

## General Anesthetics

General Anesthetics are the drugs which produce reversible loss of consciousness and all types of sensations. The main features of general anesthesia involves loss of sensation (pain), Sleep and amnesia, immobility and muscle relaxation and also involves abolition of somatic and autonomic reflexes. Modern anesthetics acts very rapidly and combination of inhaled and i.v. drugs have been used to achieve proper anesthesia.

### MECHANISM OF GENERAL ANAESTHESIA

The mechanism of action of General Anesthesia is not precisely known and it is basically related to the physicochemical properties of the drugs. Mayer and Overton (1901) gave a direct relation between lipid/water partition coefficient of the Gas and their potency. Minimal Alveolar Concentration (MAC) is the lowest concentration of anesthesia needed in pulmonary alveoli to produce immobility in response to any painful stimuli. It is valid mainly for the inhalational anesthetics.

Anesthetics may be acting through different mechanism on molecular basis. The main region involved in causation of unconsciousness is in thalamus or reticular activating system. Also some findings claim that ligand gated ion channels are the main targets of the anesthetic actions. General anesthetics in contrast are reported to inhibit excitatory NMDA type glutamate receptors and they may act by depressing synaptic transmission while local anesthetics which act by blocking axonal conduction.

### STAGES OF ANAESTHESIA

Gas cause irregular descending depression of CNS, i.e. the higher functions are lost first and progressively lower areas of brain. The main four stages of anesthesia are:

**1.Stage of analgesia:** Starts from anesthetic inhalation and lasts upto the loss of consciousness. Pain is slowly decreased but patient remains conscious and amnesia appear at the end. Respiration is normal during this stage.

**2.Stage of delirium:** Consciousness during this stage is fully lost but patient may appear excited (muscle tone increases). Heart rate and BP may rise and pupils may dilate due to sympathetic stimulation.

**3.Surgical Anaesthesia:** Starts from regular respiration to cessation of breathing. It basically involves Roving eyeballs and fixed at end, loss of corneal reflexes, and pupil starts dilating (light reflex lost).

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4. **Medullary Paralysis:** Breathing stops and failure of circulation and this leads to death.

	RESPIRATION		OCULAR MOVEMENT	PUPIL SIZE (no pre-medication)	EYE REFLEXES	MUSCLE TONE	RESPIRATORY RESPONSE TO SKIN INCISION
	inter-costal	diaphragmatic					
STAGE I: ANALGESIA	Normal		Voluntary control	Normal	Normal		
STAGE II: EXCITEMENT					Lid	Tense struggle	
STAGE III: SURGICAL ANESTHESIA	Plane 1				Corneal		
	Plane 2		No eye motion				
	Plane 3				Pupillary light		No response to skin incision
	Plane 4				No light reflex		
STAGE IV: IMMINENT DEATH	Apnea					Flaccid	

CLASSIFICATION OF GENERAL ANAESTHETICS:

1. Inhalational anesthesia:
  - a. Gas: Nitrous oxide
  - b. Volatile liquids: Ether, Halothane, Enflurane, Isoflurane, Desflurane, Sevoflurane
2. Intravenous anesthetics:
  - a. Inducing agents: Thiopentone Sodium, Methohexitone Sodium, Propofol, Etomidate
  - b. Slower acting drugs: Benzodiazepines- Diazepam, Lorazepam, Midazolam  
 Dissociative anesthesia- Ketamine  
 Opioid analgesia- Fentanyl

**INHALATIONAL ANAESTHETICS**

These anesthetics diffuse across pulmonary and tissue barriers. The potency and partial pressure in brain decide the depth of anesthesia. The speed of induction of anesthetic effects depends upon:

1. Solubility: Large amount of anesthetics that are highly soluble in blood must be dissolved before PP is raised. The change in PP in blood leads to consequent induction and slow recovery. Drugs with low blood:gas partition coefficient (Nitrous oxide) induce quickly
2. Inspired Gas Partial Pressure: A higher partial pressure of the gas in lungs will result in more rapid achievement of anesthetic levels in blood. Thus, a quick induction can be made by administering the GA at high concentration at start
3. Ventilation rate: The greater the ventilation than there will be more rapid increase in alveolar and blood partial pressure of the anesthetic agent and more rapid will be onset of anesthesia.
4. Pulmonary blood flow: Higher the pulmonary blood flows, slower will be the rise in partial pressure of gas and thus onset of anesthesia is reduced. In contrast lower the blood flow rate, inset will be faster.
5. Cerebral Blood Flow: Gas is rapidly delivered to highly perfused organ (Brain). This can be hastened by inhalation of CO<sub>2</sub> which causes vasodilation which further leads to acceleration of induction and recovery.

All the inhalational anesthetics are eliminated through lungs. The factors for both induction and recovery are similar. The rate of recovery from anesthesia using agents with low blood:gas partition coefficient is faster than that of anesthetics with high blood solubility. This is one of the important property which leads to discovery of newer inhalational anesthetics like Desflurane which have low blood solubility and are characterized by recovery times that are considerably shorter than other older agents. Halothane and Isoflurane show slow recovery due to their higher lipid solubility and large amount of anesthetics enter muscle and fat which is released slowly into blood.

**PHARMACOLOGICAL ACTIONS O INHALED ANAESTHETICS**

1. CNS: Inhaled anesthetics decrease brain metabolic rate. They generally reduce vascular resistance and increase cerebral blood flow and may increase intracranial pressure. High concentration of Enflurane may cause spike and wave activity and muscle twitching, but this effect is limited to this drug only
2. Cardiovascular effects: Inhalational anesthetics decrease arterial blood pressure moderately. Enflurane and Halothane are myocardial depressants by reducing Ca<sup>2+</sup>

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concentration while Isoflurane causes peripheral vasodilation. Nitrous oxide is less likely to lower blood pressure than are other inhalational anesthetics.

3. Respiratory effects: Rate of respiration may be increased but the tidal volume is decreased which may cause increase in arterial CO<sub>2</sub> tension. Nitrous oxide may or may not effect respiration while Halothane and Isoflurane causes greater depression of respiration.

**ADVERSE EFFECTS**

- Prolonged exposure to nitrous oxide decreases methionine synthase activity and may lead to megaloblastic anaemia.
- Some Patients may develop malignant hyperthermia when exposed to halogenated anesthetics.
- Renal insufficiency may be one of the problem after using prolonged anesthesia.

**INTRAVENOUS ANAESTHETICS**

Several chemical classes of drugs are used as intravenous agents in anesthesia: for eg:

1. **BARBITURATES:** Thiopental and methohexital have high lipid solubility which promotes rapid entry into the brain, results in anesthesia less than one minute. It is used for short surgical procedures.
2. **KETAMINE:** It produces dissociative anesthesia, patient remains conscious but has marked catatonia and amnesia. The drug is a cardiovascular stimulant and this action may lead to increase in intracranial pressure.
3. **OPIOIDS:** Morphine and fentanyl are used with other CNS depressants in anesthesia regimens and are valuable in high risk patients who might not survive a full general anesthetic. If administered iv may cause chest wall rigidity and can impair ventilation.
4. **PROPOFOL:** Produces anesthesia at a rate similar to intravenous barbiturates but recovery is rapid. It may show antiemetic action. Propofol can cause marked hypotension during induction of anesthesia. Total body clearance of Propofol is greater than hepatic blood flow.
5. **BENZODIAZEPINES:** Midazolam is widely used with inhaled anesthetics and iv opioids. The onset of its CNS effects is slower than that of Thiopental and has longer duration of action.

## Local Anesthetics

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.

### CLASSIFICATION

#### *Injectable anaesthetic*

*Low potency, short duration*

Procaine, Chlorprocaine

*Intermediate potency and duration*

Lidocaine (Lignocaine), Prilocaine

*High potency, long duration*

Tetracaine (Amethocaine), Bupivacaine, Ropivacaine

#### *Surface anaesthetic*

*Soluble:* Cocaine, Lidocaine, Tetracaine.

*Insoluble:* Benzocaine Butylaminobenzoate Oxethazaine

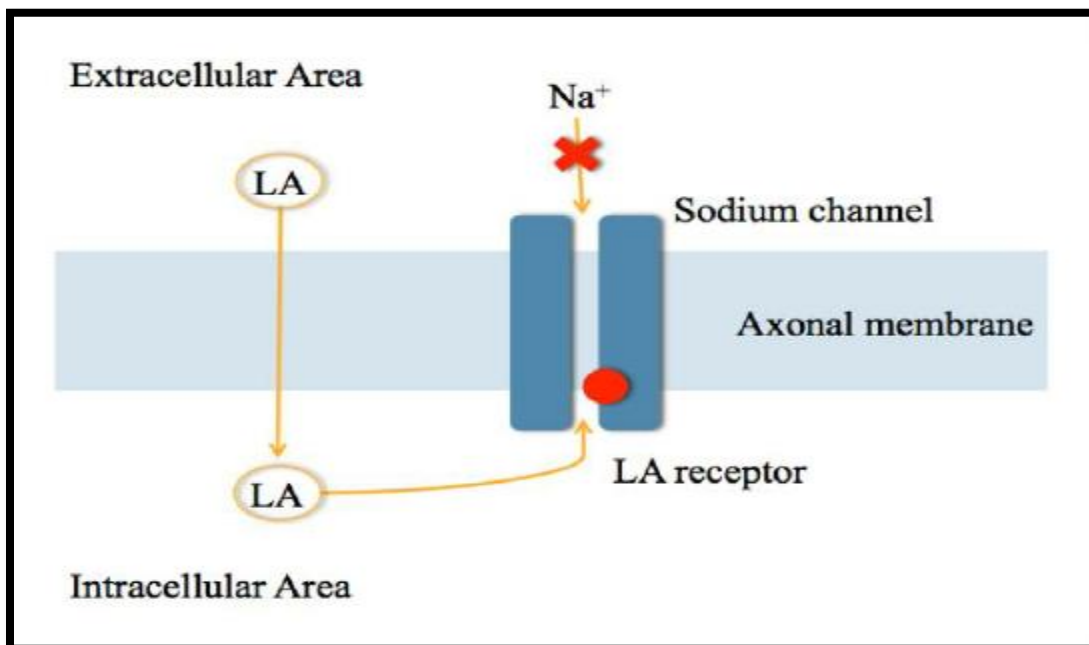
### Mechanism of Action:

All LAs are membrane-stabilizing drugs; they reversibly decrease the rate of depolarization and repolarization of excitable membranes (like nociceptors). Though many other drugs also have membrane-stabilizing properties, not all are used as LAs (propranolol, for example).

1. The mechanism of the LA's connects with the ion channel, nerves and depolarisation.
2. Block the conduction in peripheral nerves that inhibited the nerve to get excited and hence anaesthesia is created.
3. LA drugs act mainly by inhibiting sodium influx through sodium-specific ion channels in the neuronal cell membrane, in particular the so-called voltage-gated sodium channels.
4. When the influx of sodium is interrupted, an action potential cannot arise and signal conduction is inhibited.
5. The receptor site is thought to be located at the cytoplasmic (inner) portion of the sodium channel.

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6. Local anaesthetic drugs bind more readily to sodium channels in an activated state, thus onset of neuronal blockade is faster in rapidly firing neurons. This is referred to as **state-dependent blockade**.



### Mechanism of Action of Local Anaesthetics

#### Cocaine

It is a natural alkaloid from leaves of *Erythroxylon coca*, a South American plant growing on the foothills of the Andes. Cocaine is a good surface anaesthetic and is rapidly absorbed from buccal mucous membrane. It was first used for ocular anaesthesia in 1884. 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.

**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.

**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.

## SEDATIVE AND 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.

### 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 architected cyclic process. 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  $\alpha$  activity when eyes are closed and  $\beta$  activity when eyes are open. Eye movements are irregular or slowly rolling.

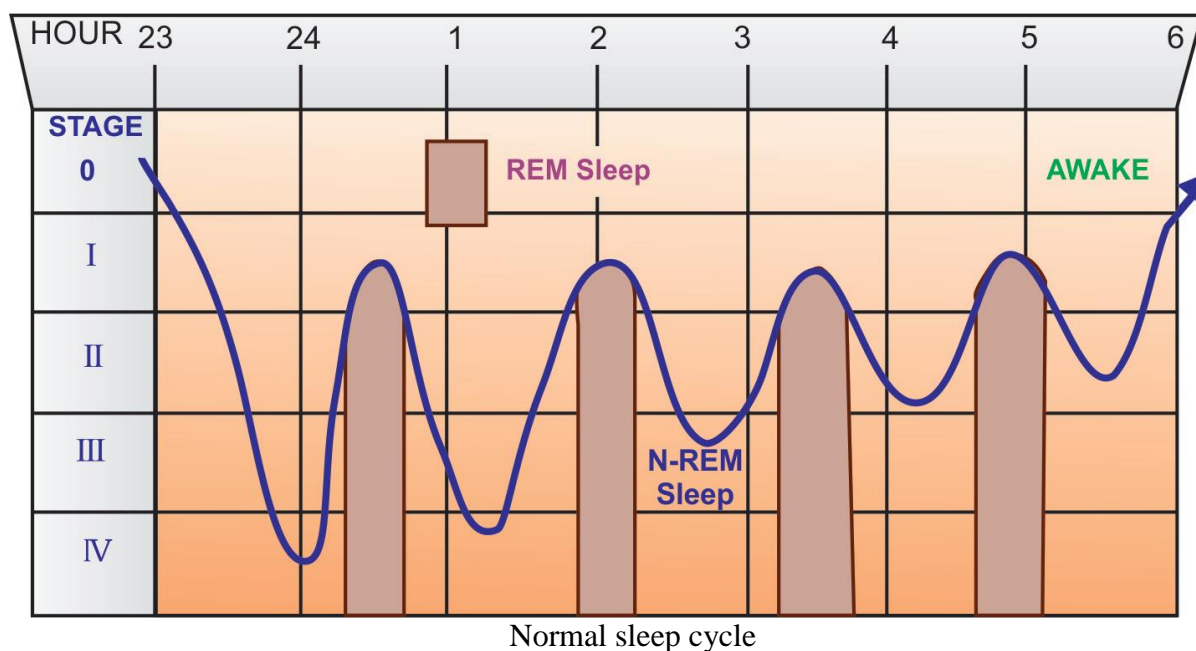
*Stage 1 (dozing)*  $\alpha$  activity is interspersed with  $\theta$  waves. Eye movements are reduced but there may be bursts of rolling. Neck muscles relax. Occupies 3–6% of sleep time.

*Stage 2 (unequivocal sleep)*  $\theta$  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  $\theta$ ,  $\delta$  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)*  $\delta$  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.



## CLASSIFICATION

### 1. Barbiturates

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

### 2. Benzodiazepines

- *Hypnotic:* Diazepam, Flurazepam, Nitrazepam, Alprazolam
- *Antianxiety:* Diazepam, Chlordiazepoxide, Flurazepam, Oxazepam, Lorazepam
- *Anticonvulsant:* Diazepam, Lorazepam, Clonazepam, Clobazam

### 3. Newer non-benzodiazepine hypnotics

Zopiclone, Zolpidem, Zaleplon.

## 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.

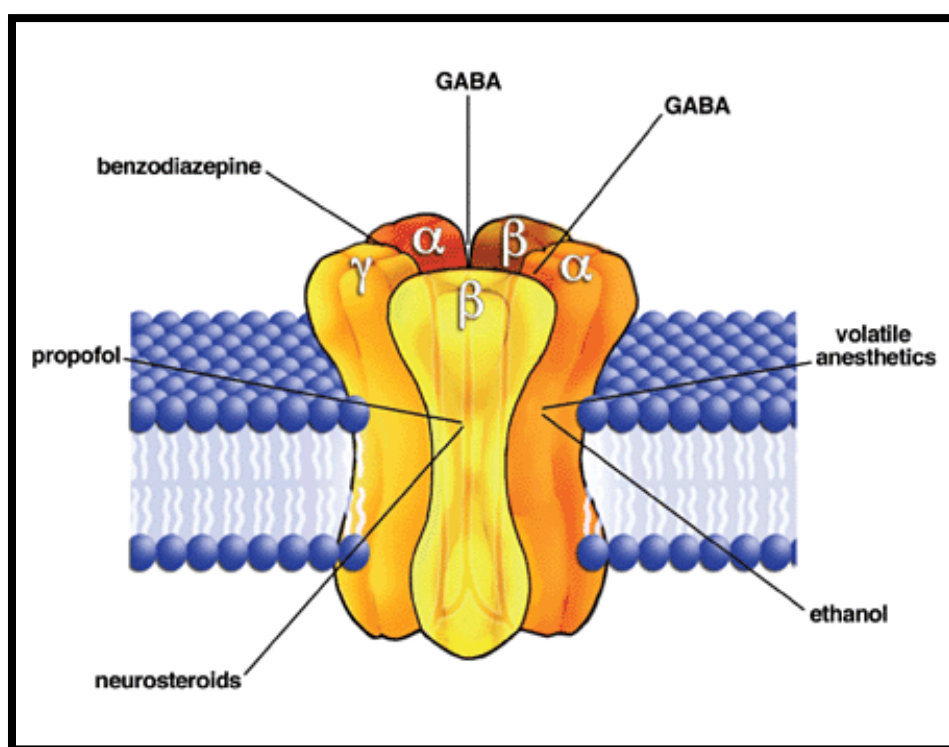
### Mechanism of action

1. Barbiturates appear to act primarily at the GABA : BZD receptor-Cl<sup>-</sup> channel complex.
2. They potentiate GABAergic inhibition by increasing the lifetime of Cl<sup>-</sup> channel opening induced by GABA (contrast BZDs which enhance frequency of Cl<sup>-</sup> channel opening).



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3. They do not bind to the BZD receptor, but bind to another site on the same macromolecular complex to exert the GABA facilitatory action.
4. The barbiturate site appears to be located on  $\alpha$  or  $\beta$  subunit, because presence of only these subunits is sufficient for their response.
5. At high concentrations, barbiturates directly increase  $\text{Cl}^-$  conductance (GABA-mimetic action; contrast BZDs which have only GABA-facilitatory action) and inhibit  $\text{Ca}^{2+}$  dependent release of neurotransmitters.
6. In addition they depress glutamate induced neuronal depolarization through AMPA receptors (a type of excitatory amino acid receptors).
7. At very high concentrations, barbiturates depress voltage sensitive  $\text{Na}^+$  and  $\text{K}^+$  channels as well.

GABA : BZD receptor- $\text{Cl}^-$  channel complex**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

***Mechanism of Action***

1. BZDs act by enhancing presynaptic/postsynaptic inhibition through a specific BZD receptor which is an integral part of the  $\text{GABA}_A$  receptor- $\text{Cl}^-$  channel complex.
2. The  $\alpha/\gamma$  subunit of macromolecular complex carries the BZD binding site.
3. The modulatory BZD receptor increases the frequency of  $\text{Cl}^-$  channel opening induced by GABA.

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4. The BZDs also enhance GABA binding to GABA<sub>A</sub> receptor. The GABA<sub>A</sub> antagonist bicuculline antagonizes BZD action in a noncompetitive manner.

#### 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  $\alpha 1$  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. They are used as hypnotic in chronic insomnia, short-term insomnia, transient insomnia, as anxiolytic, anticonvulsant and as centrally acting muscle relaxant, etc.

## Anticonvulsant 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. 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.

1. *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.

### 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

### Phenobarbitone

Phenobarbitone was the first efficacious antiepileptic introduced in 1912. The mechanism of CNS depressant action of barbiturates. The same may apply to anticonvulsant action. Enhancement of GABAA 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, ant glutamate, Ca<sup>2+</sup> entry reduction) have been noted for phenobarbitone compared to hypnotic barbiturates.

Phenobarbitone has slow oral absorption and a long plasma t<sub>1/2</sub> (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—behavioural

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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.

**Primidone**

A deoxybarbiturate, converted by liver to phenobarbitone and phenylethyl malonamide (PEMA). Its antiepileptic activity is mainly due to these active metabolites. Adverse effects are similar to phenobarbitone.

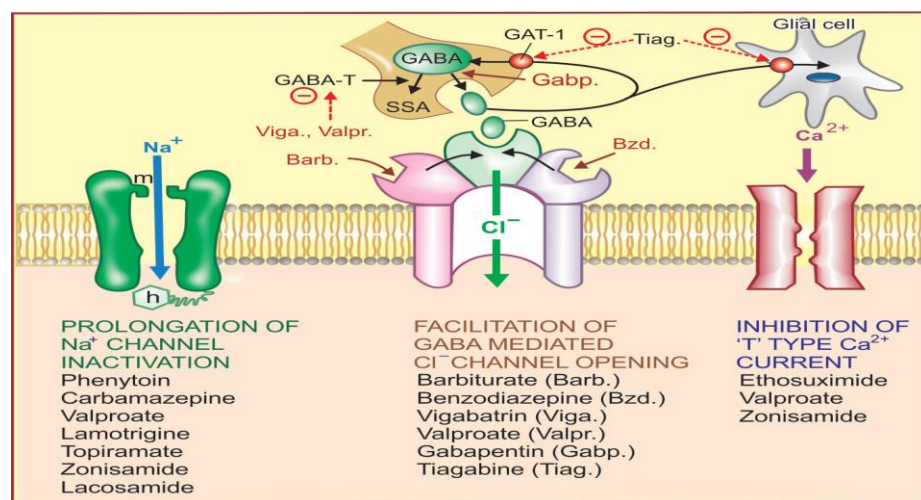
In addition, anaemia, leukopenia, psychotic reaction and lymph node enlargement occur rarely.

**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.

**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<sup>+</sup> channel that governs the refractory period of the neurone.



**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

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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.

**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. Though its action on Na<sup>+</sup> 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.

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.

**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. Thalamic neurones exhibit prominent 'T' (transient) current which is low threshold Ca<sup>2+</sup> current (due to inward flow of Ca<sup>2+</sup> through T type Ca<sup>2+</sup> channels) that acts as the pacemaker and amplifies repetitive spikes. Ethosuximide selectively suppresses T current without affecting other types of Ca<sup>2+</sup> or Na<sup>+</sup> 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 t<sub>½</sub> averages 48 hours in adults and 32 hours in children.

**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.

Valproate appears to act by multiple mechanisms:

- (i) A phenytoin-like frequency-dependent prolongation of Na<sup>+</sup> channel inactivation.
- (ii) Weak attenuation of Ca<sup>2+</sup> 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.

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*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  $t_{1/2}$  is 10–15 hours; but anticonvulsant effects are longer lasting.

*Adverse effects*

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.

**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.

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;  $t_{1/2}$  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.

**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 anti-seizure efficacy. However, it does not antagonize PTZ seizures or block NMDA type of glutamate receptors.

Lamotrigine is well absorbed orally and metabolized completely in liver. Its  $t_{1/2}$  is 24 hr, but is reduced to ~16 hr in patients receiving phenytoin, carbamazepine or phenobarbitone.

### **Gabapentin**

This lipophilic GABA derivative crosses to the brain and enhances GABA release, but does not act as agonist at GABAA 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.

Gabapentin is well absorbed orally and excreted unchanged in urine with a  $t_{1/2}$  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.

### **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  $\text{Na}^+$  channel inactivation, GABA potentiation by a postsynaptic effect, antagonism of certain glutamate receptors and neuronal hyperpolarization through certain  $\text{K}^+$  channels.

Topiramate is readily absorbed orally and mainly excreted unchanged in urine with an average  $t_{1/2}$  of 24 hours. Adverse effects are impairment of attention, sedation, ataxia, word finding difficulties, poor memory, weight loss, paresthesias and renal stones.

### **Vigabatrin**

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.



## DRUGS FOR GLAUCOMA

Glaucoma is a group of diseases characterized by a progressive form of optic nerve damage. This is generally but not necessarily associated with raised ( $> 21$  mmHg) intraocular tension (i.o.t), but the etiology is unknown and there are many risk factors.

The chief therapeutic measure is to lower i.o.t., either by reducing secretion of aqueous humor or by promoting its drainage.

### Open angle glaucoma

It is probably a genetically predisposed degenerative disease affecting patency of the trabecular meshwork which is gradually lost past middle age. The i.o.t. rises insidiously and progressively. Ocular hypotensive drugs are used on a long term basis and constitute the definitive treatment in majority of cases.

### $\beta$ Adrenergic blockers

Topical  $\beta$  blockers have been the first line drugs till recently, but PG F<sub>2</sub> $\alpha$  analogues are the preferred drugs now. In contrast to miotics, the  $\beta$  blockers do not affect pupil size, tone of ciliary muscle or outflow facility, but lower i.o.t. by reducing aqueous formation. This probably results from down regulation of adenylylcyclase due to  $\beta_2$  receptor blockade in the ciliary epithelium and a secondary effect due to reduction in ocular blood flow.

*Ocular side effects of  $\beta$  blockers* These are generally mild and infrequent—stinging, redness and dryness of eye, corneal hypoesthesia, allergic blepharoconjunctivitis and blurred vision.

**Timolol** It is the prototype of ocular  $\beta$  blockers; is nonselective ( $\beta_1 + \beta_2$ ) and has no local anaesthetic or intrinsic sympathomimetic activity. The ocular hypotensive action (20–35% fall in i.o.t.) becomes evident within 1 hour and lasts for ~12 hours. After chronic dosing, the action is smooth and well sustained. Some effect on i.o.t. persists for 1–2 weeks following discontinuation.

### $\alpha$ Adrenergic agonists

**Dipivefrine** It is a prodrug of Adr; penetrates cornea and is hydrolysed by the esterases present there into Adr, which itself has poor corneal penetration and causes ocular smarting, reactive hyperemia. The released Adr (from dipivefrine) lowers i.o.t. by augmenting uveoscleral outflow,  $\beta_2$  receptor mediated increase in hydraulic conductivity of trabecular filtering cells, as well as by reducing aqueous formation ( $\alpha_1 + \alpha_2$  receptor mediated). Though better tolerated and longer acting than Adr, dipivefrine still produces significant ocular burning and other side effects. It is infrequently used for add on therapy.

### Prostaglandin analogues

Low concentration of PGF<sub>2</sub> $\alpha$  was found to lower i.o.t without inducing ocular inflammation. It acts by increasing uveoscleral outflow, possibly by increasing permeability of tissues in ciliary muscle or by an action on episcleral vessels. An effect on trabecular outflow has also been

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demonstrated, but is less marked. Ciliary body COX-2 has been found to be down regulated in wide angle glaucoma indicating a physiological role of PGs in aqueous humor dynamics.

**Latanoprost** Instilled in the eye, this PGF<sub>2α</sub> derivative has shown efficacy similar to timolol (i.o.t. reduction by 25–35%) and the effect is well sustained over long-term. It reduces i.o.t. in normal pressure glaucoma also.

**Carbonic anhydrase inhibitors**

**Acetazolamide** Oral treatment with acetazolamide (0.25 g 6–12 hourly) reduces aqueous formation by limiting generation of bicarbonate ion in the ciliary epithelium. It is used to supplement ocular hypotensive drugs for short term indications like angle closure, before and after ocular surgery/laser therapy.

**Miotics:** Till the 1970s topical pilocarpine and/or antiChEs were the standard antiglaucoma drugs. However, because of several drawbacks, they are now used only as the last option. In open angle glaucoma, they lower i.o.t. by increasing ciliary muscle tone thereby improving patency of trabeculae.

**Angle closure glaucoma**

It occurs in individuals with a narrow irido-corneal angle and shallow anterior chamber. The i.o.t. remains normal until an attack is precipitated, usually by mydriasis. The i.o.t. rises rapidly to very high values (40–60 mmHg). It is an emergent condition with marked congestion of eyes and severe headache. Failure to lower i.o.t. quickly may result in loss of sight. Vigorous therapy employing various measures to reduce i.o.t. is instituted.

1. *Hypertonic mannitol or glycerol:* infused i.v. decongest the eye by osmotic action. A retention enema of 50% glycerine is also sometimes used.
2. *Acetazolamide:* 0.5 g i.v. followed by oral twice daily is started concurrently.
3. *Miotic:* Once the i.o.t. starts falling due to the above i.v. therapy, pilocarpine 1–4% is instilled every 10 min initially and then at longer intervals. Contraction of sphincter pupillae changes the direction of forces in the iris to