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**General anesthesia (G.A)**

General anesthesia is used as an adjunct to surgical procedure in order to render the patient unaware of and unresponsive to painful stimuli. Davy at 1800 first discovered nitrous oxide and tests this on the people lead to analgesia, euphoria and loss of consciousness so this gas called (laughing gas). American dentist (wells) first used it for tooth extraction.

* Ether discovered by dentist student named Morton 1846.
* Chloroform discovered by obstetrics Simpson.
* The G.A act on the cell membrane and interact with cellular lipid and protein, therefore there are two theories:-
1. **Lipid theory:** high lipid solubility of G.A lead to interact with membrane phospholipid and produce effects, therefore the potency of G.A correlated with lipid solubility.
2. **Protein theory:** G.A act on membrane proteins which found as receptor so inhibit excitatory receptor like glutamate receptor, acetylcholine receptor, 5HT receptor or enhancing the inhibitory receptor like GABA and glycin receptor.
* Therefore, the G.A acts on both lipid and protein of cell membrane.

**Mechanism of G.A:**

1. Facilitate the effect of GABA on GABA receptor.
2. Activation of GABA receptor.
3. Inhibition of excitatory neurotransmitters.
4. Activation of liganed gated K+-channel.
5. Increase frequency and duration of Cl--channel opening.
6. Inhibit axonal transmission by reduction of transmitter release and ↓ post-synaptic excitability and responsiveness.

All these effects occurred at (RAS) reticular activating system which is responsible for arousal state, but at high concentration all brain can be inhibited even the medullary centers lead to death.

**Stages of G.A:**

* Stage **I** **(analgesia)** → ↓ response to painful stimuli.
* Stage **II** **(excitement)** → ↓ response to painful stimuli and loss of consciousness but other reflexes are present (dangerous stage).
* Stage **III** **(surgical anesthesia)** → most reflex disappears.
* Stage **IV** **(medullary paralysis)** → inhibiting of respiratory and vasomotor center lead to death.

**Note:**

Induction → onset the G.A effects

Maintenance → duration of G.A effects

**Preoperative medication:**

1. **Benzodiazepine** for **sedation**.
2. **Atropine** for **inhibiting salivation** and **bronchorea** during surgery.
3. **Analgesic** for painful conditions.
4. **Anti-histamine** to ↓ allergic reactions for anesthetic agents.
5. **Neuromuscular blockers.**

**Types of G.A**

1. **Inhalation G.A:**

Taken by mask lead to slow induction and rapid recovery, the effects of inhaled G.A depend on the blood solubility, so soluble G.A need time for solubility so cause relative slow induction and slow recovery so can't interfere with O2 entrance at alveolar level, but less soluble G.A need no time for blood solubility lead to rapid induction and rapid recovery so interfere with O2 entrance at alveolar level lead to diffusion hypoxia, so this type should be mixed with O2 during anesthesia.

**Types of inhaled G.A agents**

1. **Halothan:**
* Weak analgesic.
* Potent anesthetic.
* Solubility is high, not causing diffusion hypoxia.
* Cause CVS stimulation due to sensitization of β1 receptor on the heart, so not used during myocardial infarction.
* It metabolized to triofluroacetate which is hepatotoxic so lead to hepatotoxicity with repeat using.
* Cause malignant hyperthermia in patients with cholin esterase deficiency.
* Not used for labor because it ↓ uterine contraction.

**Mechanism:** Halothane activates GABAA and glycine receptors, NMDA receptor antagonist, inhibits nACh and voltage-gated sodium channels, and activates 5-HT3 and twin-pore K+ channels.

**Halothan analogue**

* **Enflurane:**
* Less potent than halothan.
* Less cardiac sensitization of β1 to catecholamine.
* Metabolized to florid ion cause renal damage.
* Has curare like effect lead to skeletal muscle relaxation.
* Cause CNS excitation.
* Myocardial depression
* **Isofllurane:**
* Not metabolized to florid so less toxic for the kidneys.
* Not cause cardiac sensitization.
* ↑ Coronary blood flow so it safe in ischemic heart disease.
* **Desflurane:**
* Not toxic.
* ↓ Vascular resistance so it safe in hypertension.
* Very irritant to children because it cause laryngospasm.
* **Sevoflurane**:
* Nephrotoxic because it metabolized to florid ion.
* Safe in children because it not cause laryngospasm.
1. **Nitrous oxide (N2O)**

**Mechanism:**blocks NMDA and β2-subunit-containing nAChchannels,weakly inhibits AMPA, kainate, GABAC, and 5-HT3receptors, and slightly potentiates GABAA and glycine receptors.activate two-pore-domain K+ channelsPotent analgesic so can be used for labor and sever painful condition like fracture.

* Cause diffusion hypoxia because it poor soluble in blood.
* Cause megaloblastic anaemia due to ↓ B12.
* Used for maintenance of anesthesia only.
* Poor anesthetic.
* Not affect the uterine muscle, so it safe in labor.
* Prolong exposure at low dose (as in operating theater staff) lead to inhibition of methionine synthase so ↓ DNA and protein synthesis lead to anaemia and leukopenia and malformation for pregnant women.
1. **Other inhaled G.A:**
* **Chloroform** → hepatotoxic and cause cardiac dysrhythmias.
* **Diethylether** → explosive and highly irritant to respiratory tract.
* **Cyclopropane** → explosive, respiratory depressant and cause hypotension.
1. **Intravenous G.A**

Cause rapid induction and slow recovery

* **Barbiturate**:
	+ Potent anesthetic.
	+ Not analgesic, but cause hyperalgeisa i.e. cause severe pain.
	+ CNS and respiratory depressant.
	+ Used for brain surgery because it ↓ glucose uptake.
	+ When given intra-arterial it leads to crystallization and thrombosis.
	+ CVS inhibition due to vasodilatation and myocardial inhibition.
	+ ↓ Muscle tone and contraction.
	+ Cause severe laryngospasm so not used for ENT surgery.
	+ ↓ Sympathetic effects because it ↑ GABA – Cl- ion complex duration opening so may lead to coma.
	+ It enzyme inducer so precipitate porphyria.
	+ Highly lipid soluble, so highly stored in fatty tissue so lead to prolong hangover especially in obese patients.
1. **Ketamine:**

**Mechanism:** Non-competitive antagonist of the NMDA receptor , Negative allosteric modulator of the nACh receptor, Weak agonist of the μ-opioid and κ-opioid receptors, Agonist of the D2 receptor, Weak mACh receptor antagonist, Inhibitor of the reuptake of serotonin, dopamine, and norepinephrine, Voltage-gated sodium channel and L-type calcium channel blocker, Inhibitor of nitric oxide synthase.

* + Weak anesthetic but potent analgesic cause little sleep lead to dissociative anesthesia.
	+ CNS stimulation, lead to sever postoperative hallucination and dysphoria, also ↑ cerebral blood flow so contraindicated in brain surgery.
	+ ↑ Skeletal muscle contraction so not used for abdominal surgery.
	+ ↑ Sympathetic stimulation because it act on NMDA receptor.
	+ Not cause laryngospasm so indicated for ENT surgery.
	+ It derived from phencyclidine but cause less euphoria and sensory distortion.
	+ Can be given I.M.
	+ Not affect the respiratory system.

**Other indications:**

###  Chronic pain, bipolar disorder, major depressive disorder due to blocking NMDA receptors for glutamate, a different mechanism from most modern antidepressants that operate on other targets. Recreational uses due to depersonalization and derealization and treatment for alcohol addiction.

1. **Propofol**:

**Mechanism**: potentiation of GABAA receptor activity, thereby slowing the channel-closing time, and also acting as a sodium channel blocker. Modulation of the endocannabinoid system.

## Other uses: use of propofol to execute prisoners condemned to death, the short-term effects sought via recreational use include mild euphoria, hallucinations, and disinhibition.

**Side effects**: decreased systemic vascular resistance, myocardial blood flow, and oxygen consumption, possibly through direct vasodilation, green discolouration of the urine. Diminishing cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure are also characteristics of propofol administration. dystonia. Mild myoclonic movements are common, as with other intravenous hypnotic agents. Propofol appears to be safe for use in porphyria, and has not been known to trigger malignant hyperpyrexia, Priapism, suppresses REM sleep stage and to worsen the poor sleep quality in some patients.

* + Poor analgesic, has sedative effect, rapid onset so can be used during emergency.
	+ Not cause vomiting because it has antiemetic effect.
	+ ↓ Intracranial pressure so used for brain surgery.
	+ Safe for spinal surgery because it ↓ spinal reflexes.
	+ Not CNS depressant.
	+ Short acting and not cause hangover.
	+ The main side effects are apnea and bradycardia.
1. **Midazolam**:

Short acting and short duration and fewer side effects, used for minor surgical procedure like endoscopy.

1. **Neuroleptic anesthesia:**

It is combination of Doperidol + Fentanyl + N2O used for elderly that can't tolerate the G.A due to impairment of homeostatic status.

1. **Etomidate:**

**Mechanism**:  modulator at GABAA receptors.

* Not analgesic, rapid onset, less CNS and respiratory depression.
* ↑ Muscle involuntary movement.
* Inhibit the adrenal steriodogenesis during prolong exposure so not used for severely ill patients, only used as induction and not for maintenance of anesthesia.

**Skeletal muscle relaxant**

1. **Neuromuscular blockers**:
2. Competitive.
3. Non – competitive.
4. **Benzodiazepine.**
5. **Baclofen: act by**:
* Activate GABA – B receptor.
* Spinal cord hyperpolarization by ↑ K+ conductance.
* Inhibit substance P release.
* Presynaptic inhibition for excitatory neurotransmitters release.

 **Used for:**

1. **Chronic pain.**
2. **Spasticity.**
3. **Migraine prophylaxis.**
4. **Alcoholism.**
5. **Tizanidine:**

α2 agonist, cause presynaptic and postsynaptic inhibition at spinal cord and block pain transmission at dorsal horn, used for sever spasticity. Used for  spasms, cramping, and tightness of muscles caused by medical problems such as multiple sclerosis,  spastic diplegia, back pain, migraine headaches, anticonvulsant, fibromyalgia.

1. **Idrocilamide:** Block central glutamergic transmission, used for sever muscle spasm. Skeletal muscle relaxant and anti-inflammatory actions used as a topical cream to treat lumbago and other kinds of muscular pain.
2. **Dantrolen:** Derivative of phenytoin, block ryanodin receptor at skeletal muscle sacroplasmic reticulum so ↓ Ca+ release, used for muscle spasticity and malignant hyperthermia, is a postsynaptic muscle relaxant that lessens excitation-contraction coupling in muscle cells. It achieves this by inhibiting Ca2+ ions release from sarcoplasmic reticulum stores by antagonizing ryanodine receptors. It is the primary drug used for the treatment and prevention of malignant hyperthermia, a rare, life-threatening disorder triggered by general anesthesia. It is also used in the management of neuroleptic malignant syndrome, muscle spasticity (e.g. after strokes, in paraplegia, cerebral palsy, or patients with multiple sclerosis), and dinitrophenol poisoning.

### Botulinium toxin: Prevent Ach release at neuromuscular junction, used for local muscle spasm and for ophthalmic examination. Botulinum toxin types A and B are used in medicine for, among others, upper motor neuron syndrome, focal hyperhidrosis,blepharospasm, strabismus, chronic migraine and bruxism. Also; used for  achalasia, idiopathic and neurogenic detrusor overactivity, vaginismus, spasmodic dysphonia and tremor, anal fissure,  cerebral palsy, prevent development of wrinkles by paralyzing facial muscles and chronic migraine.