UNIT- IV

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 & muscle relaxation
- Abolition of somatic and autonomic reflexes.

Mechanism of General Anaesthesia:-

The mechanism of action of GAs is not precisely known.
A wide variety of chemical agents produce general anaesthesia.
By influencing neuronal membrane proteins, general anaesthetics disrupt neuronal firing & sensory processing in the thalamus, causing loss of consciousness and analgesic effect.

- Reticular formation (interconnected nuclei that are located throughout the brain stem) → somatic motor control, cardiovascular control, pain modulation, sleep and consciousness & habituation → Depress reticular formation by enhancing the activity of inhibitory transmitters & Blocking the activity of excitatory transmitters.

Minimal alveolar concentration (MAC):- It is the lowest concentration of the anaesthetic in pulmonary alveoli need to produce immobility in response to a painful stimulus in 50% individuals.

It is accepted as a valid measure of potency of Inhala... anal GAs because it remains fairly constant for most yo... adults. The MAC of all inhalational anesthetics declines progressively as age advances beyond 50 years.

Stage of Anaesthesia :- GAs cause an irregularly descendi... 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 some-what earlier than the higher segments.

Different stages of Anaesthesia are :-

Stage I :- Stage of Analgesia

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

Stage II :- Stage of Delirium :- From loss of consciousness to beginning of regular respiration.
Apparent excitement is seen- patient may shout, struggle & hold his breath, muscle tone increase, jaws are tightly closed, vomiting etc.
Heart Rate & BP may rise and pupils dilate due to Sympathetic stimulation. This stage is inconspicuous in modern anaesthesia.

Stage 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 & light reflex is lost.

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

As anaesthesia passes to deeper planes, progressively muscle tone decrease, BP falls, HR Teases with peak pulse.

Stage IV Medullary paralysis:- Cessation (stop) of breathing to failure of circulation and death. Pupils widely dilated, muscles are totally flabby, pulse is thready or imperceptible & BP is very low.

Pharmacokinetics of Inhalational Anaesthetics:-

Inhalational anaesthetics are gases or vapours that diffuse rapidly across pulmonary alveoli & tissue barriers.

The Principles of Pharmacokinetics include induction, maintenance & recovery.

Induction:- It is the time interval between the administration of anaesthetic drug & the development of stage of surgical Anaesthesia.

lipophilicity is key factor governing pharmacokinetics of Inducing drugs.

Maintainance:- It is the period during which the patient remains in a sustained stage of surgical anaesthesia. During the stage, the anaesthesiologist monitors the patients vital signs and response to various stimuli by controlling concentration of anaesthetic to be inhaled can infused based on depth of anaesthesia.

Recovery:- The recovery phase starts when the anaesthetic drug is discontinued. During this phase the anaesthesiologist has to ensure that there are no delayed toxic reactions.

Inhalational Anaesthetics:-

(1) Nitrous oxide (N_2O):- It has a mild sweetish smell. It is used to maintain surgical anaesthesia with 50% O_2 & other volatile anaesthetics like halothane, isoflurone or propofol & a muscle relaxant if required.

(2) Halothane:- It is a halogenated volatile anaesthetics. It is a poor analgesic and poor muscle relaxant. It is used along with nitrous oxide / opioids and skeletal muscle relaxants.

(3) Ether (Diethyl ether):- Ether is a highly volatile liquid. Ether is a potent anaesthetic, produces good analgesia and marked muscle relaxation by reducing Ach output from motor nerve endings.

Parenteral Anaesthesia:- Fast Acting intravenous anaesthesi

replace the inhalation anaesthesia for induction & inhalation anaesthesia is used for maintenance.

Fast Acting Inducing Agent:

Thiopentone:- An ultrashort acting thiobarbiturates. It is highly lipid soluble hence has a rapid onset & short duration [5-8 minutes] of Action. Injected (I.V) (3.5 mg/gm/kg a 2.5%. solution thiopentone sod. Produce unconsciousness in 15-20 sec.

Opioid Analgesia:- (Slower Acting drugs)

Fentanyl:- This highly lipophilic, short-Acting (30-50min potent opioid analgesic related pethidin given I.V. at the beginning of painful surgical procedure.

Complications of General Anaesthesia:

(A) During Anaesthesia

1. Respiratory depression & hypercarbia
2. Salivation, respiratory secretions.
3. Cardiac arrhythmias
4. Fall in BP

[B] After Anaesthesia

1) Nausea & vomiting
2) Persisting sedation
3) Pneumonia
4) Organ toxicities - liver, kidney damage

Drug Interactions :-

1) Patients on antihypertensive given general anaesthetics — BP may fall markedly.

2) Halothane sensitizes the heart to Adr.

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 & apprehension preoperatively & to facilitate smooth induction.

2) Amnesia for pre-and postoperative events.

3) Supplement analgesic action of Anaesthetics & potentiate them so that less anaesthetic is needed.

4) Decrease acidity & volume of gastric juice so that it is less damaging if aspirated.

1) Sedative - Antianxiety drugs :- Benzodiazepines like diazepam (5-10mg oral) or lorazepam (2mg oral or 0.05 mg/kg i.m 1hr before) used.

In Sedation and hypnotics to BZDs, promethazine is widely used. It is an antihistamine with sedative, antiemetic & Anticholinergic actions. It causes negligible respiratory depression is useful for children.

Opioid Analgesics:- Morphine (or) pethidine is used Fentanyl is mostly injected i.v. just before induction.

(iii) Anticholinergics:- Atropine or hyoscine or glycopyrolate are used. They reduce salivary, Bronchial secretions, produce bradycardia & hypotension.

(iv) Antiemetics:- Metoclopramide, domperidone are used for gastric emptying prior to emergency surgery. Reducing post-operative vomiting.

(v) H_2 blockers / proton Pump Inhibitors:- Ranitidine or Famotidine are given in night before and in the morning before surgery.

Sedative-Hypnotics

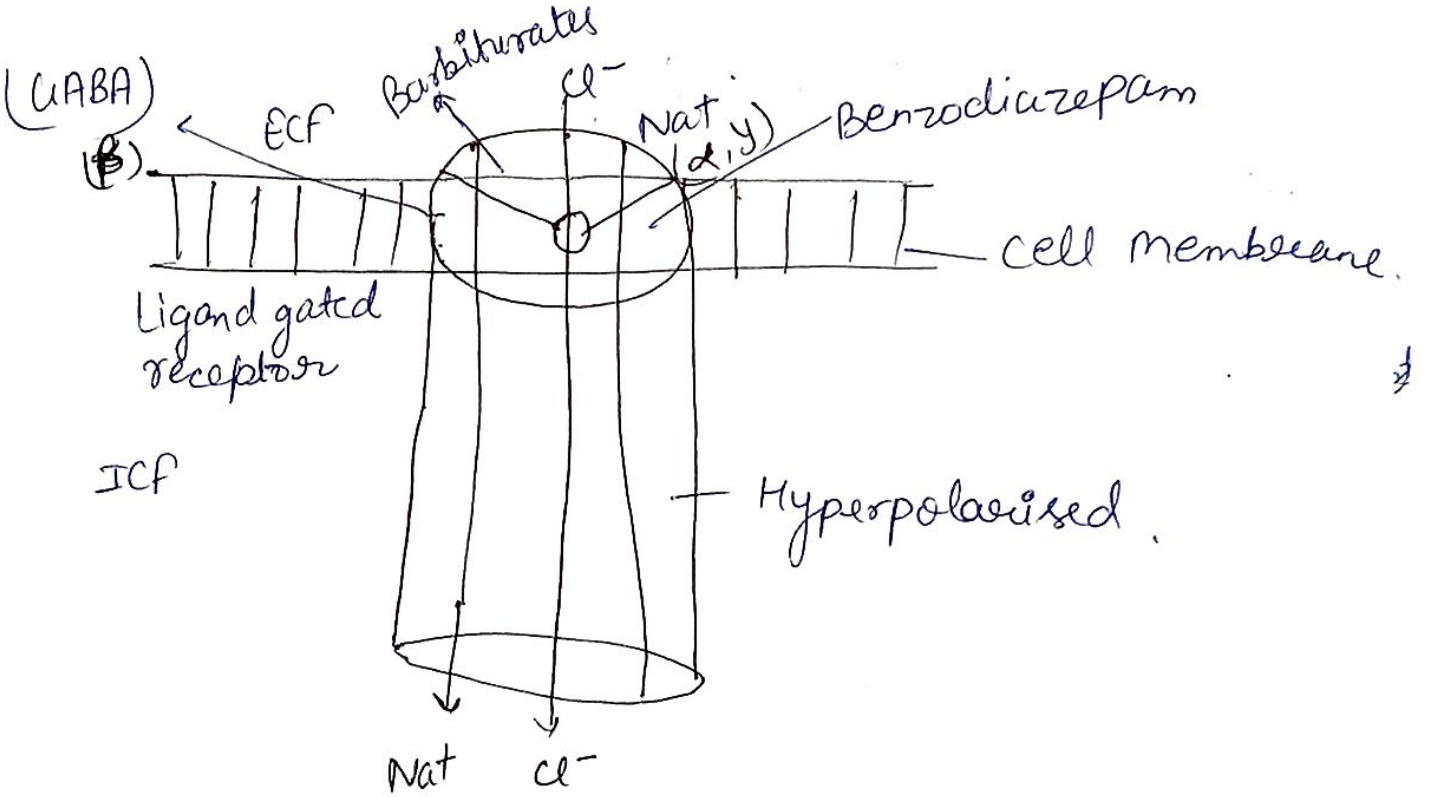
Sedative:- A drug that subdues excitement and calms the subject without inducing sleep, though drowsiness may be produced.

Sedation refers to decreased responsiveness to any kind of stimulation.

Hypnotic are the drugs that induces and/or maintain sleep, similar to normal arousable sleep. Sedative & Hypnotics are those drugs which acts on the central NS & they reduce the mental excitement, mental depress & produce the Natural sleep & sound sleep. Sedative are those drugs which do not produce sleep.

Mode of Action of Sedative & Hypnotics:-

Basically sedative and Hypnotics drugs are in Of three categ ory GABA analog, Benzodiazepines and Barbiturates. When Benzodiazepam or barbiturates any of the drug bind with their selective receptor like benzodiazepam bind with Benzodiazepam receptor and which these drugs bind the receptor the channels are becomes open and Cl^- ion goes from extracellular fluid to intracellular fluid. and when Cl^- ion moves the channels becomes hyperpolarised & when the receptor becomes hyperpolarised the transmission of Na^+ ion is compeletely stop & that cause brains becomes relax & the excitement of brain is reduce & Sedative & hypnotics action produce in our CNS.



Pharmacological Action :-

1) Action of Sedative & Hypnotics
when the barbiturates deug given in small dose then it shows sedative action & when it given in large dose shows Hypnotics Action.

2) Anaesthetic effect :- Some barbiturates deugs like Thiopental Sodium when it is given IV form then it cause Anaesthetic effect and these deug is generally given in pre Anaesthetic medication.

3) Anticonvulsant : Some catcgory of barbiturates deugs is given for the treatment of epilepsy like phenobarbiturates.

4) Effect on Respiration - Rate of respiration becomes less / slow.

5) Effect on CVS :- No effect on CVS in general dose but after a long dose it may cause decrease in the heart rate & cardiac output also decreases.

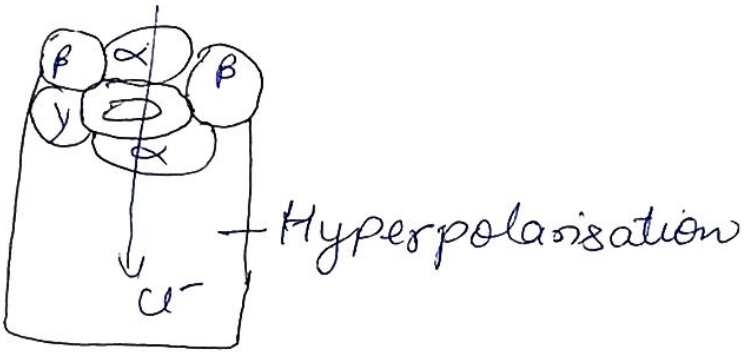
6) Effect on kidney :- when barbiturates deug is given it shows effect on kidney it reduce the Glomerular filtration rate so the urine output is reduce.

Pharmacokinetics :- It is well absorb orally from stomach and GIT. Metabolise in to the liver & secrete through urine.

Adverse effect :-

Intolerance
Anaemia
Allergy
Addiction
Respiratory depression.

Pharmacology of Benzodiazepines :- Benzodiazepines drug is a sedative Hypnotics category drugs. GABA inhibit the Action of brain or it depress the Brain. When Benzodiazepine drugs bind with the GABA receptor then GABA receptor contain five pentameric form two α and α β & one γ. After binding with the drug Benzodiazepine with GABA receptor the Cl^- channel is open & Cl^- ions goes to inside from ECF to ICF. and due to hyperpolarisation of Cl^- ion the depress.



Pharmacological Action :-

(1) Sedative & Hypnotics Action :- Benzodiazepines drugs are used to treatment of Insomnia. It is given for sedative & Hypnotics Action.

(2) Reduction of Anxiety & Aggression :- Drugs used in Anxiety Reduction and Aggression.

(3) Reduce Muscle tone :- It is also given in the case of muscle spasm.

(4) Anticonvulsant Action :- Some drugs are benzodiazepine category like Diazepam & Midazolam which is given orally for the treatment of epilepsy or as an anticonvulsant drug.

Pharmacokinetics:- It is given orally. It is well absorbed stomach & intestine. It is excercate from the urine.

Adverse effect:- Drowsiness, Dizziness, Reduce Concentration.

Anticonvulsant / Antiepileptic :-

Epilepsy:- Most commonly seizures is also known as epilepsy. It is a neurological disorder in which neurohumoral transmission of brain is completely affected. The function of all organ or body is completely change and seizure or convulsion comes out which is called epilepsy.

- Classification of seizures :-

Seizures are classified into -

(i) Generalised seizures:- These seizures arise from both cerebral hemispheres and diencephelon simultaneously involving the entire body. It is two types -

(i) Grandmal (Tonic clonic seizures)

(ii) Petimal (Absence Seizures)

Grandmal :- It is also called tonic clonic seizures It seizures starts from aurea & then after bilateral muscular jerk. In this seizure the completely loss of consciousness. ~~and the loss of~~ s involve & muscle spasm. It remain two to five minute.

(ii) Petimal :- It is also called absence seizure (minorepi. It is basically seen in the children. Completely loss of consciousness the loss of speech is generally seen. It last from 1 to 30 sec.

(2) Partial (Focal seizures) :- This type of seizure generally seen in any one part of the brain basically temporal lobes it not involves in the full brain.
It is two types - (i) Simple
(ii) Complex — Psychomotor

(i) Simple :- It is also known as Jacksonion motor Epilepsy. Some muscle are jump like thumb or toe. and do not loss any type of consciousness. Duration of time is 1 to 2 minutes.

Complex :- It is also called Psychomotor epilepsy. In this case body shows muscles behaviour like extensive, swallowing..

Mechanism of Action :-

It is two types :-

(i) General Mechanism :- Excitation of GABA
Reducing discharge Rate
Hyperpolarisation by cl^- ion.

(ii) Molecular Mechanism :- • Blockage of voltage gated Na^+ channel
• Tease of GABA Enhancement.
Barbiturates & Benzodiazepines.

(a) Mechanism in Grandmal & Partial seizures :-

(i) Inhibition of use-dependent sodium ion channels drugs like phenytoin etc Block voltage-gated Na^+ channels.

(ii) Enhancement of GABAergic Action -
Drugs like phenobarbital, Benzodiazepines activate $GABA_A$ receptor to facilitate opening of Cl^- channels.

(iii) Blockade of voltage-gated N type calcium channels.

(b) Mechanism in petitmal (Absence seizures)
Inhibit the Ca^+ channels.

Alcohols & Disulfiram :-

Alcohols (ethanol) are hydroxy derivatives (on) of aliphatic hydrocarbons.

Preparations :- Alcohol is manufactured by fermentation of sugars.

Sugar $\xrightarrow[\text{(in yeast}]{\text{zymase}}$ Starch $\xrightarrow{\text{converase}}$ Maltose $\xrightarrow{\text{Yeast}}$ alcohol

~~There~~ There are a large variety of alcoholic beverages.

(a) Malted liquors :- Obtained by fermentation of germinating cereals. eg : Beers. (alcohol content is loco 3-6%).

(b) Wines :- Produced by Fermentation of Natural Sugars as present in grapes & other fruits. eg : Light wines (9-12%) can not exceed 15%.

(1) Spirits :- These are distilled after fermentation, eg: Rum, Gin, Whiskey, Vodka etc. Alcohol content (40-55%)

Other forms of Alcohols :-

① Absolute alcohol - 99% w/w ethanol (dehydrated alcohol)

② Rectified spirit - 90% w/w ethyl alcohol produced from fermented molasses, by distillation.

③ Proof Spirit :- It is an old term. If whiskey is poured on gun powder and ignited & it explodes then it was labelled to be of proof strength.

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.

Mechanism of Action :- Alcohol has been shown to enhance GABA release at $GABA_A$ sites in the Brain. It also inhibit NMDA (N-Methyl D-aspartate Receptor) and kainate receptor-type of excitatory Amino acid receptors (operating through cation channel). 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 may also be one of the targets of Alcohol Action. Ethanol can indirectly reduce neurotransmitter release by inhibiting voltage sensitive neuronal Ca^{2+} channels.

Pharmacological Action of Alcohol :-

① Local Actions :- Ethanol is a mild rubefacient and counterirritant when rubbed on the skin by evaporat it produce cooling. By precipitating bacterial protei it acts as an antiseptic.

② CNS : Alcohol is a neuronal depressant.

③ CVS :- The effects are dependent on dose.
Small doses :- produce only cutaneous and vasodilatation.
Moderate doses :- cause tachycardia and a mild rise in BP due ↑ in muscular activity and sympathetic stimulation.
Large doses :- cause direct myocardial as well as vasomotor centre depression and fall in BP.

④ Blood :- Regular intake of small to moderate amounts of alcohol (1-2 drinks) has been found to raise HDL-cholesterol level and ↓ LDL oxidation. Mild anaemia is common in chronic alcoholics.

⑤ Body temperature :- It produce a ~~real~~ sense of warmth due to cutaneous and gastric vasodilatation, but heat loss is actually increased in cold surroundings. High doses depress temp. regul-ating centre.

⑥ Respiration :- Brandy & whiskey are reputed as respiratory stimulants in collapse. Because the direct action of alcohol on respiratory centre is only a depressent one.

⑦ GIT :- Dilute alcohol 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 inhibit gastric secretion, cause vomiting, mucosal congestion and gastritis. Alcoholism is an important cause of chronic gastritis.

8) Liver :- chronic alcoholism exposes liver to oxidative stress and causes cellular necrosis followed by fibrosis. Acetaldehyde produced during metabolism of alcohol appears to damage the hapatocytes and induce inflammation, especially on chronic ingestion of large amounts.

9) Skeletal muscle :- Alcohol produces little direct effect. weakness and myopathy occurs in chronic alcoholism.

10) Kidney :- This due to water ingested along with drinks as well as alcohol induced inhibition of ADH secretion. It does not impair renal function.

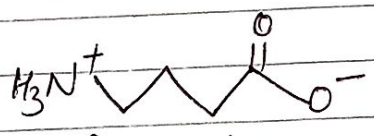
11) Uterine contractions are suppressed at moderate blood levels.

Neurotransmitter :-

Types of Neurotransmitter :-

Excitatory	Inhibitory	Both
Glutamate	Glycine	Ach
Aspartate	GABA	Norepinephrine
Nitric acid	Serotonin ✓	
	Dopamin ✓	

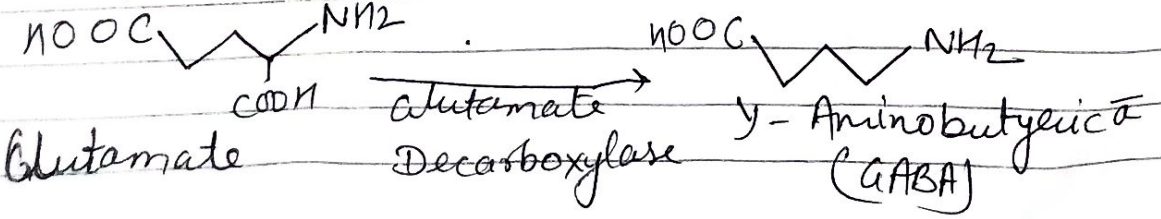
GABA :- (Gamma - Amino Butyric acid) :- It is an amino acid which acts as a neurotransmitter in the central nervous system.
It inhibits nerve transmission in the brain containing Nervous activity.
Chemical formula - $C_4H_9NO_2$
GABA is a zwitter ion with deprotonated carboxyl group & protonated amino group.



(GABA)

In 1950 Robert and Franked discovered that GABA acts as Inhibitory neurotransmitter in human brain.

Synthesis :-



Synthesis of GABA

Glutamine
↓ → Glutaminase
Glutamate
↓ → glutamatedecarboxylase
GABA

Metabolism of GABA

GABA
↓ GABA-T
Succinic semialdehyde
↓ Succinic semialdehyde dehydrogenase
Succinate

There are 2 types of GABA receptors.

(i) $GABA_A$
(ii) $GABA_B$

(i) It has pentameric structure. It has structured & functional similarity with ligand gated ion.
A receptor contain two α, two β & one γ subunit

(ii) They are hetrodimers GABA-B has been cloned to be b_1 & b_2 subunits
Two Biological Action - Decrease Ca^{2+} conductance
Tease K^+ conductance

Functions:-
- Relieving Anxiety
- Relieving Pain, Burning fat
- Stabilising Blood pressure
- Decrease Blood sugar level in diabetics