might retard ageing. Though there is no proof of benefit, melatonin (2–5 mg/day) is being consumed as a health food in USA and some other countries. It has also been tried in cluster headache. In India it is marketed as a remedy for disturbed biorhythms and sleep disorders.

MELOSET 3 mg tab, ZYTONIN, ETERNEX melatonin 3 mg + pyridoxine 10 mg tab; one tab at evening daily.

Ramelteon It is a MT_1 as well as MT_2 melatonin receptor agonist introduced in USA and now approved in India as well, as a new class of hypnotic for sleep onset insomnia, that does not produce the usual BZD-like side effects. Administered in a dose of 8 mg ½ hour before going to bed, it is shown to hasten sleep onset as well as increase sleep duration, without causing next morning sedation or impairment.

In clinical trial on chronic insomnia patients, continuous nightly treatment with ramelteon maintained its effect to shorten sleep latency and was found to be free of rebound phenomena on stoppage. No dependence producing potential has been noted so far. It is rapidly absorbed orally, undergoes extensive first pass metabolism in liver, so that bioavailability is low and elimination t½ is 1–3 hours.

Ramelteon appears to be a promizing novel hypnotic, provided its efficacy is established.

ROZEREM 8 mg tab: 1 tab 1/2 hour before going to bed.

☞ PROBLEM DIRECTED STUDY

29.1 A 70-year-old man consults his family physician for the problem of failing to fall asleep occasionally (3–4 times in a month) for the past few months. He usually sleeps well and has a 6–7 hour sleep duration. However, on certain nights he keeps lying in bed for 2–3 hours before getting sleep. Such episodes are unpredictable, and he cannot relate them to any disturbance, anxiety, worry or physical illness. He has tried relaxing, getting up and walking around or reading, but nothing helps. As a result, next day he feels lethargic, impaired, unable to concentrate and has poor creativity. He requests a sleeping pill that he can take after failing to fall asleep.

(a) Can he be prescribed a hypnotic for occasional use? If so, which drug would be suitable for late night intake without next morning sedation?

(see Appendix-1 for solution)

Chapter 30 Antiepileptic Drugs

Epilepsies These are a group of disorders of the CNS characterized by paroxysmal cerebral dysrhythmia, manifesting as brief episodes (seizures) of loss or disturbance of consciousness, with or without characteristic body movements (convulsions), sensory or psychiatric phenomena. These episodes are unpredictable and their frequency is highly variable. Epilepsy has a focal origin in the brain, manifestations depend on the site of the focus, regions into which the discharges spread and postictal depression of these regions. Recognised from the dawn of history as 'disease of lightening', it was correctly described by JH Jackson little over a century ago. Epilepsies have been classified variously; major types are described below.

I. Generalised seizures

1. *Generalised tonic-clonic seizures* (GTCS, major epilepsy, grand mal): commonest, lasts 1–2 min.
The usual sequence is aura—cry—unconsciousness—tonic spasm of all body muscles—clonic jerking followed by prolonged sleep and depression of all CNS functions.

2. *Absence seizures* (minor epilepsy, petit mal): prevalent in children, lasts about 1/2 min.
Momentary loss of consciousness, patient apparently freezes and stares in one direction, no muscular component or little bilateral jerking. EEG shows characteristic 3 cycles per second spike and wave pattern.

3. *Atonic seizures* (Akinetic epilepsy): Unconsciousness with relaxation of all muscles due to excessive inhibitory discharges. Patient may fall.

4. *Myoclonic seizures* Shock-like momentary contraction of muscles of a limb or the whole body.

5. *Infantile spasms (Hypsarrhythmia)* Seen in infants. Probably not a form of epilepsy. Intermittent muscle spasm and progressive mental deterioration. Diffuse changes in the interseizure EEG are noted.

II. Partial seizures

1. *Simple partial seizures* (SPS, cortical focal epilepsy): lasts 1/2–1 min. Often secondary. Convulsions are confined to a group of muscles or localized sensory disturbance depending on the area of cortex involved in the seizure, without loss of consciousness.

2. *Complex partial seizures* (CPS, temporal lobe epilepsy, psychomotor): attacks of bizarre and confused behaviour and purposeless movements, emotional changes lasting 1–2 min along with impairment of consciousness. An aura often precedes. The seizure focus is located in the temporal lobe.

3. *Simple partial or complex partial seizures secondarily generalized* The partial seizure occurs first and evolves into generalized tonic-clonic seizures with loss of consciousness.

Most of the cases of epilepsy are primary (idiopathic), some may be secondary to trauma/surgery on the head, intracranial tumour, tuberculoma, cysticercosis, cerebral ischaemia, etc. Treatment is symptomatic and the same whether epilepsy is primary or secondary.

Experimental models These models for testing antiepileptic drugs have also shed light on the etiopathogenesis of epilepsy.

1. *Maximal electroshock seizures* Brief high intensity shock is applied to the head of a rodent (just as in ECT): produces tonic flexion—tonic extension—clonic convulsions. The tonic phase (especially extensor) is selectively abolished by drugs effective in GTCS. Activity in this model represents action on spread of seizure discharge.

2. *Pentylenetetrazol (PTZ) clonic seizures* Injection of PTZ in rats or mice produces clonic convulsions which are prevented by drugs effective in myoclonic and absence seizures. Activity in this model represents action on seizure focus itself.

3. *Chronic focal seizures* Produced by application of alumina cream on the motor cortex of monkey.

4. *Kindled seizures* Brief bursts of weak electrical impulses are applied to the brain (especially amygdala) intermittently over days. After-discharges increase progressively and tonic-clonic seizures are produced after 10–15 shocks. With time spontaneous seizures set in, usually after >100 shocks. This indicates that seizures have a self perpetuating and reinforcing effect: more neuronal circuits are facilitated and recruited in the seizure process. Kindling is probably involved in the genesis of clinical epilepsy.

CLASSIFICATION

1.	*Barbiturate*	Phenobarbitone
2.	*Deoxybarbiturate*	Primidone
3.	*Hydantoin*	Phenytoin
		Fosphenytoin
4.	*Iminostilbene*	Carbamazepine
		Oxcarbazepine
5.	*Succinimide*	Ethosuximide
6.	*Aliphatic carboxylic acid*	Valproic acid (sodium valproate)
		Divalproex
7.	*Benzodiazepines*	Clonazepam
		Diazepam
		Lorazepam
		Clobazam
8.	*Phenyltriazine*	Lamotrigine
9.	*Cyclic GABA analogues*	Gabapentin
		Pregabalin
10.	*Newer drugs*	Topiramate
		Zonisamide
		Levetiracetam
		Vigabatrin
		Tiagabine
		Lacosamide

Felbamate, rufinamide and few other newer antiseizure drugs have been introduced in some countries as second line/add-on drugs for refractory partial seizures.

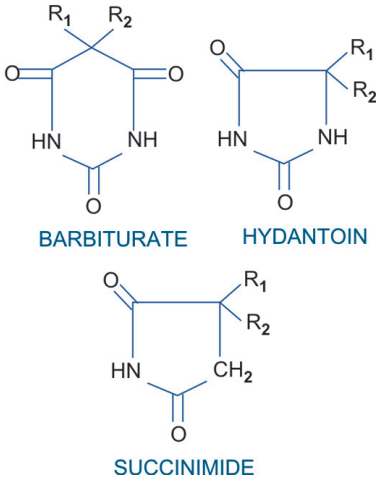


Fig. 30.1: Chemical structures of classical anticonvulsant drugs

Chemistry Most of the older anticonvulsants have close structural similarity. This is depicted in Fig. 30.1. However, benzodiazepines, carbamazepine, valproic acid and the newer drugs are chemically diverse. Presence of a phenyl substitution confers activity against tonic-clonic seizures.

Phenobarbitone (*see* Ch. 29)

Phenobarbitone was the first efficacious antiepileptic introduced in 1912. The mechanism of CNS depressant action of barbiturates is described on p. 399. The same may apply to anticonvulsant action. Enhancement of $GABA_A$ receptor mediated synaptic inhibition appears to be most important mechanism. However, phenobarbitone has specific anticonvulsant activity which is not entirely dependent on general CNS depression. Quantitative differences in the different facets of action (GABA-facilitatory, GABA-mimetic, antiglutamate, Ca^{2+} entry reduction) have been noted for phenobarbitone compared to hypnotic barbiturates. The higher anticonvulsant: hypnotic ratio of phenobarbitone may be due to its minimal effect on Ca^{2+} channels and glutamate release compared to hypnotic barbiturates. With continued use of phenobarbitone sedation wanes off but not anticonvulsant action. It has a wide spectrum of anticonvulsant property—raises seizure threshold as well as limits spread and suppresses kindled seizures.

Phenobarbitone has slow oral absorption and a long plasma t½ (80–120 hours), is metabolized in liver as well as excreted unchanged by kidney. Steady-state concentrations are reached after 2–3 weeks, and a single daily dose can be used for maintenance.

The major drawback of phenobarbitone as an antiepileptic is its sedative action. Long term administration (as needed in epilepsy) may produce additional side effects like—behavioral abnormalities, diminution of intelligence, impairment of learning and memory, hyperactivity in children, mental confusion in older people.

Rashes, megaloblastic anaemia and osteomalacia (similar to that with phenytoin) occur in some patients on prolonged use.

Uses Phenobarbitone is one of the cheapest and least toxic antiepileptics.

It has broad spectrum efficacy in generalized tonic-clonic (GTC), simple partial (SP) and complex partial (CP) seizures in a dose of 60 mg 1–3 times a day in adults; in children (3–5 mg/kg/day); However, it has become less popular than carbamazepine, phenytoin or valproate because of its dulling and behavioural side effects.

Status epilepticus: Phenobarbitone sod. may be injected i.m. or i.v. but response is slow to develop.

It is not effective in absence seizures.

GARDENAL 30, 60 mg tabs, 20 mg/5 ml syr; LUMINAL 30 mg tab, PHENOBARBITONE SODIUM 200 mg/ml inj.

Primidone A deoxybarbiturate, converted by liver to phenobarbitone and phenylethyl malonamide (PEMA). Its antiepileptic activity is mainly due to these active metabolites because t½ of primidone (6–14 hr) is less than that of its active metabolites. About 1/3 primidone is excreted unchanged by kidney. Dose to dose primidone is less potent, but antiepileptic efficacy is similar to phenobarbitone. It is infrequently used now in GTCS and partial epilepsy, mainly as an adjuvant to phenytoin or carbamazepine.

Adverse effects are similar to phenobarbitone. In addition, anaemia, leukopenia, psychotic reaction and lymph node enlargement occur rarely.

Dose: 250–500 mg BD, children 10–20 mg/kg/day.

MYSOLINE 250 mg tab.

Phenytoin (Diphenylhydantoin)

It was synthesized in 1908 as a barbiturate analogue, but shelved due to poor sedative property. Its anticonvulsant activity was specifically tested in 1938 in the newly developed electroshock seizure model and since then it is a major antiepileptic drug.

Phenytoin is not a CNS depressant; some sedation occurs at therapeutic doses, but this does not increase further with dose; rather toxic doses produce excitement and muscular rigidity. The most outstanding action is abolition of tonic phase of maximal electroshock seizures, with no effect on or prolongation of clonic phase. It limits spread of seizure activity. Threshold for PTZ convulsions is not raised. Tonic-clonic epilepsy is suppressed but paroxysmal focal EEG discharge and 'aura' persist.

Mechanism of action Phenytoin has a stabilizing influence on neuronal membrane—prevents repetitive detonation of normal brain cells during '*depolarization shift*' that occurs in epileptic patients and consists of a synchronous and unusually large depolarization over which action potentials are superimposed. This is achieved by prolonging the inactivated state of voltage sensitive neuronal Na^+ channel (Fig. 30.2) that governs the refractory period of the neurone. As a result high frequency discharges are inhibited with little effect on normal low frequency discharges which allow Na^+ channels to recover even when their inactivation is prolonged. This effect has been noted at therapeutic concentration of phenytoin, while other effects like reduction in Ca^{2+} influx, inhibition of glutamate and facilitation of GABA responses have been demonstrated at higher/toxic concentrations. Intracellular accumulation of Na^+ that occurs during repetitive firing is prevented.

Therapeutic concentrations have no effect on resting membrane potential: normal synaptic transmission is not impaired. Phenytoin, in contrast to phenobarbitone and valproate, does not interfere with kindling. Its ability to selectively inhibit high frequency firing confers efficacy in trigeminal neuralgia and cardiac arrhythmias as well.

Pharmacokinetics Absorption of phenytoin by oral route is slow, mainly because of its poor aqueous solubility. Bioavailability of different market preparations may differ. It is widely distributed in the body and is 80–90% bound to plasma proteins.

Phenytoin is metabolized in liver by hydroxylation involving CYP2C9 and 2C19 as well as by glucuronide conjugation. The kinetics of metabolism is *capacity limited*; changes from first order to zero order over the therapeutic

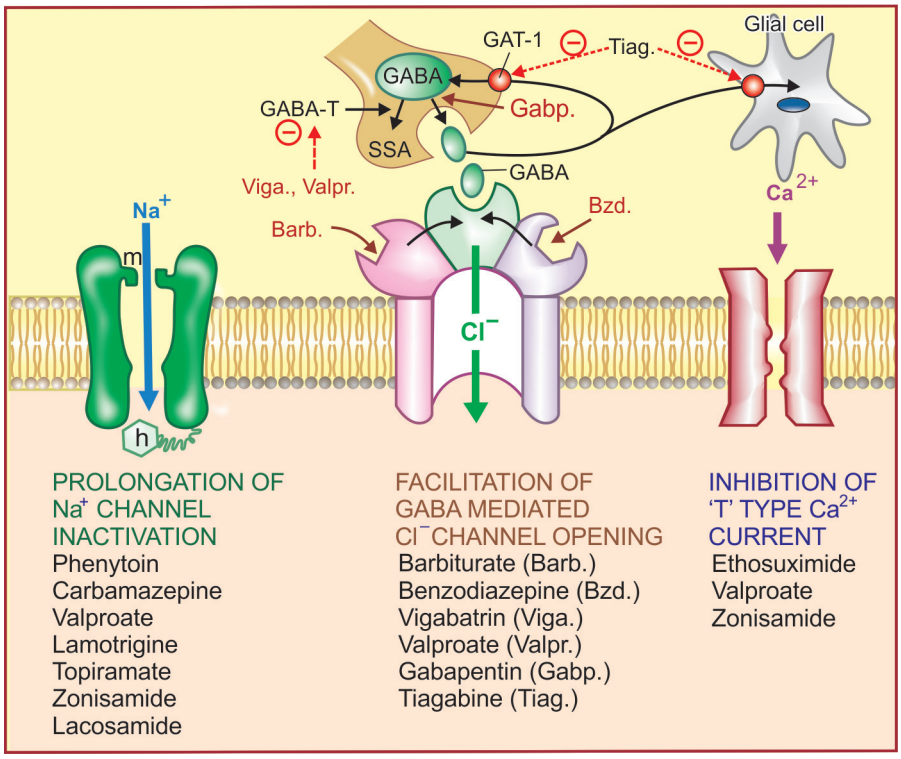


Fig. 30.2: Major mechanisms of anticonvulsant action
m: Activation gate; h: Inactivation gate; GABA-T: GABA transaminase;
SSA: Succinic semialdehyde; GAT-1: GABA transporter

range. As a result small increments in dose produce disproportionately high plasma concentrations. The t½ (12–24 hours at therapeutic levels), progressively increases (upto 60 hr) when plasma concentration rises above 10 µg/ml because metabolizing enzymes get saturated. Monitoring of plasma concentration is very helpful in tailoring dosage. Only 5% unchanged phenytoin is excreted in urine.

Adverse effects After prolonged use numerous side effects are produced at therapeutic plasma concentration; others occur as a manifestation of toxicity due to overdose.

At therapeutic levels

- Gum hypertrophy: Commonest (20% incidence), more in younger patients. It is due to overgrowth of gingival collagen fibres. This can be minimized by maintaining oral hygiene.
- Hirsutism, coarsening of facial features (troublesome in young girls), acne.
- Hypersensitivity reactions are—rashes, DLE, lymphadenopathy; neutropenia is rare but requires discontinuation of therapy.
- Megaloblastic anaemia: Phenytoin decreases folate absorption and increases its excretion.
- Osteomalacia: Phenytoin interferes with metabolic activation of vit D and with calcium absorption/metabolism.
- It can inhibit insulin release and cause hyperglycaemia.
- Used during pregnancy, phenytoin can produce *'foetal hydantoin syndrome'* (hypoplastic phalanges, cleft palate, hare lip, microcephaly), which is probably caused by its areneoxide metabolite.

At high plasma levels (dose related toxicity)

(a) Cerebellar and vestibular manifestations: ataxia, vertigo, diplopia, nystagmus are the most characteristic features.

(b) Drowsiness, behavioral alterations, mental confusion, hallucinations, disorientation and rigidity.

(c) Epigastric pain, nausea and vomiting. These can be minimised by taking the drug with meals.

(d) Intravenous injection can cause local vascular injury → intimal damage and thrombosis of the vein → edema and discolouration of the injected limb. Rate of injection should not exceed 50 mg/min. Tissue necrosis occurs if the solution extravasates.

(e) Fall in BP and cardiac arrhythmias occur only on i.v. injection which, therefore, must be given under continuous ECG monitoring.

Interactions Phenytoin is a potent inducer of CYP2C8/9, CYP3A4/5 and some other CYPs. It competitively inhibits CYP2C9/19.

- Phenobarbitone competitively inhibits phenytoin metabolism, while by enzyme induction both enhance each other's degradation—unpredictable overall interaction.
- Carbamazepine and phenytoin induce each other's metabolism.
- Valproate displaces protein bound phenytoin and decreases its metabolism: plasma level of unbound phenytoin increases.
- Chloramphenicol, isoniazid, cimetidine and warfarin inhibit phenytoin metabolism—can precipitate its toxicity.
- Phenytoin competitively inhibits warfarin metabolism.
- Phenytoin induces microsomal enzymes and increases degradation of steroids (failure of oral contraceptives), doxycycline, theophylline.
- A number of acidic drugs displace it from protein binding sites. However, rise is free phenytoin level enhances its clearance. Thus, concentration of free form does not change much.
- Sucralfate binds phenytoin in g.i. tract and decreases its absorption.

Uses Phenytoin is a first line antiepileptic drug, but less commonly used now because side effects are frequent and marginal overdose causes steep rise in plasma concentration, producing neurotoxicity. Indications are:

1. Generalized tonic-clonic, simple and complex partial seizures. It is ineffective in absence seizures.

Dose: 100 mg BD, maximum 400 mg/day; Children 5–8 mg/kg/day.

2. Status epilepticus: occasionally used by slow i.v. injection (fosphenytoin has replaced it).
3. Trigeminal neuralgia: second choice drug to carbamazepine.

DILANTIN 25 mg, 100 mg cap., 100 mg/4 ml oral suspension, 100 mg/2 ml inj; EPSOLIN 100 mg tab, 100 mg/2 ml inj; EPTOIN 50, 100 mg tab, 25 mg/ml syr; FENTOIN-ER 100 mg extended release cap.

Fosphenytoin This water soluble prodrug of phenytoin has been introduced to overcome the difficulties in i.v. administration of phenytoin, which it has replaced for use in status epilepticus. In the body, it is rapidly converted to phenytoin; its doses are expressed as phenytoin equivalents (PE). On i.v. injection it is less damaging to the intima; only minor vascular complications are produced and it can be injected at a faster rate (150 mg/min), but like phenytoin sod., it requires ECG monitoring. While phenytoin cannot be injected in a drip of glucose solution (because it gets precipitated), fosphenytoin can be injected with both saline and glucose.

FOSOLIN 50 mg/ml in 2 ml, 10 ml inj.

Carbamazepine

Chemically related to imipramine, it was introduced in the 1960s for trigeminal neuralgia. Now it is a first line antiepileptic drug. Its pharmacological actions resemble phenytoin, but important differences have been noted in experimental studies. Carbamazepine modifies maximal electroshock seizures as well as raises threshold to PTZ and electroshock convulsions. It also

inhibits kindling. Though its action on Na^+ channels (prolongation of inactivated state) is similar to phenytoin, the profile of action on neuronal systems in brain is different.

Carbamazepine exerts a lithium-like therapeutic effect in mania and bipolar mood disorder. It also has antidiuretic action, probably by enhancing ADH action on renal tubules.

Pharmacokinetics Oral absorption of carbamazepine is slow and variable because of poor water solubility. It is 75% bound to plasma proteins and metabolized in liver by oxidation to an active metabolite (10-11 epoxy carbamazepine) as well as by hydroxylation and conjugation to inactive ones. It is a substrate as well as inducer of CYP3A4 and CYP2C9. Initially its plasma t½ is 20–40 hours but, decreases to 10–20 hr on chronic medication due to autoinduction of metabolism.

Adverse effects Carbamazepine produces dose-related neurotoxicity—sedation, dizziness, vertigo, diplopia and ataxia. Vomiting, diarrhoea, worsening of seizures are also seen with higher doses. Acute intoxication causes coma, convulsions and cardiovascular collapse.

Hypersensitivity reactions are rashes, photosensitivity, hepatitis, lupus like syndrome, rarely agranulocytosis and aplastic anaemia. Some degree of leucopenia due to hypersensitivity is more common.

Water retention and hyponatremia can occur in the elderly because it enhances ADH action. Increased incidence of minor foetal malformations has been reported. Its combination with valproate doubles teratogenic frequency.

Interactions Carbamazepine is an enzyme inducer; can reduce efficacy of haloperidol, oral contraceptives, lamotrigine, valproate and topiramate. Metabolism of carbamazepine is induced by phenobarbitone, phenytoin, and *vice versa*. Erythromycin, fluoxetine, isoniazid inhibit metabolism of carbamazepine.

Uses Carbamazepine is the most effective drug for CPS and also the most commonly used drug for GTCS and SPS.

Trigeminal and related neuralgias: Carbamazepine is the drug of choice. These neuralgias are characterized by attacks of high intensity electric shock-like or stabbing pain set off by even trivial stimulation of certain trigger zones in the mouth or on the face. Drugs benefit by interrupting temporal summation of afferent impulses (by a selective action on high frequency nerve impulses). Carbamazepine is not an analgesic, but has a specific action (almost diagnostic) in these neuralgias. About 60% patients respond well. Phenytoin, lamotrigine and baclofen are less efficacious alternatives. Gabapentin can be tried in nonresponders.

Carbamazepine is not useful in diabetic, traumatic and other forms of neuropathic pain.

Manic depressive illness and acute mania: as an alternative to lithium (*see* Ch. 32).

Dose: 200–400 mg TDS; Children 15–30 mg/kg/day.
TEGRETOL, MAZETOL 100, 200, 400 mg tab, 100 mg/5 ml syr; CARBATOL 100, 200, 400 mg tab.
MAZETOL SR, TEGRITAL CR 200, 400 mg sustained release/continuous release tabs. to avoid high peaks and low troughs in plasma concentration. These are the preferred formulations.

Oxcarbazepine This newer congener of carbamazepine is rapidly converted to an active metabolite that is only glucuronide conjugated but not oxidized. Toxic effects due to the epoxide metabolite are avoided. Drug interactions and autoinduction of own metabolism are less marked, because it is a weak enzyme inducer. Risk of hepatotoxicity is estimated to be lower than carbamazepine; but that of hyponatraemia is more. Indications are the same as for carbamazepine, but it may be better tolerated. Dose to dose it is 1½ times less potent.
OXETOL, OXCARB, OXEP 150, 300, 600 mg tabs.

Ethosuximide

The most prominent action of ethosuximide is antagonism of PTZ induced clonic seizures at doses which produce no other discernable action. It raises seizure threshold but does not modify maximal electroshock seizures or inhibit kindling. Clinically it is effective only in absence seizures.

The primary action appears to be exerted on thalamocortical system which is involved in the generation of absence seizures. The EEG in absence seizures shows characteristic bilaterally synchronous 3 Hz spike and wave rhythm generated by reciprocal activation and oscillation of impulses between thalamus and neocortex through reverberatory synaptic connections. Thalamic neurones exhibit prominent 'T' (transient) current which is low threshold Ca^{2+} current (due to inward flow of Ca^{2+} through T type Ca^{2+} channels) that acts as the pacemaker and amplifies repetitive spikes. Ethosuximide selectively suppresses T current without affecting other types of Ca^{2+} or Na^{+} currents. It also does not potentiate GABA at therapeutic concentrations. This correlates well with its selective action in absence seizures.

Ethosuximide is rather slowly but completely absorbed, not protein bound, evenly distributed in body, and largely metabolized in liver by hydroxylation and glucuronidation, and excreted in urine—about ¼th in the unchanged form. Plasma t½ averages 48 hours in adults and 32 hours in children.

Adverse effects Dose-related side effects are gastrointestinal intolerance, tiredness, mood changes, agitation, headache, drowsiness and inability to concentrate.
Hypersensitivity reactions like rashes, DLE and blood dyscrasias are rare. No liver or kidney damage.

Use The only indication for ethosuximide is absence seizures; in that also it has been superseded by valproate.
Dose: 20–30 mg/kg/day; ZARONTIN 250 mg/5 ml syr.

Valproic acid (Sodium valproate)

It is a branched chain aliphatic carboxylic acid with a broad spectrum anticonvulsant action. It is more potent in blocking PTZ seizures than in modifying maximal electroshock. Establishment of chronic experimental seizure foci and kindling are also prevented. Remarkably, at anticonvulsant doses, valproate produces little sedation or other central effects. Likewise, it is effective in partial seizures and GTCS as well as absence seizures.
Valproate appears to act by multiple mechanisms:
(i) A phenytoin-like frequency-dependent prolongation of Na^{+} channel inactivation.
(ii) Weak attenuation of Ca^{2+} mediated 'T' current (ethosuximide like).
(iii) Augmentation of release of inhibitory transmitter GABA by inhibiting its degradation (by GABA-transaminase) as well as probably by increasing its synthesis from glutamic acid. However, responses to exogenously applied GABA are not altered.

Pharmacokinetics Oral absorption of valproic acid is good. It is 90% bound to plasma proteins; completely metabolized in liver by oxidation mainly by CYP2C9 and 2C19 (some metabolites are active) and glucuronide conjugation, and then excreted in urine. Plasma t½ is 10–15 hours; but anticonvulsant effects are longer lasting.

Adverse effects The toxicity of valproate is relatively low.
Anorexia, vomiting, loose motions and heart burn are common but mild. Drowsiness, ataxia and tremor are dose-related side effects. However, cognitive and behavioral effects are not prominent.
Alopecia, curling of hair, weight gain and increased bleeding tendency have been observed.
Rashes and thrombocytopenia are infrequent hypersensitivity phenomena.
Asymptomatic rise in serum transaminase is often noted; monitoring of liver function is advised.
A rare but serious adverse effect is fulminant hepatitis; occurs only in children (especially below 3 yr). Those with hepatic disease or who receive other anticonvulsant or hepatotoxic drug are at greater risk. Pancreatitis is also reported. Long-term use of valproate in young girls has been associated with higher incidence of polycystic ovarian disease and menstrual irregularities.
Used during pregnancy, it has produced spina bifida and other neural tube defects in the offspring; should be avoided.

Dose: Adults—start with 200 mg TDS, maximum 800 mg TDS; children—15–30 mg/kg/day.
VALPARIN CHRONO 200, 300, 500 mg tabs, 200 mg/5 ml syr; ENCORATE 200, 300, 500 mg regular and controlled release tabs, 200 mg/5 ml syr, 100 mg/ml inj.

Uses Valproic acid is the drug of choice for absence seizures.

It is an alternative/adjuvant drug for GTCS, SPS and CPS.

Myoclonic and atonic seizures—control is often incomplete, but valproate is the drug of choice.

Mania and bipolar illness: as alternative to lithium. It has also been used for panic attacks.

Valproate has some prophylatic efficacy in migraine.

Interactions

- Valproate increases plasma levels of phenobarbitone and lamotrigine by inhibiting their metabolism.
- It displaces phenytoin from protein binding site and decreases its metabolism → phenytoin toxicity.
- Valproate inhibits hydrolysis of active epoxide metabolite of carbamazepine.
- Concurrent administration of clonazepam and valproate is contraindicated because absence status may be precipitated.
- Foetal abnormalities are more common if valproate and carbamazepine are given concurrently.

Divalproex (Semisodium valproate) It is the coordination compound of valproic acid with sodium valproate (1:1). Oral absorption is slower, but bioavailability is the same. Gastric tolerance may be better.

DIPROEX, VALANCE, 125, 250, 500 mg tabs; DEPAKOTE 250, 500 mg tabs.

Clonazepam

It is a benzodiazepine with prominent anticonvulsant properties: blocks PTZ seizures at doses which produce mild sedation. Efficacy in modifying maximal electroshock seizures is low. Though in experimental models of chronic epilepsy it inhibits spread rather than the focus itself, it is singularly ineffective in GTCS. Production of generalized seizures by kindling is suppressed, but local after-discharges persist.

Benzodiazepines potentiate GABA induced Cl^- influx to produce sedation and the same mechanism has been held responsible for the anticonvulsant property, but the sites of action in the brain may be different. At large doses, high frequency discharges are inhibited akin to phenytoin.

Pharmacokinetics Oral absorption of clonazepam is good. It is 85% bound to plasma proteins, completely metabolized in liver and excreted in urine; t½ averages 24 hours. It does not produce any active metabolite.

Adverse effects The most important side effect of clonazepam is sedation and dullness. This can be minimized by starting at low dose; some tolerance develops with chronic therapy. Lack of concentration, irritability, temper and other behavioral abnormalities may occur in children. Motor disturbances and ataxia are dose-related adverse effects. Salivation and increased respiratory secretions may be complained of.

Uses Clonazepam has been primarily employed in absence seizures. It is also useful as an adjuvant in myoclonic and akinetic epilepsy and may afford some benefit in infantile spasms. However, its value is limited by development of tolerance to the therapeutic effect within six months or so. It has also been used to suppress acute mania.

Dose: adults 0.5–5 mg TDS, children 0.02–0.2 mg/kg/day.

LONAZEP, CLONAPAX, RIVOTRIL 0.5, 1.0, 2.0 mg tab.

Clobazam It is a 1,5 benzodiazepine (diazepam and others are 1,4 benzodiazepines) introduced first as anxiolytic and later found to possess useful antiepileptic efficacy in partial, secondarily generalized tonic-clonic as well as absence and atonic seizures, including some refractory cases. Sedation and psychomotor retardation are less prominent, but side effect profile is similar to other BZDs. It appears to act by facilitating GABA action.

Oral bioavailability of clobazam is ~90% and elimination t½ 18 hrs, but an active metabolite is produced which has longer t½ (>35 hr). It is generally used as adjuvant to other antiepileptic drugs like phenytoin, carbamazepine or valproate in refractory epilepsy.

Dose: start with 10–20 mg at bedtime, can be increased upto 60 mg/day; FRISIUM, LOBAZAM, CLOZAM, 5, 10, 20 mg cap.

Diazepam (*see* Ch. 29)

It has anticonvulsant activity in a variety of models but is not used for long term therapy of epilepsy because of prominent sedative action and rapid development of tolerance to the antiepileptic effect. However, it is a first line drug

for emergency control of convulsions, e.g. status epilepticus, tetanus, eclampsia, convulsant drug poisoning, etc.

For this purpose 0.2–0.5 mg/kg slow i.v. injection is followed by small repeated doses as required; maximum 100 mg/day. Thrombophlebitis of injected vein is not uncommon. Marked fall in BP and respiratory depression can occur; resuscitative measures should be at hand before the drug is injected.

Rectal instillation of diazepam is now the preferred therapy for febrile convulsions in children.

Lorazepam 0.1 mg/kg injected i.v. at a rate not exceeding 2 mg/min is better suited than diazepam in status epilepticus or for emergency control of convulsions of other etiology, because of lesser local thrombophlebitic complications and more sustained action than that of diazepam which is rapidly redistributed.

Lamotrigine A new anticonvulsant having carbamazepine-like action profile: modifies maximal electroshock and decreases electrically evoked as well as photic after-discharge duration. Prolongation of Na^+ channel inactivation and suppression of high frequency firing has been demonstrated. In addition, it may directly block voltage sensitive Na^+ channels, thus stabilizing the presynaptic membrane and preventing release of excitatory neurotransmitters, mainly glutamate and aspartate. This may account for its broader-spectrum of antiseizure efficacy. However, it does not antagonize PTZ seizures or block NMDA type of glutamate receptors.

Lamotrigine is a broad-spectrum antiepileptic. Initially found useful as add-on therapy in refractory cases of partial seizures and GTCS, it has now been shown effective as monotherapy as well. Absence and myoclonic or akinetic epilepsy cases have also been successfully treated. Reduction in seizure frequency or complete control is obtained as frequently as with carbamazepine.

Lamotrigine is well absorbed orally and metabolized completely in liver. Its t½ is 24 hr, but is reduced to ~16 hr in patients receiving phenytoin, carbamazepine or phenobarbitone. On the contrary valproate inhibits glucuronidation of lamotrigine and doubles its blood level, but valproate levels are lowered by lamotrigine. Reduce the dose of lamotrigine to half in patients taking valproate. However, metabolism of other anticonvulsants and oral contraceptives is not altered.

Side effects are sleepiness, dizziness, diplopia, ataxia and vomiting. In some comparative trials lamotrigine has been found to be better tolerated than carbamazepine or phenytoin. Negative effect on cognitive function is not reported. Rash may be a severe reaction, particularly in children, requiring withdrawal.
Dose: 50 mg/day initially, increase upto 300 mg/day as needed; not to be used in children.
LAMETEC, LAMITOR, LAMIDUS 25, 50, 100 mg tabs.

Gabapentin This lipophilic GABA derivative crosses to the brain and enhances GABA release, but does not act as agonist at $GABA_A$ receptor. It modifies maximal electroshock as well as inhibits PTZ induced clonic seizures.

Gabapentin and its newer congener pregabalin exert a specific analgesic effect in neuropathic pain. Recently they have been found to modulate a subset of neuronal voltage sensitive Ca^{2+} channels which contain $\alpha 2\delta$-1 subunits. It is postulated that decreased entry of Ca^{2+} into the presynaptic neurone through these channels could reduce glutamate release, lowering neuronal excitability. However, whether $\alpha 2\delta$-1 Ca^{2+} channel modulation or the GABA enhancing action is responsible for the anticonvulsant/analgesic effect of gabapentin and pregabalin, is not known.

Added to a first line drug, gabapentin reduces seizure frequency in refractory partial seizures with or without generalization. Though gabapentin monotherapy as well has been found effective in SPS and CPS, it is mostly employed as add-on drug. Gabapentin is considered to be a first line drug for neuralgic pain due to diabetic neuropathy and postherpetic neuralgia. It has some prophylactic effect in migraine and is an alternative drug for phobic states.

Gabapentin is well absorbed orally and excreted unchanged in urine with a t½ of 6 hrs. No drug interactions have been noted, and no change in dose of primary antiepileptic drug is required when gabapentin is added. Side effects are mild sedation, tiredness, dizziness and unsteadiness.

Dose: Start with 300 mg OD, increase to 300–600 mg TDS as required; NEURONTIN 300 mg, 400 mg cap, GABANTIN, GABAPIN 100, 300, 400 mg cap.

Pregabalin This newer congener of gabapentin has similar pharmacodynamic, pharmacokinetic properties and clinical indications in seizure disorders. It has been particularly used for neuropathic pain, such as diabetic neuropathy, postherpetic neuralgia, complex regional pain syndrome (CRPS) and certain other types of chronic pain. Sedative side effects are claimed to be less prominent, but poor concentration, rashes and allergic reactions have been complained.

Dose: 75–150 mg BD, max 600 mg/day

PREGABA, NEUGABA, TRUEGABA 75, 150 mg caps.

Topiramate This weak carbonic anhydrase inhibitor has broad spectrum anticonvulsant activity in maximal electroshock, PTZ induced clonic seizures and in kindling model. It appears to act by multiple mechanisms, *viz* phenytoin like prolongation of Na^+ channel inactivation, GABA potentiation by a postsynaptic effect, antagonism of certain glutamate receptors and neuronal hyperpolarization through certain K^+ channels.

Topiramate is indicated as monotherapy as well as for supplementing primary antiepileptic drug in refractory SPS, CPS and GTCS. Promising results have been obtained in myoclonic epilepsy. Topiramate is readily absorbed orally and mainly excreted unchanged in urine with an average t½ of 24 hours. Adverse effects are impairment of attention, sedation, ataxia, word finding difficulties, poor memory, weight loss, paresthesias and renal stones.

Recently, topiramate has been approved for prophylaxis of migraine; may be used when β blockers/other prophylactics are contraindicated or are not effective.

Dose: Initially 25 mg OD, increase weekly upto 100–200 mg BD as required.

TOPEX, EPITOP, TOPAMATE, NEXTOP 25, 50, 100 mg tabs.

Zonisamide Another newer anticonvulsant with weak carbonic anhydrase inhibitory action that modifies maximal electroshock seizures and inhibits kindled seizures, but does not antagonize PTZ. Prolongation of Na^+ channel inactivation resulting in suppression of repetitive neuronal firing has been observed. It has also been found to suppress T-type of Ca^{2+} currents in certain neurones.

Zonisamide is well absorbed orally and mainly excreted unchanged in urine with a t½ of > 60 hours. A small fraction is oxidized and conjugated with glucuronic acid. It is indicated as add-on drug in refractory partial seizures. Side effects are somnolence, dizziness, headache, irritability and anorexia. Metabolic acidosis and renal stones can occur. Zonisamide is to be avoided in patients sensitive to sulfonamides.

Dose: 25–100 mg BD. Not to be given to children.

ZONISEP, ZONICARE, ZONIT 50, 100 mg cap.

Levetiracetam A unique anticonvulsant which suppresses kindled seizures, but is ineffective against maximal electroshock or PTZ. Clinical efficacy has been demonstrated both as adjuvant medication as well as monotherapy in refractory partial seizures with or without generalization. The mechanism of action is not known. None of the major anticonvulsant mechanisms appear to be applicable. However, it may modify synaptic release of glutamate/GABA by binding to a specific synaptic protein labelled 'SV_2A'. This may or may not account for the antiepileptic property.

Levetiracetam is completely absorbed orally, partly hydrolysed, but mainly excreted unchanged in urine with a t½ of 6–8 hours. It is neither oxidized by CYP enzymes nor induces or inhibits them. As such, it is free of drug interactions. Few side effects like sleepiness, dizziness, weakness and rarely behavioural changes are reported. Driving may be impaired. Because of good tolerability, levetiracetam is being increasingly used in CPS, GTCS and myoclonic epilepsy, mainly as add-on drug. It is not approved for use in children below 4 years.

Dose: 0.5 g BD, increase upto 1.0 g BD (max 3 g/day), children 4-15 year 10–30 mg/kg/day.

LEVOREXA, TORLEVA, LEVTAM 0.25, 0.5, 1.0 g tabs.

Tiagabine This newer anticonvulsant potentiates GABA mediated neuronal inhibition by depressing GABA transporter GAT-1 which removes synaptically released GABA into neurones and glial cells. Maximal electroshock and kindled seizures are suppressed. Currently it is approved only for add-on therapy of partial seizures with or without secondary generalization, when not adequately controlled by standard antiepileptic drugs alone. Side effects are mild sedation, nervousness, asthenia, amnesia and abdominal pain.

Vigabatrin (γ vinyl GABA) It is an inhibitor of GABA-transaminase, the enzyme which degrades GABA. Anticonvulsant action may be due to increase in synaptic GABA concentration. It is effective in many patients with refractory epilepsy, especially CPS with or without generalization. It is approved only for adjuvant medication.

Visual field contraction and production of behavioural changes, depression or psychosis has restricted its use to only as a reserve drug.

Lacosamide This recently approved (in 2010 in India) antiseizure drug is indicated in adults only for add-on therapy of partial seizures with or without generalization. It acts by enhancing Na^+ channel inactivation and suppressing repetitive firing of neurones. Lacosamide is metabolized by CYP2C19 and excreted in urine. No alteration in dose of companion antiepileptic drug is needed, because it neither induces nor inhibits drug metabolizing enzymes. Adverse effects are ataxia, vertigo, diplopia, tremour, depression and cardiac arrhythmia.
Dose: Initially 50 mg BD, increase upto 200 mg BD.

TREATMENT OF EPILEPSIES

Antiepileptic drugs suppress seizures, but do not cure the disorder; the disease may fadeout though after years of successful control. The aim of drugs is to control and totally prevent all seizure activity at an acceptable level of side effects. With the currently available drugs, this can be achieved in about half of the patients. Another 20–30% attain partial control, while the rest remain refractory. The cause of epilepsy should be searched in the patient; if found and treatable, an attempt to remove it should be made. Some general principles of symptomatic treatment with antiepileptic drugs are:

(i) Choice of drug (Table 30.1) and dose is according to the seizure type(s) and need of the individual patient.

(ii) Initiate treatment early, because each seizure episode increases the propensity to further attacks, probably by a process akin to kindling. Start with a single drug, preferably at low dose—gradually increase dose till full control of seizures or side effects appear. If full control is not obtained at maximum tolerated dose of one drug, substitute another drug. Use combinations when all reasonable monotherapy fails. Combining drugs with different mechanisms of action, such as those which prolong Na^+ channel inactivation with those facilitating GABA appears more appropriate. Pharmacokinetic interactions

TABLE 30.1 Choice of antiseizure drugs

	Type of seizure	*First choice drugs*	*Second choice drugs*	*Alternative/Add-on drugs*
1.	Generalised tonic-clonic/ simple partial with or without generalization	Carbamazepine, Phenytoin	Valproate, Phenobarbitone	Lamotrigine, Gabapentin, Topiramate, Primidone, Levetiracetam
2.	Complex partial with or without generalization	Carbamazepine, Valproate, Phenytoin	Gabapentin, Lamotrigine, Levetiracetam	Clobazam, Zonisamide, Topiramate
3.	Absence	Valproate	Ethosuximide, Lamotrigine	Clobazam, Clonazepam
4.	Myoclonic	Valproate	Lamotrigine, Topiramate	Levetiracetam, Clonazepam
5.	Atonic	Valproate	Clonazepam, Clobazam	Lamotrigine
6.	Febrile seizures	Diazepam (rectal)	—	—
7.	Status epilepticus	Lorazepam (i.v.), Diazepam (i.v.)	Fosphenytoin (i.v.) Phenobarbitone (i.v., i.m.)	Gen. anaesthetics

among anticonvulsants are common; dose adjustment guided by therapeutic drug monitoring is warranted.

(iii) A single tonic-clonic seizure in a subject with no predisposing factor for development of epilepsy (history of head injury, family history of epilepsy, neurological abnormality, abnormal EEG or brain scan) may not merit initiation of antiepileptic therapy.

(iv) Therapy should be as simple as possible. A seizure diary should be maintained.

(v) All drug withdrawals should be gradual (except in case of toxicity. Abrupt stoppage of therapy without introducing another effective drug can precipitate status epilepticus. Prolonged therapy (may be life-long, or at least 3 years after the last seizure) is needed. Stoppage of therapy may be attempted in selected cases. Features favourable to withdrawal are:

- childhood epilepsy,
- absence of family history,
- primary generalized tonic-clonic epilepsy,
- recent onset at start of treatment,
- absence of cerebral disorder and normal inter-seizure EEG.

Even with these features recurrence rates of 12–40% have been reported.

(vi) Dose regulation may be facilitated by monitoring of steadystate plasma drug levels. Monitoring is useful because:

(a) Therapeutic range of concentrations has been defined for many older drugs.
(b) There is marked individual variation in the plasma concentration attained with the same daily dose.
(c) Compliance among epileptic patients is often poor.

Plasma levels given in Table 30.2 are to serve as rough guides:

(vii) When women on antiepileptic therapy conceive, antiepileptic drugs should not be stopped. Though, most antiseizure drugs increase the incidence of birth defects, discontinuation of therapy carries a high risk of status epilepticus. Fits occurring during pregnancy themselves increase birth defects and may cause mental retardation in the offspring (anoxia occurs during seizures). An attempt to reduce the dose of drugs should be cautiously made. It may be advisable to substitute valproate.

Prophylactic folic acid supplementation in 2nd and 3rd trimester along with vit. K in the last month of pregnancy is recommended, particularly in women receiving antiepileptic drugs to minimise neural tube defects and bleeding disorder respectively in the neonate.

(viii) Individual seizure episodes do not require any treatment. During an attack of tonic-clonic seizures, the first priority is to prevent injury due to fall or biting. The patient should be put in prone

TABLE 30.2 **Plasma half life, therapeutic and toxic plasma concentration range of some important antiepileptic drugs**

Drug	*Half life (hr)*	*Plasma concentration (μg/ml)*	
		Therapeutic	*Toxic*
Phenobarbitone	80–120	10–30	> 30 mild > 60 severe
Phenytoin	12–36	10–20	> 20 mild > 35 severe
Carbamazepine	10–40	5–10	> 12
Ethosuximide	30–50	50–100*	>200
Valproate	10–15	40–100*	–
Clonazepam	20–40	0.01–0.1*	–

* Poorly correlated with response.

or lateral position and a gag should be placed between the teeth. The head should be turned and patency of airway ensured. The attack usually passes off in 2–3 min, but the patient may not be roadworthy for a couple of hours.

1. Generalised tonic-clonic and simple partial seizures In large comparative trials, considering both efficacy and toxicity, carbamazepine and phenytoin have scored highest, phenobarbitone was intermediate, while primidone was lowest among the older drugs. Carbamazepine was the best in partial seizures, while valproate was equally effective in secondarily GTCS. Valproate is a good second line drug but should be used cautiously in young children for fear of hepatic toxicity. Carbamazepine is preferred in young girls because of cosmetic side effects of phenytoin.

Lamotrigine, gabapentin and topiramate have emerged as good alternatives. Levetiracetam is another close contender. Clonazepam is a short-term alternative. Newer drugs are mostly used as add-on therapy in cases with incomplete/poor response. They are being increasingly used for monotherapy as well, either to initiate therapy or as alternative medication, particularly when drug interactions are to be avoided. The newer drugs generally are less sedating and produce fewer side effects. However, experience with them is less extensive and comparative trials are few.

Complete control can be obtained in upto 90% patients with generalized seizures, but in only 50% or less patients with partial seizures.

Phenobarbitone, phenytoin, valproate and carbamazepine have been used to treat early post-head injury seizures. Phenobarbitone and phenytoin are often prescribed empirically for prophylaxis of late-onset (8 days to 2 yrs later) post-traumatic epilepsy, but risk/benefit ratio of such use is not clear. Decision has to be taken on individual basis.

2. Complex partial seizures This type of epilepsy is difficult to control completely; relapses are more common on withdrawal. Carbamazepine is the preferred drug, but phenytoin or valproate may have to be added to it. The newer drugs levetiracetam, lamotrigine, gabapentin, topiramate or zonisamide may be added in refractory cases.

3. Absence seizures Ethosuximide and valproate are equally efficacious, but the latter is more commonly used because it would also prevent kindling and emergence of GTCS. Valproate is clearly superior in mixed absence and GTCS, which is more common than pure absence seizures. Lamotrigine has emerged as a good alternative. Clonazepam is a second line drug limited by its sedative property and development of tolerance. Clobazam is an alternative with promise of more sustained response.

4. Myoclonic and atonic seizures Valproate is the preferred drug and lamotrigine is an effective alternative. Topiramate may be added in case of poor response. Levetiracetam is generally added in nonresponsive cases.

5. Febrile convulsions Some children, especially under 5 years age, develop convulsions during fever. Seizures may recur every time with fever and few may become chronic epileptics. Every attempt should be made to see that they do not develop fever, but when they do, temperature should not be allowed to rise by using paracetamol and external cooling.

The best treatment of febrile convulsions is rectal diazepam 0.5 mg/kg given at the onset of convulsions. The i.v. preparation can be used where the rectal formulation is not available. A rectal solution (5 mg in 2.5 ml) in tubes is available in the UK and some other countries. Seizures generally stop in 5 min; if not, another dose may be given. The drug is repeated 12 hourly for 4 doses. If fever is prolonged a gap of 24–48 hr is given before starting next series of doses.

In recurrent cases or those at particular risk of developing epilepsy—intermittent prophylaxis with diazepam (oral or rectal) started at the onset of fever is recommended. Chronic prophylaxis with phenobarbitone advocated earlier has been abandoned, because of poor efficacy and behavioural side effects.

6. Infantile spasms (hypsarrhythmia) Therapy is unsatisfactory, antiepileptic drugs are generally useless. Corticosteroids afford symptomatic relief. Valproate and clonazepam have adjuvant value. Vigabatrin has some efficacy.

7. Status epilepticus When seizure activity occurs for >30 min, or two or more seizures occur without recovery of consciousness, the condition is called *status epilepticus*. Recurrent tonic-clonic convulsions without recovery of consciousness in between is an emergency; fits have to be controlled as quickly as possible to prevent death and permanent brain damage.

- *Lorazepam* 4 mg (0.1 mg/kg in children) injected i.v. at the rate of 2 mg/min, repeated once after 10 min if required, is the first choice drug now. It is effective in 75–90% cases and produces a more sustained anticonvulsant effect (lasting 6–12 hours) than diazepam, because of lower lipid solubility and slower redistribution. Moreover, thrombophlebitis of injected vein is less likely with lorazepam.
- *Diazepam* 10 mg (0.2–0.3 mg/kg) injected i.v. at 2 mg/min, repeated once after 10 min if required, has been the standard therapy till recently. However, its anticonvulsant effect starts fading after 20 min, and many supplemental doses may be required. It is also more damaging to the injected vein.
- *Fosphenytoin* 100–150 mg/min i.v. infusion to a maximum of 1000 mg (15–20 mg/kg) under continuous ECG monitoring is a slower acting drug which should be given if the seizures recur or fail to respond 20 min after onset, despite lorazepam/diazepam. It may also be employed to continue anticonvulsant cover after the seizures have been controlled by the BZD.
- *Phenytoin sod.* It should be used only when fosphenytoin is not available, because it can be injected only at the rate of 25–50 mg/min and causes more marked local vascular complications.
- *Phenobarbitone sod.* 50–100 mg/min i.v. injection to a maximum of 10 mg/kg is another slower acting drug which can be used as alternative to fosphenytoin. It is also employed to maintain seizure free state over short term before definitive oral therapy is instituted.
- Refractory cases who fail to respond to lorazepam and fosphenytoin within 40 min of seizure onset may be treated with i.v. midazolam/propofol/thiopentone anaesthesia, with or without curarization and full intensive care.
- General measures, including maintenance of airway (intubation if required), oxygenation, fluid and electrolyte balance, BP, normal cardiac rhythm, euglycaemia and care of the unconscious must be taken.

☞ PROBLEM DIRECTED STUDY

30.1 A young lady aged 25 years comes for consultation along with her husband for having suffered two episodes of fits lasting 2–3 min each over the past one week. Just before each fit, she experienced flickering in her right arm. Description of the fit given by the husband corresponds to generalized tonic-clonic seizures. She gave the history of having met a car accident about one year back in which she received head injury. There is no family history of epilepsy. General physical and neurological examination revealed no abnormality. Investigations, including EEG and MRI scan of the brain, were ordered.

(a) What instructions should be given to the husband regarding care to be taken, if and when, the next fit occurs?

(b) Should antiepileptic drug/drugs be started right away, or therapy be delayed till findings of the investigations become available or till more fits occur?

(c) In case antiseizure therapy has to be started right away, should a single drug or a combination of drugs be given? Which drug(s) would be the most appropriate for this patient?

(see Appendix-1 for solution)