

Anesthetic Agents			Adjuvants to Anesthesia	
General Anesthesia (the triad of anesthesia)			Local anesthesia	Benzodiazepines For amnesia & to eliminate anxiety
Hypnosis	Analgesia	Muscle relaxation		
Intravenous	Opioids	Neuromuscular blocking drugs	1. Lidocaine 2. Bupivacaine 3. Ropivacaine	1. Midazolam 2. Lorazepam 3. Diazepam
1. Barbiturates 2. Propofol 3. Etomidate 4. Ketamine	1. Fentanyl 2. Sufentanil 3. Alfentanil 4. Remifentanyl 5. Meperidine <sup>1</sup> 6. Morphine	1. Succinylcholine 2. Mivacurium 3. Atracurium 4. Cisatracurium 5. Doxacurium 6. Pancuronium		
Inhalational				
1. Sevoflurane 2. Isoflurane 3. Desflurane 4. Halothane 5. Nitrous Oxide				

<sup>1</sup> AKA: Pethidine.

## ★ Intravenous Anesthetics:

### 1. Barbiturates:

Thiopental (thiopentone sodium) is a thiobarbiturate. **most common**

- **MOA:**

- Facilitate inhibitory neurotransmission by enhancing GABAA receptor function.
- Inhibit excitatory neurotransmission via glutamate and nicotinic acetylcholine receptors.

- **Pharmacokinetics:**

- Metabolic and elimination is Hepatic. **It takes hours to excreted from body, but patient wakes up because brain concentration becomes low by redistribution of drug over the body.**

- Multiple doses or prolonged infusions may produce prolonged sedation or unconsciousness

- **Pharmacodynamics:**

CNS	CVS	Respiratory system
Dose-dependent CNS depression. ↓ in (CMRO <sub>2</sub> ), cause ↓ in ICP and(CBF). <b>Considered advantage in patients with head injury.</b>	-Depress myocardial contractility, leading to dose-dependent ↓ in BP and cardiac output, -Baroreceptor reflexes remain largely intact. <b>Cause reflex tachycardia</b>	-Dose-dependent decrease in RR and TV. -Apnea may last for 30 to 90 seconds after induction dose. <b>Therefore oxygen must be provided.</b> -Laryngeal reflexes remain more intact compared to propofol so higher incidence of cough and laryngospasm.

- **Primary use:** Induction of anesthesia. **Also used as infusion (if I cannot use Halothane as infusion in patients with malignant hyperpyrexia or in airway surgeries)**

Advantages	Adverse effects
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- Rapid onset (30-45 sec), short duration (5-8 min) initial dose; redistributed from brain to muscle resulting in return of consciousness. so we should maintain the anesthesia then.
- It has potent anticonvulsant properties.
- Given to patients with status epilepticus.

Dose dependent histamine release. in some patients will cause rash, bronchospasm.

- Myoclonus and hiccups.
- **Absolutely contraindicated in Porphyria**(take good history)
- Venous irritation and tissue damage. It will cause pain with injecting because the drug is highly alkaline PH=10.5.

- Thiopental can cause severe pain & tissue necrosis if injected subcutaneously or intra arterially. it will damage the artery also the perfusion distal to the injection site will compromised. May cause limb loss or digit loss.
- If intra-arterial administration occurs, heparin, vasodilators, and regional sympathetic blockade may be helpful in treatment. Inject heparin in the same artery to prevent clot formation.
- **Dosage & Administration:**
  - Induction: IV 3-6 mg/kg
  - Sedation IV 0.5-1.5 mg/kg

N.B. Reduce doses in hypovolemic, elderly, or hemodynamically compromised patients. it causes hypotension.

## 2. Propofol (2,6-diisopropylphenol):

It is the most widely used induction agent. 1% isotonic oil-in- water emulsion, which contains egg lecithin, glycerol, and soybean oil. Can be used as an anesthetic agent if infused.

- **MOA:**
  - Facilitates inhibitory neurotransmission by enhancing the function (GABAA) receptors in the CNS.
- **Pharmacokinetics:**
  - Hepatic and extrahepatic metabolism leads to inactive metabolites which are excreted by renal route
- **Pharmacodynamics:**

CNS

CVS

Respiratory system

<ul style="list-style-type: none"> <li>○ Less (PONV)<sup>1</sup> occurs. Compared to</li> </ul>	<p>Heart rate (HR) is minimally</p>	
<ul style="list-style-type: none"> <li>● <b>Primary use</b> <ul style="list-style-type: none"> <li>○ A sedative/hypnotic in OR &amp; ICU.</li> </ul> </li> </ul>		
<p>Induction: <b>rapid onset of unconsciousness</b> (30 to 45 seconds), <b>followed by a rapid termination of effect</b> by redistribution, emergence is rapid. So, the patient will wake up if we don't maintain the anesthesia</p> <ul style="list-style-type: none"> <li>○ Weak analgesic effects. so give analgesics with it like narcotic.</li> <li>○ ↓ (ICP) and ↓ (CPP) due to markedly ↓ (MAP). for neurosurgery.</li> <li>○ Anticonvulsant. used in status epilepticus thiopentone sodium.</li> <li>○ (some research: the drug by itself</li> </ul>	<p>Dose-dependent ↓ in preload, afterload, and contractility lead to ↓ <b>in (BP)</b> and COP. You have to be very careful and reduce the dose in hypovolemic patients</p> <p>Hypotension may be marked in hypovolemic, elderly, or hemodynamically compromised patients.</p> <p>affected, and baroreceptor reflex is blunted. No reflex tachycardia antiemetic)</p>	<ul style="list-style-type: none"> <li>○ Dose-dependent decrease in (RR) and (TV).</li> <li>○ ↓ Ventilatory response to hypoxia and hypercarbia. (Normally if I got hypoxia the RR and TV will increase) this response will be blunted if I use propofol</li> </ul>
<ul style="list-style-type: none"> <li>○ Induction of anesthesia.</li> <li>○ Maintenance of anesthesia (TIVA).</li> </ul>		
Advantages	Adverse effects	

<ul style="list-style-type: none"> <li>○ Rapid Produces Laryngeal &amp; pharyngeal muscle relaxation, allowing LMA insertion. <b>less incidence of laryngeal spasm.</b></li> <li>○ Safe in Malignant hyperthermia (MH) &amp; Porphyria patients.</li> <li>○ <b>Antiemetic properties.</b></li> <li>○ Suitable for day case surgery to avoid prolonged postoperative hangover (drowsiness, ataxia).</li> <li>○ Situations where volatile anesthetics cannot be used (MH, transfer of sedated patients, airway surgery).</li> </ul>	<p>Venous irritation. <b>Injecting this drug is also</b></p> <ul style="list-style-type: none"> <li>○ <b>painful</b> even more painful than thiopentone sodium so we have to use local anesthesia before administration.</li> <li>○ Bacterial growth Propofol contains lipids so if it is kept open for hours it can lead to bacterial growth.</li> <li>○ <b>Contraindicated in</b> Lipid disorders. used cautiously in disorders of lipid metabolism (e.g., hyperlipidemia and pancreatitis). <b>it contains lipids.</b></li> <li>○ Myoclonus and hiccups</li> <li>○ <b>Propofol infusion syndrome: if used for long hours or days like in ICU</b> A rare fatal disorder that occurs in critically ill patients (usually children) subjected to prolonged, high-dose propofol infusions. (Rhabdomyolysis, metabolic acidosis, cardiac failure, and renal failure). <b>So, we shouldn't use it for prolonged sedation in pediatric patients</b></li> </ul>
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- **Dosage & Administration:**

- Induction: IV 1-2.5mg/kg
- Sedation IV 25-100 µ/kg/min. **for endoscopy.**

Titrate with incremental doses in hypovolemic, elderly, or hemodynamically compromised patients or if administered with other anesthetics. **reduce the dose.**

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<sup>2</sup> Post op nausea and vomiting

### 3. Etomidate: It's a carboxylated imidazole

- **MOA:**

- Facilitates inhibitory neurotransmission by enhancing the function (GABAA) receptors.

- **Pharmacokinetics:**

- Effects of a single bolus dose are terminated by redistribution.
- Very high clearance in the liver and by circulating esterases to inactive metabolites.

- **Pharmacodynamics:**

CNS	CVS	Respiratory system
<ul style="list-style-type: none"> <li>○ No analgesic properties. ↓ (CBF), cerebral metabolic rate (CMR), and (ICP). <u>used in patients with head injury or raised ICP.</u></li> </ul>	<p><b>Minimal changes</b> in HR, BP, and COP.</p> <p><b>Good for hypovolemic unstable patient, elderly.</b></p>	<p>Dose-dependent ↓ in (RR) &amp; (TV). Transient apnea may occur</p>

- **Primary use:** Induction of anesthesia in patients with cardiovascular problems. **Because there is less hypotension compared to thiopentone sodium and propofol.**

Advantages	Adverse effects
<p>Short acting and potent, with CVS and RS stability, suitable for <u>elderly and shocked patients.</u></p>	<ul style="list-style-type: none"> <li>○ Excitatory phenomena (Involuntary limb twitches), myoclonus</li> <li>○ Nausea and vomiting. <b>give antiemetic</b></li> <li>○ Venous irritation and superficial thrombophlebitis</li> <li>○ <b>Adrenal suppression, (Inhibits 11β &amp; 17 α hydroxylase ICU patients can go to adrenal crisis.</b></li> <li>○ <b>A single dose suppresses adrenal steroid synthesis for up to 24 hours. Repeated doses /infusion is associated with increased mortality in ICU patients. So, this drug cannot be used in sedation for ICU patients</b></li> </ul>

- **Dosage & Administration:**

- Induction: IV 0.2-0.5 mg/kg

**4. Ketamine:** It is phencyclidine derivative causing ‘dissociative anesthesia’ **means the patients may be eyes open and looking at you but he is anesthetized can’t feel the pain.**

- **MOA:**

- Mainly attributed to noncompetitive antagonism of NMDA receptors in the CNS

- **Pharmacokinetics:**

- Unconsciousness in 30 to 60 s after an IV.
- Terminated by redistribution in 15 to 20 minutes.
- Metabolized rapidly in the liver to multiple metabolites, some of which have modest activity (e.g., norketamine).
- Elimination half-life is 2 to 3 hours.

- **Pharmacodynamics:**

CNS	CVS	Respiratory system
<ul style="list-style-type: none"> <li>○ Amnesia and profound analgesia.</li> <li>○ No need to give opioids ↑ (CBF), ↑ (CMR), and ↑ (ICP) pressure. We <b>can't</b> use it in patients with head injury.</li> </ul>	<ul style="list-style-type: none"> <li>○ ↑ HR, COP, and BP . Used in hemodynamically compromised patients. Good for trauma patients in shock (Bleeding, hypovolemia)</li> </ul>	<ul style="list-style-type: none"> <li>○ Mild depression of ( RR) and (TV).</li> <li>○ <b>Potent bronchodilator.</b></li> <li>○ Laryngeal protective reflexes are maintained. So, Incidence of aspiration is less.</li> </ul>

- **Primary use:**

- Sedation and analgesia..
- Induction of general anesthesia.

Advantages	Disadvantages
<ul style="list-style-type: none"> <li>○ CVS stability makes it suitable for shocked patients.</li> <li>○ Preservation of airway reflexes &amp; less respiratory depression makes it suitable for procedures – radiological interventions, radiotherapy, burns &amp; dressing changes Very cheap</li> </ul>	<ul style="list-style-type: none"> <li>○ ↑ salivatio. you have to do oral suction and give anticholinergic, PONV (post op nausea and vomiting).</li> <li>○ Emotional disturbance, agitation &amp; hallucinations. Must give other drugs for sedation.</li> <li>○ <b>Contraindicated in patients with head trauma</b></li> </ul>

- **Dosage & Administration:**

- Induction: IV 1-2 mg/kg, IM 3-5mg/kg

N.B. Useful for IM induction in patients with no IV access (e.g., children).



## ★ Inhalational anesthetics:

## Characteristics of the ideal inhaled anesthetic agent:

- Non - toxic, non-.allergenic, non - irritant.
- Stable in storage, non – flammable
- No extra specialist equipment required.
- Low solubility in blood and tissues. Less solubility means it will leave the body faster and will cross the BBB.
- Resistance to physical and metabolic degradation.
- Analgesic.
- CVS: no effect.
- No respiratory depression.
- Environmentally inert.
- No reaction to soda lime/ breathing circuit.soda lime used to remove the byproduct and reuse it.
- Not a malignant hyperthermia (MH) trigger.

- 1.Sevoflurane
- 2.Isoflurane
- 3.Desflurane
- 4.Halothane
- 5.Nitrous Oxide



## Volatile anesthetics

Present as liquids at room temperature and pressure.

Vaporized into gases for administration.

Vaporizer: special equipment required to convert the liquid to vapor form ... every anesthetic agent has his own vaporizer.

## The minimum alveolar concentration (MAC)

'The amount of vapor (%) needed to render 50% of spontaneously breathing patients unresponsive to a standard painful surgical stimulus.'

((the amount of vapor required to make 50% of the individual non-responsive to standard surgical stimulus)).

- Halothane 0.75% when we use 0.75% → 50% of patient will not move so I will give slightly more, about 0.9% to cover the remaining 50%.
- Isoflurane, 1.15%
- **Sevoflurane, 1.85%**
- Desflurane 6.0% at one atmosphere.
- **MOA:**



- Various ion channels in the CNS involved in synaptic transmission (including GABAA, glycine, and glutamate receptors) may play a role. They depress the function of glycine and glutamate receptors & enhance the activity of GABA receptors.

- **Pharmacokinetics:**

- The higher the vapor pressure, the more volatile the anesthetic. Blood solubility determines the speed of build-up / elimination from blood / brain. if the drug more soluble in the blood → first the blood will be saturated so, brain concentration will achieve slower → the onset will be slower → leaving the body will be delayed.
- Lower blood solubility means (faster induction/recovery)  
**Inspired air → Alveolar air → Blood → Brain**
- drug highly fat soluble → stay in the body for 10-15 min.
- less soluble → leave the body in less than 5 min.
- Metabolism: hepatic.
- Exhalation: This is the predominant route of elimination. ●

**Pharmacodynamics:**

CNS		CVS	Respiratory system	
<ul style="list-style-type: none"> <li>○ Unconsciousness &amp; amnesia . ↑ cerebral blood flow (CBF).</li> <li>○ lead to ↑ ICP</li> </ul>		<ul style="list-style-type: none"> <li>○ Myocardial depression &amp; systemic vasodilation.</li> <li>○ HR tends to be unchanged, except desflurane will ↑ HR Sensitize the myocardium to the arrhythmogenic effects of catecholamines sometime cause premature ventricular contraction of the heart</li> </ul>	<ul style="list-style-type: none"> <li>○ Dose-dependent respiratory depression</li> <li>○ Airway irritation and, during light levels of anesthesia, may precipitate coughing, laryngospasm, or bronchospasm (sevoflurane makes it more suitable ) Bronchodilator (with the exception of desflurane).</li> <li>○ Inhibit hypoxic pulmonary vasoconstriction</li> </ul>	
Renal system		Neuromuscular system		Hepatic system

<ul style="list-style-type: none"> <li>○ ↓ Renal blood flow.</li> </ul>	<ul style="list-style-type: none"> <li>○ Dose-dependent ↓ in skeletal muscle tone.</li> <li>○ May precipitate <b>malignant hyperthermia ... A dramatic increase in body temperature</b>, acidosis, electrolyte imbalance and shock.</li> </ul> <p>Inhalational agents induce calcium release and contracture of muscles So, the contracture increase in the metabolism of muscles &amp; potassium comes extracellular leads to arrhythmia, hypotension, rise in temperature, electrolyte imbalance and acidosis.</p>	<ul style="list-style-type: none"> <li>○ ↓ Hepatic perfusion.</li> </ul>
	<p>If the temperature keeps rising patient will die.</p> <ul style="list-style-type: none"> <li>○ Management is removal of triggering agent, 100% Oxygen, active cooling measures &amp; Dantrolene (1 to 10 mg/kg)</li> <li>○ Dantrolene: calcium channel inhibitor lead to reversing the effect.</li> </ul>	

✓ **Desflurane:**

Advantages	Disadvantages
<ul style="list-style-type: none"> <li>○ Rapid onset and recovery of anesthesia (outpatient procedures)</li> <li>○ <b>One of least metabolized to toxic byproducts.</b> Gets excreted immediately.</li> </ul>	<ul style="list-style-type: none"> <li>○ Requires a special vaporizer</li> <li>○ Pungent <b>smell</b> and irritating to the airway (leading to more coughing, laryngospasm) <b>Make it not good for induction.</b></li> <li>○ High inspired gas concentrations lead to a significant ↑ in the patient's BP &amp; HR.</li> </ul>

✓ **Sevoflurane:** most commonly used

Advantages	Disadvantages
<ul style="list-style-type: none"> <li>○ Low solubility in blood- <b>produces rapid induction</b> and emergence</li> <li>○ <b>Pleasant smelling (suitable for children) good for induction</b></li> <li>○ Has good bronchodilating properties</li> <li>○ Agent of choice in asthma, bronchitis, and COPD.</li> <li>○ It has little effect on the heart rate.</li> <li>○ Mild respiratory and cardiac suppression</li> </ul>	<ul style="list-style-type: none"> <li>○ Carbon dioxide absorbents in anesthesia machines degrade sevoflurane to Compound A</li> </ul> <p>if we use it for more than 6 hours there will be reaction with soda lime which leads to production of substance called compound A which is nephrotoxic</p>

✓ **Isoflurane:** not used anymore

Advantages	Disadvantages
<ul style="list-style-type: none"> <li>○ It causes peripheral vasodilation and increased coronary blood flow</li> </ul>	<ul style="list-style-type: none"> <li>○ Moderate solubility, so recovery from anesthesia may be delayed</li> <li>○ Isoflurane can make the heart “more sensitive” to circulating catecholamines (like epinephrine)</li> <li>○ arrhythmia</li> </ul>

✓ **Halothane:** not used anymore

- Used for induction in children (sweet pleasant odor)
- Sensitize the myocardium to the arrhythmogenic effects of catecholamines.
- Blood pressure usually falls. Peripheral vasodilation
- Very soluble in blood and adipose tissue
- Prolonged emergence
- “Halothane hepatitis” (rare). When we use Halothane repeatedly

✓ **Nitric oxide:**

MAC is 104% at one atmosphere means if I have to anesthetize somebody with nitric oxide, I have to give them more than 100%:

- 1- since I can't give more than 100% it can't be anesthetic
- 2- suppose if I am using 100% of nitric oxide then I have to give them oxygen also. Normally 21% so, if I give 21% oxygen, I can't give more than 79% of nitric oxide so, nitric oxide is not used for anesthesia, but it is very good analgesic used in:
  - 1- intraoperative
  - 2- during labor. few breathes immediate pain relief.
  - 3- to reduce the MAC of other anesthetics.

■ **CNS:**

- Antagonism of NMDA receptors in CNS. Weak anesthetic, produce analgesia.
- Usually combined with other anesthetics. To reduce side effects
- Used alone e.g. dental procedures.

■ **Cardiovascular system:**

- Mild myocardial depressant & a mild sympathetic stimulant
- HR and BP are usually unchanged.
- ↑ pulmonary vascular resistance.

Respiratory system Little effect on respiration

- Respiratory system: little effect on the respiratory system.
- Nausea/vomiting.
- Risk of bone marrow depression in prolonged use especially for physicians.
- Inhibits vitamin B-12 metabolism.
- Expansion of closed gas spaces. Nitrous oxide is 35 times more soluble in blood than nitrogen.  
Contraindicated in (e.g. air embolus it will increase the size of the embolus, pneumothorax: increase its size , Middle Ear Surgery etc)
- Diffuse into the cuff of ETT. Increase the size of cuff cause pressure on the trachea
- Diffusion hypoxia. After discontinuation, its rapid elimination from the blood into the lung may lead to a low partial pressure of oxygen in the alveoli.

## ★ Opioids:

Opioids produce moderate sedation and profound analgesia.

*Fentanyl, Sufentanil, Alfentanil, Remifentanil, Meperidine (also known as Pethidine), Morphine.*

- **MOA:**
  - They exert their effects by binding with opioid receptors in CNS 3 major opioid receptors  $\mu$  (mu),  $\kappa$  (kappa), and  $\delta$  (delta)
  - Opioids have some sedation effect so, if we give huge dose, we don't need to administer another anesthetize agent. leads to euphoria, addiction.
- **Primary use:**
  - They mimic endogenous compounds: Endorphins, enkephalins & dynorphins.
  - Principally provides analgesia and some degree of sedation.
  - Large doses can produce general anesthesia.

Advantages	Adverse effects
Minimal cardiac effects (no myocardial depression) So, in cardiac surgeries we use opioid in huge doses.	<ul style="list-style-type: none"> <li>○</li> <li>○ Miosis</li> <li>○ <b>Nausea &amp; vomiting</b>, slow gastric emptying, constipation</li> <li>○ Drowsiness or sedation</li> <li>○ Chest wall rigidity (we will be unable to ventilate) &amp; respiratory depression</li> <li>○ Bradycardia in large doses</li> <li>○ Some peripheral vasodilation and histamine release –hypotension</li> </ul>

- Itching
- Urinary retention & biliary colic.
- Addiction formation

✓ **Fentanyl:** most commonly used in operating room

- A potent synthetic opioid agonist with 100 times more potent than Morphine, the analgesic potency of morphine.
- Used for induction and maintenance of G.A and to supplement regional and spinal anesthesia.
- Ability to maintain cardiac stability.

✓ **Sufentanil citrate (sufenta):**

- 10 times as potent as fentanyl
- Rapid elimination
- Relatively more rapid recovery as compared with fentanyl.
- More profound analgesia for short duration surgeries (no respiratory depression no drowsiness).

✓ **Alfentanil:**

- Shorter duration of action compared to fentanyl and sufentanil.

✓ **Remifentanil (Ultiva):**

- Ultra short acting and rapidly cleared. used for infusion
- Widespread extrahepatic metabolism by blood and tissue non specific esterases.

✓ **Morphine:**

- May produce hypotension and bronchoconstriction as a consequence of its histamine-releasing action.
- Morphine may be a poor choice for a patient with renal failure due to active metabolites and prolonged duration of action so it's good for postoperative analgesic.

■ **Naloxone:**

- A specific opiate receptor antagonist, binding the receptor. Acting on  $\mu$  (mu) receptor.
- The effective dose is 1 to 4  $\mu\text{g/kg}$  IV, and the duration of action is 30 to 45 min.
- Dose may need to be repeated or as an infusion. for example in morphine toxicity.

**Adverse effects:-**

- Reversal of analgesia, nausea, vomiting,

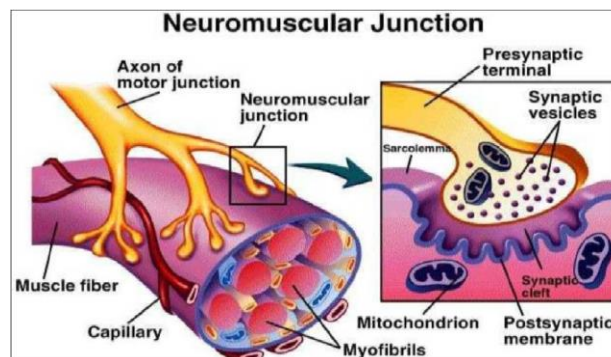
- Increased sympathetic nervous system activity (tachycardia, hypertension, pulmonary edema, and cardiac dysrhythmias).

When we use Naloxone? if accidentally given a huge dose of opioids or if the surgery finished early.

## ★ Neuromuscular blocking drugs:

### Skeletal muscle relaxants

- **Primary use:**
  - Perform tracheal intubation.
  - Facilitate ventilation
  - Provide optimal surgical operating conditions



Depolarizing	Non-depolarizing	
<b>Short acting:</b> <ul style="list-style-type: none"> <li>○ Succinylcholine</li> </ul>	<b>Short acting:</b> <ul style="list-style-type: none"> <li>○ Mivacurium</li> </ul> <b>Intermediate acting:</b> <ul style="list-style-type: none"> <li>○ Atracurium</li> </ul>	<b>Long acting:</b> <ul style="list-style-type: none"> <li>○ Doxacurium</li> <li>○ Pancuronium</li> </ul>
	<ul style="list-style-type: none"> <li>○ Cisatracurium</li> <li>○ Vecuronium</li> <li>○ Rocuronium</li> </ul>	<ul style="list-style-type: none"> <li>○ Pipecuronium</li> </ul>

### Depolarizing blockers: (Succinylcholine) also known as Suxamethonium

- Structurally similar to acetylcholine ... activate the acetylcholine receptors (ACh) ... depolarization of post junctional membrane. **Not followed by repolarization**
- **There is fasciculation:** simultaneous contraction of agonist & antagonist muscles which leads to tissue trauma → hyperkalemia. fasciculation followed by relaxation.
- Very short duration of action (onset 60 seconds/ duration 10 minutes)
- **For short time intubation (Rapid sequence induction)** in emergencies or patients with full stomach. Airway must be controlled to prevent regurgitation.
- Metabolized very quickly by plasma cholinesterase. In patients with plasma cholinesterase deficiency → prolonged effect up to 6 or 8 hours.
- Characterized by transient muscle fasciculations followed by relaxation.
- Acetylcholine esterase (AChE) inhibitors potentiate rather than reverse the block.

### Adverse effects:

- Cardiac dysrhythmias: sinus bradycardia, junctional rhythm, and even asystole after the first dose in children and following repeated dose within a short time interval in adults.
- Hyperkalemia. Normal increase to a certain limit but patients with some conditions may have severe rises to 10 that lead to cardiac arrest (so, its contraindicated with: **burns**, RF, muscular dystrophies & paraplegia myopathy)
- **A transient increase in intraocular pressure (IOP)**
  - Increase in intracranial & intragastric pressure.
  - **Myalgia**: abdomen, back, and neck. ■ Histamine release.
  - Dual block. This is above your level!
  - Succinylcholine apnea: drug will not be metabolized which causes it to stay in the body for hours.
    - Low levels of plasma cholinesterase (severe liver or **kidney disease**) also in pregnancy
    - A drug-induced inhibition of its activity, a genetically atypical enzyme.
    - Management is supportive, especially to avoid awareness.(benzodiazepine for amnesia, analgesics & artificial ventilation)
    - Anaphylaxis. over 50% of anaphylactic reactions to NMBDs.
    - **Malignant hyperthermia (MH)**.patient with previous history don't give succinylcholine and inhaled anesthetic.

### Non depolarizing blockers:

- They act by competitively blocking the binding of ACh to its receptors and inhibit muscular contraction
- **It is characterized by:**
  - Absence of fasciculation.
  - Potentiation by other nondepolarizing NMBDs and volatile anesthetic agents. ○ Reversal by AChE inhibitors.
- ✓ **Mivacurium:**
  - Short acting
  - Rapidly hydrolyzed by **plasma cholinesterase**
  - Histamine release causing a transient hypotension and tachycardia.

✓ **Atracurium:**

- Widely used and have an intermediate onset and duration of action
- Histamine release.
- No direct cardiovascular effects. → Vasodilation because of histamine release
- Metabolism is by Hofmann degradation (it means the drug automatically degraded by the body PH) and ester hydrolysis in the plasma. Its duration of action is independent of renal and hepatic function. So, useful in renal and liver failure.
- A breakdown product of atracurium, (laudanosine) may accumulate and cause seizures when used in hours as infusion

✓ **Cisatracurium:** Isomer of atracurium

- Hofmann degradation and does not accumulate in renal failure.
- Relatively slow onset of action.
- Does not release histamine.
- Less laudanosine.

✓ **Rocuronium:**

- The most rapid onset of the clinically available non-depolarizing NMBDs.
- Intubating conditions can be achieved in 60-90 seconds after an induction dose of 0.6 mg/Kg.
- Increasing the dose to 1.2 mg/kg shortens the time can be used for rapid sequence induction when Suxamethonium is contraindicated.
- An intermediate duration of action. Histamine is not released.
- Higher incidence of anaphylactic reaction.

**Choice of NMBD:**

- Urgency for tracheal intubation. Suxamethonium: fastest onset
- Duration of the procedure,
- Coexisting medical conditions that may affect the NMJ.
- Side effects & metabolism
- Cost-effectiveness
- Suxamethonium makes it a good choice for rapid intubation .
- Rocuronium will decrease the risk of hyperkalemia in patients with burns.
- Pancuronium can produce a tachycardia that is undesirable in patients with severe IHD, but it's vagolytic effects may be appropriate in pediatrics

**Peripheral nerve stimulation:**



- Check the depth and quality of neuromuscular blockade by stimulating the nerve if there is no contraction → 100% neuromuscular blocking
  - Determine that neuromuscular blockade is reversed
  - At least 3 twitches on a train of four should be detected before attempting reversal.
- **Anticholinesterases (Neostigmine):** reversal neuromuscular blockers
- They inhibit the action of the acetylcholinesterase enzyme at the NMJ resulting in an increase in the concentration of Ach at NMJ by displace the neuromuscular blocking agent from the receptor site → blocking agent will come to circulation → goes to liver for metabolism.
  - Clinical tests of adequate resolution of neuromuscular block include the ability to lift the head from the bed for 5 seconds.
  - Intravenous injection at a dose of 0.05 mg/kg (maximum 5mg).
  - To minimize adverse effects such as bradycardia, miosis, GI upset, nausea, bronchospasm, increased sweating, salivation & bronchial secretions, an antimuscarinic such as **glycopyrronium 0.01 mg/kg or atropine 0.02 mg/kg** must be administered along with the anticholinesterase.

## ★ Benzodiazepines:

*Midazolam, Lorazepam, Diazepam*

midazolam used mainly because of it's short acting

- **MOA:**
  - Enhance inhibitory neurotransmission by increasing the affinity of GABAA receptors for GABA.
- **Pharmacokinetics:**
  - Effects are terminated by redistribution.
  - All are metabolized in the liver.
  - Hydroxymidazolam is a metabolite cause sedation in Pt with renal failure. Effect will be prolonged because even the metabolite has some activity.
  - Diazepam clearance is reduced in the elderly. So, we reduce the dose
- **Pharmacodynamics:**

CNS	CVS	Respiratory system
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<ul style="list-style-type: none"> <li>○ Amnesic, anticonvulsant, anxiolytic, and sedative-hypnotic (dose-dependent manner).</li> <li>○ No analgesia.</li> </ul>	<p>Mild systemic vasodilation and <b>mild</b> ↓ in cardiac output</p> <p>HR is usually unchanged.</p>	<ul style="list-style-type: none"> <li>○ Mild dose-dependent ↓ in RR and TV.</li> <li>○ Respiratory depression may be more if administered with an opioid</li> </ul>
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● **Primary use:** Sedation, Amnesia, **anxiolytic use as premedication** during regional anesthesia **or as adjunct to GA**

#### Adverse effects

- Drug interactions with anticonvulsants (valproate) **it releases the valproic acid from its binding site. so, the free concentration of valproic acid will increase & the effect of anticonvulsant will be enhanced.**
- **Pregnancy and labor:**
  - Risk of cleft lip and palate in the first trimester.
  - CNS depression in the neonate. **If given during delivery**
- Superficial thrombophlebitis and injection pain by diazepam and lorazepam.
- They cause mild respiratory depression but can be marked in elderly leading to apnea.

#### ✓ **Midazolam (Dormicum):**

- Water soluble, so drug of choice for IV administration
- More rapid onset and more rapid elimination. **shortest acting 20-30 minutes.** ➤ The most potent amnestic

#### ✓ **Diazepam (Valium):** given IM or oral

- Water-insoluble, so IV use can cause local irritation/pain

#### ✓ **Lorazepam (Ativan):** longer duration of action(6-8 hrs) so, we are using it only as anxiolytic preoperative.

- Water-insoluble

#### ■ **Flumazenil:**

- A competitive **antagonist** at the benzodiazepine binding site of GABAA receptors in the CNS.
- Reversal of sedative effects occurs within 2 min; peak effects at 10 min.
- **Half-life is shorter** than the benzodiazepine. **(you have to repeat the dose)**
- Metabolized to inactive metabolites in the liver.
- Dose. 0.3 mg IV every 30 to 60 seconds (to a maximum dose of 5 mg).
- Initial dose in pediatric: 0.01 mg/kg IV over 15 seconds

- Contraindicated in patients receiving benzodiazepines for the control of seizures or elevated ICP. Because after giving Flumazenil ICP will rise and the patient will have seizure.

## ★ Local anesthetics:

LAs are drugs which reversibly prevent the transmission of pain stimuli locally at their site of administration by blocking the conduction of nerve impulse.

- **MOA:** Reversibly blocking sodium channels to prevent depolarization

**The effect depends on:**

- **Lipid solubility:** potency, plasma protein binding determines, duration of action of local anesthetics. more lipid soluble → more potent → more duration of action.
- **Addition of vasoconstrictor:** Prolongation of anesthetic action, decreased risk of toxicity and decrease in bleeding from surgical manipulation. like epinephrine.

### 1. Esters (metabolized by plasma cholinesterase) not used.

- Cocaine (out of date)
- Benzocaine
- Procaine
- Tetracaine

### 2. Amides (metabolized by cytochrome p-450)

- Lidocaine
- Bupivacaine
- Mepivacaine
- Prilocaine
- Ropivacaine

### Applications of local anesthesia

- Nerve block: (e.g., dental and other minor surgical procedures)
- Topical application: To skin for analgesia (e.g., benzocaine) or mucous membranes (for diagnostic procedures) swallow the anesthetic → esophagus anesthetize, eye examination.
- Spinal & epidural anesthesia
- Local infiltration: At end of surgery to produce long-lasting post-surgical analgesia (reduces need for narcotics)

- I/V infusion: For control of cardiac arrhythmias (e.g., lidocaine for ventricular arrhythmias)

### Choice of local anesthetics

- Onset
- Duration
- Sensory vs. motor block
- Potential for toxicity

**LIDOCAINE:** The most commonly used amide type local anesthetic.

- Rapid onset and a duration of 60-75 minutes, extended with epinephrine for up to 2 hours.
- Metabolized in the liver and excreted by the kidneys.
- Contraindicated in patients with a known sensitivity.
- Has also antiarrhythmic action.

**BUPIVACAINE:** most common after lidocaine

- Onset of action is slower than lidocaine and anesthesia is long acting - 2-4 hours, extended with epinephrine for up to 7 hours.
- More cardio-toxic than lidocaine and ropivacaine and difficult to treat. So, we have to be careful **not to give inside the vein.**
- Metabolized in the liver and excreted by the kidneys
- Contraindication: known hypersensitivity
- **Antidote:** 20% intralipid drug to stop cardiac toxicity.

**ROPIVACAINE:**

- Less toxic, long-lasting LA.
- Undergoes extensive hepatic metabolism, with only 1% of the drug eliminated unchanged in the urine.
- Ropivacaine is slightly less potent and less cardiotoxic than bupivacaine. **Local Anesthetic**

**Toxicity: CNS:**

- Initially **circumoral numbness**, dizziness, **tinnitus**, visual change. Later drowsiness, **disorientation**, **slurred speech**, loss of consciousness, **convulsions** & finally respiratory depression **Cardiovascular**

**System:**

- Myocardial depression and vasodilation
- hypotension and circulatory collapse

**Allergic reactions:**

- rare (less than 1%) rash, bronchospasm

### Prevention and Treatment of Toxicity

All Cases: Assure adequate ventilation & administer supplemental Oxygen. IV access.

- Seizures: Midazolam
- Hypotension: Trendelenburg position (head down , legs up),
- IV fluid bolus (Isotonic Saline or LR),
- Vasopressor (Dopamine if refractory to above).
- Dysrhythmias: As per ACLS protocol (but do not administer further Lidocaine)

### CASE DISCUSSION

A 4 years old male patient booked for Rt. eye squint surgery.

- How you will assess this patient preoperatively?
- Discuss fasting time & premedication?  
The patient seen in preoperative anesthesia clinic & cleared
- What are the physiological difference b/w adult & pediatric patient?
- Discuss anesthesia consideration & special concern for such surgery?
- Discuss anesthesia plan?  
During surgery the patient developed severe bradycardia
- Discuss the cause and treatment?

Surgery lasted for 2 hours, extubated & shifted to recovery

- What is your post-operative treatment plan?