Reviewed By
RAAOUM M. JABOR

8- Pharmacology of Anesthesia

Objectives

- Understand pharmacokinetics and pharmacodynamics of general anaesthetic agents: intravenous agents, inhalation agents, Opioids, neuromuscular blocking agents and reversal agents as well as local anaesthetic agents.
- Learn about the main uses, advantages and disadvantages of these agents.
- How to deal with adverse reactions diagnosis and management of **Malignant hyperthermia** and **Succinylcholine apnea.**

Color Index:

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- 41 Doctor's notes
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- Reference
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Editing file

Case discussion

Pharmacology of Anesthesia

Classification of anesthetic agents:

Anesthetic Agents

Adjuvants to Anesthesia

Benzodiazepines: They are not analgesia, it is used for **sedation**

1. Midazolam
2. Lorazepam
3. Diazepam

Dexmedetomidine is very special analgesic quality and sedation quality

General Anesthesia (the triad of anesthesia)

Local anesthesia

Injected close to the nerve, usually the patient is awake

1. Lidocaine
2. Bupivacaine
3. Ropivacaine

Skeletal Muscle Relaxation

Neuromuscular blocking drugs:

1. Succinylcholine
2. Mivacurium
3. Atracurium
4. Cisatracurium
5. Doxacurium
6. Pancuronium

Analgesia

Opioids: (synthetic)

1. Fentanyl
2. Sufentanil
3. Alfentanil
4. Remifentanil
5. Meperidine
6. Morphine

Hypnosis

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

Intravenous:

1. Barbiturates
2. Propofol
3. Etomidate
4. Ketamine

Intravenous Anesthetics

1- Barbiturates:

Thiopental (thiopentone sodium) is a thiobarbiturate

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 is very fast in metabolism, it take 10 min
- Multiple doses or **prolonged infusions** may produce **prolonged sedation** or unconsciousness.

Pharmacodynamics

CNS:

- Dose-dependent CNS depression Higher doses can result in coma.
- ↓ **in (CMRO2** cerebral metabolic rate oxygen conception), cause ↓ **in ICP** and **(Cerebral Blood Flow).**

CVS:

- Depress **myocardial contractility**, leading to dose-dependent ↓ **in BP** Can result in tachycardia and cardiac output.
- **Baroreceptor reflexes** remain largely intact.

Respiratory system:

- Dose-dependent decrease in RR and **T**idal **V**olume.
- If you give it as a bolus it can cause **apnea** may last for **30 to 90 seconds** after induction dose.
- **Laryngeal reflexes** remain more intact compared to propofol so higher incidence of cough and laryngospasm during LMA insertion.

Primary use

- **Induction of anesthesia**

Advantages

- **Rapid onset** (30-45 sec), **short duration** (5–8 min) initial dose; redistributed from brain to muscle resulting in return of consciousness.
- It has potent **anticonvulsant properties**.

Adverse effects

- Dose dependent histamine release.
- Myoclonus and hiccups → because of the uncoordinated muscle movement
- **Absolutely contraindicated in Porphyria.**
- Venous irritation because it is highly alkaline, and tissue damage make sure that you inject in big vein that has high flow → less pain
- Thiopental can cause severe pain & **tissue necrosis** if **injected subcutaneously or intra arterially**.
- If intra-arterial administration occurs, **heparin**, **vasodilators**, and **regional sympathetic blockade** may be helpful in treatment ask for help of vascular surgeon of plastic to remove the thrombus.

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.

Intravenous Anesthetics

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.

MOA	Facilitates inhibitory neurotransmission by enhancing the function (**GABAA**) receptors in the CNS.
Pharmaco-kinetics	**Hepatic** and **extrahepatic metabolism** leads to **inactive metabolites** which are excreted by **renal** route.
Pharmaco-dynamics	**CNS:** - Induction: **rapid onset** of unconsciousness (30 to 45 seconds), followed by a rapid termination of effect by redistribution, emergence is rapid 8-10 minutes and the patient wakes up - Weak analgesic effects. So you need to add analgesic along with it - **↓ (ICP) and ↓ (CPP) due to markedly ↓ (MAP).** - **Anticonvulsant**. - Less (PONV) occurs So it's preferred drug compared to thiopentone sodium **CVS:** - Dose-dependent **↓ in preload, afterload**, and contractility lead to **↓ in (BP) and C**ardiac **OutP**ut. - **Hypotension** may be marked in **hypovolemic**, elderly, or hemodynamically compromised patients → just reduce the dose given - Heart rate (HR) is minimally affected, and baroreceptor reflex is blunted. **Respiratory system:** - Dose-dependent decrease in (RR) and (TV). - ↓Ventilatory response to hypoxia and hypercarbia. - (potent bronchodilator)
Primary use	- **A sedative/hypnotic in OR & ICU** & endoscopic procedures. - Induction of anesthesia. - Maintenance of anesthesia (TIVA). total IV anesthesia. Propofol most common usage for induction but can be used as **IV maintenance of anesthesia** according surgical requirements Instead of inhalation. Useful for people with malignant hyperthermia
Advantages	- Produces more Laryngeal & pharyngeal muscle relaxation , **allowing LMA insertion**. - Safe in **Malignant hyperthermia** (MH) → it is condition which develops in the patient who are genetically prone to develop this reaction, or patient who administered inhalation anesthesia so in this patient's DO NOT administer **succinylcholine** or any **inhalation anesthesia, you can do regional anesthesia or total IV anesthesia** & **Porphyria patients**. - **Antiemetic properties.** - **Suitable for day case surgery** to avoid prolonged postoperative hangover (drowsiness, ataxia). - Situations where volatile anesthetics cannot be used (MH, transfer of sedated patients, airway surgery).
Adverse effects You should know these	- **Venous irritation.** Injecting this drug is painful. So, we give lidocaine first to relieve the pain - Bacterial growth → if you open an ampoule and didn't use it for 6 hrs then you have to dispose it - Lipid disorders. used cautiously in disorders of lipid metabolism (e.g., **hyperlipidemia and pancreatitis**). - Myoclonus and hiccups. **Propofol infusion syndrome:** 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**).
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.

Intravenous Anesthetics

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:** - No analgesic properties → you gonna have to use a strong analgesic - ↓ (CBF), cerebral metabolic rate (CMR), and (ICP). **CVS:** - **Minimal changes in HR,** BP, and CO **Preferred in patients** who are hemodynamically compromised, hypovolemic and **elderly**. **Respiratory system:** - Dose-dependent ↓ in (RR) & (TV). Transient apnea may occur.
Primary use	- **Induction of anesthesia** in patients with cardiovascular problems.
Advantages	- **Short acting and potent, with CVS and RS stability, suitable for elderly, shocked, and hypovolemic patients.**
Adverse effects	- Excitatory phenomena (**Involuntary limb twitches**), **myoclonus**. - Nausea and vomiting. - Venous irritation and superficial thrombophlebitis → administer in big vein - **Adrenal suppression**, so you should not use it in forum of infusion because it is Inhibits enzyme **11β & 17 α hydroxylase**). Adrenal suppression → **no cortisol production** → adrenal crisis - A single dose suppresses adrenal steroid synthesis for up to 24 hours. Repeated doses /infusion is associated with increased mortality in ICU patients.
Dosage and Administration	- Induction: IV 0.2-0.5 mg/kg

Intravenous Anesthetics

4- Ketamine:

It is **phencyclidine derivative** causing 'dissociative anesthesia '

MOA	Mainly attributed to noncompetitive antagonism of **NMDA** (N-methyl-D-aspartate) receptors in the CNS. It's causes antagonise in these receptors which causes anesthesia, it's the anesthesia where the Pt breathing spontaneously and have open eyes but his brain is separated from reality
Pharmacokinetics	- Terminated by redistribution in **15 to 20 minutes**. - Metabolized rapidly in the **liver** to multiple metabolites, some of which have modest activity (e.g., **norketamin**). If you administer infusion for long period, one of the metabolite is active so it will be prolonged action of ketamine . - Elimination half-life is **2 to 3 hours**.
Pharmacodynamics	**CNS:** - **Unconsciousness** in 30 to 60 s after an IV. - Amnesia and **profound analgesia** → very strong analgesia, so no need for analgesic - ↑ (**CBF**), ↑ (**CMR**), and ↑(**ICP**) → **Absolute contraindicated in head injury and increased ICP** **CVS:** - ↑ **HR** , **COP** , and **BP**. - Used in hemodynamically compromised patients. Produce desirable effect in the CVS system, increased cardiac output in patients undergoing cardiogenic shock **Respiratory system:** - Mild depression of (**RR**) and (**TV**). - **Potent bronchodilator.** It can be very suitable in asthmatic patients. - Laryngeal protective reflexes are maintained this drug may not good during LMA insertion.
Primary use	- **Sedation** and **analgesia**. - **Induction** of general **anesthesia**.
Advantages	- CVS stability makes it suitable for **shocked patients**. - Preservation of airway reflexes & less respiratory depression makes it suitable for procedures in the remote areas – radiological interventions We use it in pediatric patients undergoing MRI (they shouldn't move for 20 mins) , radiotherapy, burns Analgesia during dressing change & dressing changes.
Adverse effects	- ↑ **salivation**, PONV (post op nausea and vomiting). Administer antiemetic along with it - **Emotional disturbance**, agitation & hallucinations → administer sedative (Midazolam) along with it - **Nightmare** - **Contraindicated** in patients with head trauma. And ↑ **ICP**
Dosage and administration	- Induction: IV 1-2 mg/kg, IM 3-5 mg/kg, it can be administered orally 5-10 mg and rectally but the absorption lower so we have to increase the dose N.B. Useful for IM induction in patients with no IV access (e.g., children).

Analgesia

Opioids

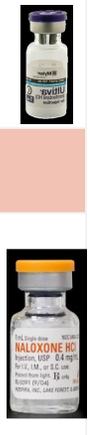
Opioids produce moderate sedation and **profound analgesia**.
There's **long acting** and **short acting** drug depends on surgery but we don't prefer long acting drugs
Very short acting, **strong opioid**: **Fentanyl, Sufentanil, Alfentanil, Remifentanil**
Long acting opioids: Meperidine, Morphine.

MOA	They exert their effects by binding with opioid receptors in CNS **3 major opioid receptors μ (mu), κ (kappa), and δ (delta)**
Primary use	- They mimic endogenous compounds: **Endorphins, enkephalins & dynorphins.** - Principally provides analgesia and some **degree of sedation**. - Large doses can produce **general anesthesia**.
Advantages	- Minimal cardiac effects (**no myocardial depression**) → used in cardiac surgeries in much bigger disease of opioids
Adverse effects	- Miosis: constriction of the pupil (**pin-point pupil**) - **Nausea & vomiting**, slow gastric emptying, constipation - Drowsiness or sedation - Chest wall rigidity (we will be unable to ventilate) & respiratory depression - **Bradycardia in large doses** - Some peripheral vasodilation and **histamine release** e.g morphine → hypotension - Itching, Addiction - Urinary retention & biliary colic.
Fentanyl	- A potent synthetic opioid agonist with 100 times, the analgesic potency of morphine → used intraoperatively - Used for **induction** and **maintenance** of G.A and to supplement **regional** and spinal anesthesia. - Ability to maintain cardiac stability. 
Alfentanil	- **Shorter duration of action compared to fentanyl and sufentanil** → once you stop the infusion the Pt will wake up
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** Pt may not awake due to prolonged action - Long duration of action 4-6 hours so we use it postoperative analgesia
Sufentanil citrate (sufenta)	- 10 times as potent as fentanyl & thousands time potent than morphine - Rapid elimination - Relatively more rapid recovery as compared with fentanyl. 
Remifentanil (Ultiva)	- **Ultra short acting and rapidly cleared** → the shortest - Widespread extrahepatic metabolism by blood and tissue non specific esterases 

Naloxone (opiate receptor antagonist)

- A specific opiate receptor antagonist, binding the receptor. Acting on μ (mu) receptor.
- The effective dose is 1 to 4 μg/kg IV, and the duration of action is 30 to 45 min.
- Dose may need to be repeated or as an infusion.

Side effects: - **Reversal of analgesia, nausea, vomiting**. - Increased sympathetic nervous system activity (tachycardia hypertension, pulmonary edema, and cardiac dysrhythmias) → use it carefully in small doses with monitoring



Adjuvants to Anesthesia

Benzodiazepines

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 cause sedation in Pt with renal failure. It won't be secreted so sedation will be prolonged. - Diazepam clearance is reduced in the elderly.
Pharmacodynamics	**CNS:** - Amnesic, anticonvulsant, anxiolytic, and sedative-hypnotic (dose-dependent manner). - No analgesia. **CVS:** - Mild systemic vasodilation and ↓ **in cardiac output.** - HR is usually unchanged. **Respiratory system:** - Mild dose-dependent ↓ in RR and TV. - Respiratory depression may be more if administered with an opioid
Primary use	**Sedation**, **amnesia, anxiolytic** use as **premedication** or as adjunct to GA and for regional anesthesia
Adverse effects	- Drug **interactions** with **anticonvulsant** (valproate) displaces its binding site so ↑free concentration of valproate → severe respiratory depression - Pregnancy and labor : Risk of cleft lip and palate in the first trimester, CNS and respiratory depression in the neonate if administered 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 20 - 30 minutes - The **most potent amnestic** the patient may not remember things 
Diazepam (Valium)	- Water-insoluble, so **IV** use can cause local irritation/pain. used orally or IM
Lorazepam (Ativan)	- Water-insoluble. - Long acting and used for sedation preoperatively

Flumazenil (benzodiazepine antagonist)

- 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 may 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.**

Adjuvants to Anesthesia

Dexmedetomidine Precedex

MOA	New generation highly selective central **α2-adrenergic receptor** (α2 -AR) agonist
Advantages	- **Sedative and analgesic** sparing effects preferred over opioids - Reduced **delirium** and **agitation** - Perioperative sympatholysis - When administer in form of bolus it causes hypotension, when administer slowly on form of infusion it may have some hypotension - Cardiovascular stabilizing effects - Preservation of **respiratory function** (No respiratory depression)
Primary use	For sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting, also used in pain relief; anxiety reduction and analgesia
Adverse effects	- Decrease cerebral blood flow without significant changes in ICP an CMRO2. - It has the potential to lead to the development of tolerance and dependence - Moderate decrease in heart rate and systemic vascular resistance and subsequently decrease in systemic blood pressure - Small to moderate decrease in tidal volume and very little change in the respiratory rate

Summary

Intravenous anesthesia

Drug		Character	S.E	CI	Uses
Barbiturates	Thiopental	Rapid onset of action short duration (Redistribution) potent anesthetic Dec ICP	CVS and respiratory depression Precipitate porphyria attack Hypersensitivity reaction	Hypotensive patient chronic obstructive lung disease porphyria patient	Induction in major surgery and alone in minor surgery in head injury
Hypnotic	Propofol	Dec ICP antiemetic action	Excitation involuntary movement	-	Safe in Malignant hyperthermia (MH) & Porphyria patients.
Hypnotic	Etomidate	Rapidly metabolized in the liver less hangover Minimal CVS and respiratory effect	Involuntary movement during induction like diazepam **adrenal suppression**	-	Save for cardiovascular and respiratory risk profile
Ketamine		can be given IV or I M especially in children increase central sympathetic affect potent bronchodilator	Psychotomimetic effect after recovery hallucination VIVID dream increased ICP salivation hypertension cerebral hemorrhage	Head injury hypertensive pt cardiovascular disorder	Hypovolemic shock elderly patient
Opioids	Fentanyl	potent analgesia	Bronchospasm hypotension increased ICP prolong labor and fetal distress urinary retention	Head injury pregnancy bronchial asthma COPD hypovolemic shock	They mimic endogenous compounds: Endorphins, enkephalins & dynorphins. Principally provides analgesia and some degree of sedation. Large doses can produce general anesthesia.
Opioids	Alfentanil				
Opioids	Sufentanil				
Opioids	Remifentanil				
Benzodiazepines	Diazepam	Anxiolytics and amnesic action	-	Respiratory patients	Induction of general anesthesia alone in minor procedure like endoscopy in balance anesthesia midazolam
Benzodiazepines	Lorazepam				
Benzodiazepines	Midazolam				

Inhalational Anesthetics

Characteristics of the ideal inhaled anesthetic agent
So far there is no an Ideal inhalation anesthetic yet

- Non - toxic, non-.allergenic, non - irritant
- Stable in storage, non – flammable
- No extra specialist equipment required
- Low solubility in blood and tissues
- Resistance to physical and metabolic degradation
- Analgesic
- CVS-no effect
- No respiratory depression
- Environmentally inert
- No reaction to soda lime/ breathing circuit
- Not a malignant hyperthermia (MH) trigger

Volatile anesthetic

- Present as liquids at room temperature and pressure
- Vaporized into gases for administration by the action of vaporizer


Isoflurane


Sevoflurane


Desflurane

The minimum alveolar concentration (MAC):

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

- It's suitable for only 50% of population and the other 50% will feel pain and will move in response to surgical stimulus so, if the Inhaled anesthetic is not enough then increase the dose to suit your patient

Agent	1 MAC of agent equals
Halothane	0.75%
Isoflurane	1.15%
Sevoflurane	1.85%
Desflurane	6.0%

Table 9.2 Factors affecting minimum alveolar concentration (MAC)

MAC ↓	Age (peak at 6 months)
	Premedication (e.g. benzodiazepines)
	Opioids
	Pregnancy
	Acute alcohol intoxication
	Other volatiles (MACs are additive. 0.6 of one agent + 0.4 of another = 1 MAC)
	Nitrous oxide
	Hypothermia
MAC ↑	Chronic alcohol consumption (liver enzyme induction)
	Increased sympathetic activity (e.g. amphetamine, cocaine)
	Hypermetabolic states (e.g. thyrotoxicosis, pyrexia)
	Anxiety
	Some antidepressants (tricyclics, monoamine oxidase inhibitors)

Inhalational Anesthetics

MOA

Various ion channels in the CNS involved in synaptic transmission (including GABAA, glycine, and glutamate receptors) may play a role

Pharmacokinetics

- The higher the vapor pressure, the more volatile the anesthetic.
- Blood solubility determines the speed of build-up / elimination from blood / brain
- Lower blood solubility means (faster induction / recovery) inverse association Inspired air → Alveolar air → Blood → Brain
- Metabolism: hepatic. 1-2% is metabolized
- Exhalation: This is the predominant route of elimination of all inhaled anesthetics

Pharmacodynamics

CNS:

- Unconsciousness & amnesia
- ↑ cerebral blood flow (CBF)

CVS:

- Myocardial depression & systemic vasodilation.
- HR tends to be unchanged, except desflurane There will be some tachycardia Sensitize the myocardium to the arrhythmogenic effects of catecholamines If you administer cathecholanoines with them there will be an exaggerated response and arrhythmia.

Respiratory system:

- Dose-dependent respiratory depression
- Airway irritation and, during light levels of anesthesia, may precipitate coughing, laryngospasm, or bronchospasm (sevoflurane and halothane makes it more suitable) They won't produce coughing so can be used for induction of anesthesia unlike the rest
- Bronchodilator (with the exception of desflurane)
- Inhibit hypoxic pulmonary vasoconstriction

Neuromuscular system:

- Dose-dependent ↓ in skeletal muscle tone.
- May precipitate **malignant hyperthermia** Genetically determined but it's rare, Associated with inhalational anesthetics and depolarizing muscle relaxant (Succinylcholine) ... A dramatic increase in body temperature, acidosis, electrolyte imbalance and shock.
- Management is removal of triggering agent, 100% Oxygen, active cooling measures & **Dantrolene** CCB that relaxes the skeletal muscles. Has a major role in reducing the mortality of MH (1 to 10 mg/kg)

Renal system:

- ↓ Renal blood flow.

Hepatic system:

- ↓ Hepatic perfusion.

Inhalational Anesthetics

Agent	Advantages	Disadvantages
Sevo flurane	• Low solubility in blood produces **rapid induction and emergence** • Pleasant smelling (suitable for Sevoflurane **children**) good for induction • Has good bronchodilating properties • **Agent of choice in asthma, bronchitis, and COPD** • It has little effect on the heart rate. Mild respiratory and cardiac suppression.	• Carbon dioxide absorbents in anesthesia machines degrade sevoflurane to "compound A" which have a nephrotoxic quality. That's why it's not used in low flow or prolonged procedures to reduce the risk of this compound.
Des flurane	• **Rapid onset and recovery of anesthesia.** less metabolized in the body • Most insoluble inhaled anesthetic • (outpatient procedures) • One of least metabolized to toxic byproducts	• Bad smell, **not** used for induction • Requires a special vaporizer • Pungent and irritating to the airway (leading to more coughing, laryngospasm) • Bronchoconstrictor Not suitable for induction but **maintenance** • High inspired gas conc. lead to a significant ↑ in the patient's BP & HR
Iso flurane	• Peripheral vasodilation & increase coronary blood flow good for cardiac patients • Slow induction & recovery	• Moderate solubility in blood and fatty tissues, so recovery from anesthesia may be delayed • Isoflurane can make the heart "more sensitive" to circulating catecholamines (like epinephrine) → higher incidence of arrhythmia
Halo thane	• Used for induction in children (sweet pleasant odor)	• **Sensitize** the myocardium to the arrhythmogenic effects of **catecholamines** Blood pressure usually falls • Very soluble in blood and adipose tissue → Slow and prolonged emergence, more soluble than isoflurane • Prolonged emergence • "**Halothane hepatitis**" (rare 1:17000). → With repeated exposure

Inhalational Anesthetics

Nitric oxide

MAC is 104% an one atmosphere
Not used as anesthetic, only an adjuvant

Pharmacodynamics

CNS	CVS	Respiratory system
• **Antagonism** of **NMDA** receptors in CNS. Weak anesthetic, produce analgesia • Usually **combined** with **other anesthetics** → reduced dose → reduced side effects • Used **alone** e.g. **dental** procedures, during **delivery** for **analgesia**	• Mild myocardial **depressant** & a mild **sympathetic stimulant** • HR and BP are usually **unchanged** • ↑ pulmonary vascular **resistance** → **contraindicated** in Pt with **pulmonary HTN**	• Little effect on respiration

Disadvantages

- Nausea/vomiting. Administer of antiemetic
- Risk of bone marrow depression
- Inhibits vitamin B-12 metabolism (megaloblastic anemia) → with prolonged procedures
- **Expansion of closed gas paces**. Nitrous oxide is 35 times more soluble in blood than nitrogen
- **Contraindicated** in (e.g. **air embolism** worsen, pneumothorax worsen, **Middle Ear Surgery** the graft will be displaced causing surgical failure, laparoscopic surgeries (abdomen and intestines will be inflated)
- Diffuse into the cuff of ETT → lead to tissue damage
- 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 In the end of the anesthesia, administer 100% O2 until all the NO leave the body (for 5-10 min), Otherwise it will cause diffusion hypoxia. It's not used in our hospital as anesthetic anymore because of its complications

Neuromuscular blocking drugs

Choice of NMBD

- **Urgency** for tracheal intubation Succinylcholine. If contraindicated use Rocuronium
- **Duration** of the procedure
- **Coexisting medical conditions** that may affect the NMJ Myopathy: succinylcholine is contraindicated
- Suxamethonium makes it a good choice for **rapid intubation**
- **Rocuronium** will decrease the risk of **hyperkalemia** in patients with burns, paraplegia, renal failure
- **Pancuronium** can produce a **tachycardia** that is undesirable in patients with severe **IHD**, but it's **vagolytic** effects may be appropriate in **pediatrics**.
- **Cost-effectiveness**

Neuromuscular blocking drugs

Neuromuscular blocking drugs

- **Primary use:** Perform tracheal intubation We have to paralyze the tracheal muscle. So, patient will not fight the ETT
- Facilitate ventilation
- Provides optimal surgical operating conditions → intra abdominal surgeries

Are two types 1) Depolarizing 2) Nondepolarizing

1) Depolarizing
Succinylcholine

- Structurally similar to acetylcholine > activate the acetylcholine receptors (Ach) > partial depolarization of post junctional membrane
- Metabolized very quickly by plasma cholinesterase Deficiency in this enzyme will prolong duration of action 5-6 hrs (can't be metabolized) so the patient will have a prolonged apnea after depolarizing muscle relaxant usage
- Characterized by transient muscle fasciculations followed by relaxation Uncoordinated muscle movement will lead to muscle trauma and joints injury
- Acetylcholine esterase (AChE) inhibitors potentiate rather than reverse the block We use ACHe as a reversal for other non-depolarizing muscle relaxants, but it's not the case here. plasma cholinesterase will act as a reversal for succinylcholine

Duration Of action

- Very short (onset 60 seconds/ duration 8-10 minutes)
- **For short time intubation (Rapid sequence induction)** in **emergency surgeries** (patient not fasting) + applying pressure on the cricoid cartilage to compress the esophagus to prevent aspiration.

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**. (contraindications: **burns, RF**, muscular dystrophies & paraplegia)
- A transient increase in intraocular pressure (IOP), **acute angle glaucoma** and Increase in intracranial & intragastric pressure
- **Myalgia**: abdomen, back, and neck → fasciculation and uncoordinated muscle movements (movement of agonist and antagonist muscles at the same time) will cause hyperkalemia and myalgia
- Histamine release and dual block

Succinylcholine apnea:
1- Low levels of plasma cholinesterase (severe liver or kidney disease)
2- A drug-induced inhibition of its activity, a genetically atypical enzyme.
3- Management is supportive, especially to avoid awareness.
4- Anaphylaxis. over 50% of anaphylactic reactions to NMBDs → avoid it unless in emergencies
5- **Malignant hyperthermia (MH)**.

Management of succinylcholine apnea:
1- artificial **ventilation**
2- maintain sedation and co2
3- ensure good analgesia It will take 5-6 hours

Neuromuscular blocking drugs

2) Nondepolarizing

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
- (**Hypocalcemia**)

Agents	Duration Of action	Others
Mivacurium	Short acting	• Rapidly hydrolyzed by plasma cholinesterase • Histamine release causing a transient hypotension & tachycardia
Atracurium	Intermediate onset and duration of action	• Widely used • **Histamine Release** • No direct cardiovascular effects • **Metabolism is by Hofmann degradation** Elimination dependent in body PH, temperature & ester hydrolysis in the plasma • Its duration of action is independent of renal and hepatic function → **used in renal, hepatic failure** • A breakdown product of atracurium, (**laudanosine**) may accumulate and cause seizures → when you use it for long time
Cisatracurium	Relatively slow onset of action	• **Hofmann degradation** and does not accumulate in renal failure • Does not release histamine → does not cause hypotension and laryngeal spasms • Less laudanosine • **Suitable for renal failure patients**
Rocuronium	An intermediate duration of action	• 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** • Histamine is not released • Higher incidence of anaphylactic reaction compared to cistacronium

Neuromuscular blocking drugs

Peripheral nerve stimulator

- Check the **depth** of neuromuscular blockade
- Determine that neuromuscular blockade is **reversed**
- At least **3 twitches on a train of four** should be detected **before attempting reversal**

How to use it?

- Apply electrodes to superficial nerve like **ulnar nerve** then give 4 stimulus in half seconds (this called train of four)
- If there is blockage there will be no response or if less than 3 switches.
- A response of 3 twitches or more means Our patient has metabolizes sufficient amount of muscle relaxant and is ready to get a reversal
- With Rocuronium + Sugammadex in bigger dose = immediate reverse of the effect of NMBA, no need to wait for the 3 twitches

Reversal of Neuromuscular Blockade (NMB)

	Anticholinesterase (neostigmine)	Sugammadex
MOA	• inhibit action of acetylcholinesterase enzyme at the NMJ • resulting in increase in the concentration of Ach at NMJ displace the NMBA	• Selective relaxant binding agent for immediate reversal of neuromuscular blockade (NMB) induced by **rocuronium** or **vecuronium** in adults.
Pharmacokinetics	• Clinical tests of **adequate resolution of neuromuscular block** include the ability to lift the head from the bed for 5 sec. Used with the Nondepolarizing NMBA not for the depolarizing NMBA	• eliminated unchanged via the kidneys, Contraindicated in renal failure
Disadvantage	• **minimize adverse effects such as bradycardia**, miosis, GI upset, nausea, • bronchospasm, increased sweating, salivation & bronchial secretions, parasympathomimetic effect an antimuscarinic such as glycopyrronium 0.01 mg/kg or **atropine 0.02 mg/kg must be administered along with the anticholinesterase**	• Not effective in reversing nondepolarizing neuromuscular blockade • secondary to benzylisoquinoline relaxants •
Dosage	• Intravenous injection at a dose of 0.05 mg/kg (maximum 5mg)	• Dose is 2, 4 and 16 mg/kg. For immediate action

Local Anesthetics

Local anesthetics (LAs)

drugs which reversibly prevent the transmission of pain stimuli locally at their site of administration

MOA	Reversibly blocking sodium channels to prevent depolarization
Lipid solubility	↑ lipid solubility → ↑ potency / ↑ plasma protein binding → ↑ duration of action potency, plasma protein binding determines, duration of action of local anesthetics
Addition of vasoconstrictor	Prolongation of anesthetic action, decreased risk of toxicity and decrease in bleeding from surgical manipulation

Esters metabolized by plasma cholinesterase	Amides metabolized by cytochrome p-450
• Cocaine • Benzocaine • Procaine • Tetracaine Esters are Not used these days because of the higher complication rate	• Lidocaine • Bupivacaine • Mepivacaine • Prilocaine • Ropivacaine

Amides

Lidocaine	Bupivacaine	Ropivacaine
Rapid onset and a duration of 60-75 minutes, extended with epinephrine for up to 2 hours	Onset of action is slower than lidocaine and anesthesia is long acting 2-4 hours, extended with epinephrine for up to 7 hours	long-lasting LA
• 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	• More cardiotoxic than lidocaine and ropivacaine and difficult to treat. • Metabolized in the liver and excreted by the kidneys • Contraindication: known hypersensitivity • Aspirate before you inject to make sure you don't inject inside a vein and recheck the dose	• Less cardiotoxic • Undergoes extensive hepatic metabolism, with only 1% of the drug eliminated unchanged in the urine. • Ropivacaine is slightly **less** potent than bupivacaine. • More sensory blockage and less motor blockage than bupivacaine

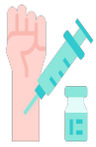
Local Anesthetics

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)

Plexus block, 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 anesthesia

1. Onset
2. Duration
3. Sensory vs motor block
4. Potential for toxicity

Local Anesthetic Toxicity

CNS:

Initially circumoral numbness **Anesthesia around the oral cavity -the tongue-**, dizziness, tinnitus, visual change.
Later drowsiness, disorientation, slurred speech, loss of consciousness, convulsions & finally respiratory depression

CVS:

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.

Seizures: Midazolam

Hypotension: Trendelenburg position (head down , legs up), IV fluid bolus (Isotonic Saline or LR), Vasopressor (Dopamine if refractory to above), IV Intralipid 20%.(Very life saving) will bind to the local anesthetic and decrease its cardiotoxicity

Dysrhythmias: As per ACLS protocol (but do not administer further Lidocaine) bc it will potentiate the cardiovascular toxic effect of other local anesthetics

- Start always with calculating the dose and double check with your colleague, aspirate before injecting and inject in small doses(2ml) and observe

Team leader: Rand Aldajani

Team member & Note taker:
Ayah Sayed
Reema Alrashedi