Editing file

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:

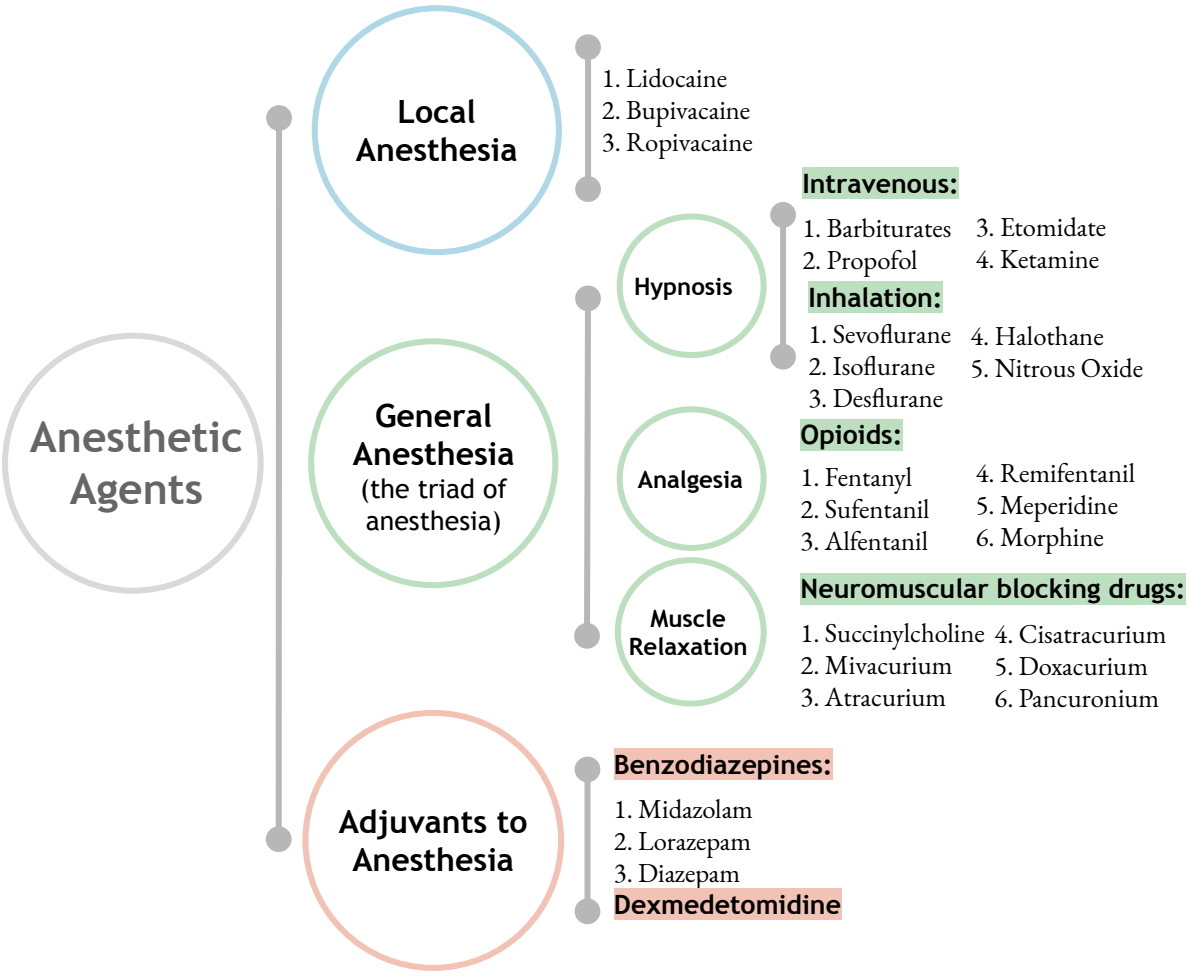
- Red: important /
- Black: content slides
- Gray: extra
- Green: dr. Notes

IMPORTANT

Anesthesia 438 teamwork

Pharmacology of Anesthesia

Classification of anesthetic agents:



1- Enter neuromuscular junction and block the conduction of nerve impulse

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

Pharmacodynamics

CNS: Dose-dependent CNS depression [1]. ↓ in (CMRO2), cause ↓ in ICP and (Cerebral Blood Flow).

CVS:

- Depress myocardial contractility, leading to dose-dependent ↓ in BP [2] and cardiac output.
- Baroreceptor reflexes remain largely intact.

Respiratory system:

- Dose-dependent decrease in RR and TV.
- 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 [3].
- 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 [4].

Dosage and 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.

1- Higher doses can result in coma
2- Can result in reflex tachycardia
3- Make sure that you inject in big vein that has high flow
4- You can use the help of GS to remove the clots

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.

Pharmacokinetics

Hepatic and extrahepatic metabolism leads to inactive metabolites which are excreted by renal route.

Pharmacodynamics

CNS:

- Induction: rapid onset of unconsciousness (30 to 45 seconds), followed by a rapid termination of effect by redistribution, emergence is rapid [1]
- Weak analgesic effects.
- ↓ (ICP) and ↓ (CPP) due to markedly ↓ (MAP).
- Anticonvulsant.
- Less (PONV) occurs post-operative nausea & vomiting.

CVS:

- Dose-dependent ↓ in preload, afterload, and contractility lead to ↓ in (BP) and COP.
- 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.

Primary use

- A sedative/hypnotic in OR & ICU & endoscopic procedures.
- Induction of anesthesia.
- Maintenance of anesthesia (TIVA [2]).

Advantages

- Produces Laryngeal & pharyngeal muscle relaxation [3], allowing LMA insertion.
- Safe in Malignant hyperthermia (MH) & 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

- 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 and 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.

1- 5-8 minutes and the patient wakes up
2- TIVA: total IV anesthesia. Propofol most common usage for induction but can be used as IV maintenance of sedation. Useful for people with malignant hyperthermia
3- Facilitate intubation. There will be no coughing, laryngeal spasms or increased oral secretion.

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 [1]. **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, (Inhibits 11β & 17 α hydroxylase) [2]. - 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

1- Preferred in patients who are hemodynamically compromised or elderly.
2- Adrenal suppression → no cortisol production → adrenal crisis

Intravenous Anesthetics

4- Ketamine: It is phencyclidine derivative causing 'dissociative anesthesia [1]'

MOA

Mainly attributed to noncompetitive antagonism of NMDA (N-methyl-D-aspartate) receptors in the CNS.

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., norketamine [2]).
- Elimination half-life is 2 to 3 hours.

Pharmacodynamics

CNS:

- Unconsciousness in 30 to 60 s after an IV.
- Amnesia and profound analgesia → no need for analgesic
- ↑ (CBF), ↑ (CMR), and ↑(ICP) pressure [3].

CVS:

- ↑ HR , COP , and BP.
- Used in hemodynamically compromised patients [4].

Respiratory system:

- Mild depression of (RR) and (TV).
- Potent bronchodilator.
- Laryngeal protective reflexes are maintained.

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 – radiological interventions [5], radiotherapy, burns & dressing changes.

Adverse effects

- ↑ salivation, PONV (post op nausea and vomiting).
- Emotional disturbance, agitation & hallucinations → administer midazolam
- Contraindicated in patients with head trauma.

Dosage and administration

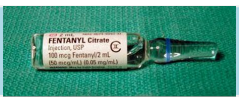
- Induction: IV 1-2 mg/kg, IM 3-5 mg/kg, orally 5-10 mg and rectally

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

1- It's the anesthesia where the Pt breathing spontaneously and have open eyes but his brain is separated from reality
2- If it accumulates there will be prolonged action of ketamine
3- Absolute contraindicated in head injury and increased ICP
4- Produce desirable effect in the CVS system, increased cardiac output in patients undergoing cardiogenic shock
5- We use it in pediatric patients undergoing MRI (they shouldn't move for 20 mins)

Analgesia

Opioids



Opioids produce moderate sedation and profound analgesia. Fentanyl, Sufentanil, Alfentanil, Remifentanil, 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
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 → hypotension - Itching - 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
- Long duration of action 3-4 hours

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 Midazolam, lorazepam, and diazepam.

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 [1].
- 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

Adverse effects

- Drug interactions with anticonvulsant (valproate)
- Pregnancy and labor : Risk of cleft lip and palate in the first trimester, CNS 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 minutes
- The most potent amnestic

Lorazepam (Ativan)

Water-insoluble.

Diazepam (Valium) used orally or IM

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

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
- 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.

1- It won't be secreted so sedation will be prolonged

Adjuvants to Anesthesia

Dexmedetomidine

MOA	New generation highly selective α2-adrenergic receptor (α2 -AR) agonist
Advantages	- sedative and analgesic sparing effects - reduced delirium and agitation - perioperative sympatholysis - 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 Anesthetics

Drugs:		Characters	S/E	C/I	Uses:
Barbiturates (Ultrashort acting)	Thiopental	•Rapid onset of action •Short duration (Redistribution) •Potent anesthetic •↓ ICP	•CVS & respiratory depression •precipitate porphyria attack •hypersensitivity reaction(sulfat)	•Hypotensive patient •porphyria patients •chronic obstructive lung disease	•induction in major surgery and alone in minor surgery. (dentistry) •in head injuries
	Methohexital				
Hypnotic(NonBarbiturate)	Propofol	↓ICP Has Antiemetic action.	Excitation (involuntary movements)1	---	---
	Etomidate	•Rapidly metabolized in liver (less hangover). •Minimal CVS and respiratory depressant effects.	•Involuntary movements during induction (like diazepam). •Adrenal suppression	---	a safe Cardiovascular and respiratory risk profile
Ketamine		•Dissociative anesthesia (Analgesic activity Amnesic action) •Can be given IV or IM (especially in children) •↑central sympathetic activity2 •Potent bronchodilator.	•Psychotomimetic effect after recovery (hallucination vivid dreams) •↑ICP - salivation •hypertension •cerebral hemorrhage.	•Head injury •Hypertensive patient •Cardiovascular disorders	hypovolemic, shock & elderly patients
Opioids	fentanyl	Potent analgesia.	•bronchospasm (wooden rigidity). •Hypotension •↑ICP •prolong labor and fetal distress •Urinary retention.	•Head injury. •Pregnancy. •Bronchial asthma +COPD •Hypovolemic shock	Neuroleptanalgesia Neuroleptanesthesia
	Alfentanil				
	Sufentanil				
	Remifentanil				
Benzodiazepines	diazepam	anxiolytic and amnesic action	---	Respiratory patients	•induction of general anesthesia. •Alone in minor procedure (endoscopy). •In balanced anesthesia (Midazolam)
	lorazepam				
	Midazolam (pre-anesthetic)				

Inhalational Anesthetics

Characteristics of the ideal inhaled anesthetic agent [1]

1. Non - toxic, non-.allergenic, non - irritant
2. Stable in storage, non – flammable
3. No extra specialist equipment required
4. Low solubility in blood and tissues
5. Resistance to physical and metabolic degradation
6. Analgesic
7. CVS: no effect
8. No respiratory depression
9. Environmentally inert [2]
10. No reaction to soda lime/ breathing circuit
11. Not a malignant hyperthermia (MH) trigger

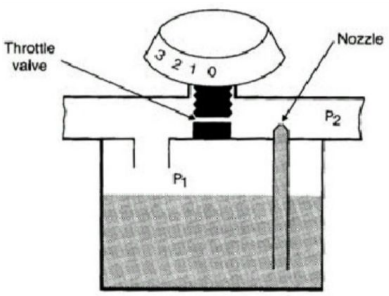
Volatile anesthetics

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

Used for isoflurane

Used for sevoflurane

Used for desflurane



The minimum alveolar concentration (MAC):

IMPORTANT

'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 so, if the IA is not enough then increase the dose to suit your Pt

Halothane 0.75%

Isoflurane 1.15%

Sevoflurane 1.85%

Desflurane 6.0% at one atmosphere

1- So far there is no an Ideal inhalation anesthetic yet
2- Because eventually the patient will exhale them into the atmosphere so they must be environment friendly

Inhalational Anesthetics

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)

  Inspired air → Alveolar air → Blood → Brain
- Metabolism: hepatic.
- Exhalation: This is the predominant route of elimination of all inhaled anesthetic

Pharmacodynamics

CNS:

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

CVS:

- Myocardial depression & systemic vasodilation.
- HR tends to be unchanged, except desflurane [1].
- Sensitize the myocardium to the arrhythmogenic effects of catecholamines [2].

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 [3])
- Bronchodilator (with the exception of desflurane).
- Inhibit hypoxic pulmonary vasoconstriction.

Neuromuscular system:

- Dose-dependent ↓ in skeletal muscle tone.
- May precipitate malignant hyperthermia [4] ... A dramatic increase in body temperature, acidosis, electrolyte imbalance and shock.
- Management is removal of triggering agent, 100% Oxygen, active cooling measures & Dantrolene (1 to 10 mg/kg)

Renal system:

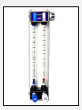
- ↓ Renal blood flow.

Hepatic system:

- ↓ Hepatic perfusion.

1- There will be some tachycardia
2- If you administer cathecholanoines with them there will be an exaggerated response and arrhythmia
3- They won't produce coughing so can be used for induction of anesthesia unlike the rest
4- Genetically determined but it's rare. Associated with inhalational anesthetics and depolarizing muscle relaxant (Succinylcholine)

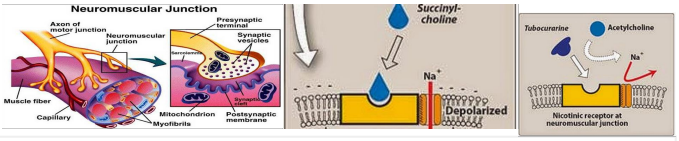
Inhalational Anesthetics

Agent	Advantages	Disadvantages
1- Desflurane: 	- Rapid onset and recovery of anesthesia. - (outpatient procedures). - One of least metabolized to toxic byproducts.	- Requires a special vaporizer. - Pungent and irritating to the airway (leading to more coughing, laryngospasm)[1]. - High inspired gas concentrations lead to a significant ↑ in the patient's BP & HR.
2- Sevoflurane: Most common 	- Low solubility in blood- produces rapid induction and emergence. - Pleasant smelling (suitable for 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. We need to remove CO2 from the circuit. So, we can circulate and reuse the agent to reduce the anesthesia cost and reduce air pollution into atmosphere. We use as an adsorbent to 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.
3- Isoflurane: 	- It causes peripheral vasodilation and increased coronary blood flow → used in cardiac anesthesia	- Moderate solubility, so recovery from anesthesia may be delayed. - Isoflurane can make the heart "more sensitive" to circulating catecholamines (like epinephrine) → higher incidence of arrhythmia
4- Halothane: 	- 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 - Prolonged emergence - "Halothane hepatitis" (rare). → With repeated exposure	
5- Nitric oxide: MAC is 104% an one atmosphere. Not used as anesthetic   Available in cylinders	**Pharmacodynamics** **CNS:** - 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 for analgesia **CVS:** - Mild myocardial depressant & a mild sympathetic stimulant - HR and BP are usually unchanged. - ↑ pulmonary vascular resistance → contraindicated in Pt with pulmonary HTN **Respiratory system:** - Little effect on respiration. **Disadvantages :** - Nausea/vomiting. - Risk of bone marrow depression → with prolonged procedures - Inhibits vitamin B-12 metabolism → 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 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 [2].	

1- Not suitable for induction but maintenance
2- In the end of the anesthesia, administer 100% O2 until all the NO leave the body. It's not used in our hospital as anesthetic anymore because of its complications

Neuromuscular blocking drugs

- Skeletal muscle relaxant
- Block neuromuscular junction



Primary use

- Perform tracheal intubation [1].
- Facilitate ventilation.
- Provides optimal surgical operating conditions → intra abdominal surgeries

Depolarizing

Succinylcholine

Duration of action

- **Very short** (onset 60 seconds/ duration 10 minutes)
- For short time intubation (Rapid sequence induction) in emergency surgeries (patient not fasting)

- Structurally similar to acetylcholine > activate the acetylcholine receptors (Ach) > depolarization of post junctional membrane.
- Metabolized very quickly by plasma cholinesterase [2].
- Characterized by transient muscle fasciculations followed by relaxation [3]
- Acetylcholine esterase (AChE) inhibitors potentiate rather than reverse the block [4].

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) 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
3- ensure good analgesia
It will take 5-6 hours

1- We have to paralyze the tracheal muscle. So, patient will not fight the ETT
2- Deficiency in this enzyme will prolong duration of action (can't be metabolized) so the patient will have a prolonged apnea after depolarizing muscle relaxant usage
3- Uncoordinated muscle movement will lead to muscle trauma and joints injury
4- 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

Neuromuscular blocking drugs

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.

Agents	Duration of action	Others
Mivacurium 	Short-acting	- Rapidly hydrolyzed by plasma cholinesterase. - Histamine release causing a transient hypotension and tachycardia.
Atracurium 	Intermediate onset and duration of action	- Widely used - Histamine Release. - No direct cardiovascular effects. - Metabolism is by Hofmann degradation [1] and 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: isomer of atracronium Superior to atracronium 	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 .
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

1- Elimination dependent in body PH, temperature

Neuromuscular blocking drugs

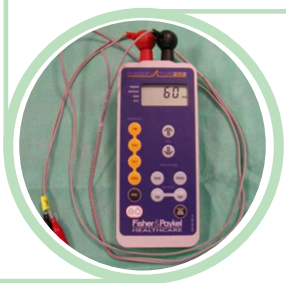
Choice of NMBD

1. Urgency for tracheal intubation [1]
2. Duration of the procedure
3. Coexisting medical conditions that may affect the NMJ [2]
4. Side effects & metabolism
5. Cost-effectiveness
6. Suxamethonium makes it a good choice for rapid intubation
7. Rocuronium will decrease the risk of hyperkalemia in patients with burns, paraplegia, renal failure
8. 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 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 switches or more means Our patient has metabolizes sufficient amount of muscle relaxant and is ready to get a reversal

1- Succinylcholine. If contraindicated use Rocuronium
2- Myopathy: succinylcholine is contraindicated

Reversal of Neuromuscular Blockade (NMB)

Anticholinesterase (neostigmine)

MOA	They inhibit the action of the acetylcholinesterase enzyme at the NMJ resulting in increase in the concentration of Ach at NMJ
Pharmacokinetics	Clinical tests of adequate resolution of neuromuscular block include the ability to lift the head from the bed for 5 seconds.
Disadvantage	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.
Dosage	Intravenous injection at a dose of 0.05 mg/kg (maximum 5mg).

Sugammadex

MOA	Selective relaxant binding agent for reversal of neuromuscular blockade (NMB) induced by **rocuronium** or **vecuronium** in adults.
Pharmacokinetics	Sugammadex is essentially eliminated unchanged via the kidneys. Contraindicated in renal failure
Disadvantage	Sugammadex is not effective in reversing nondepolarizing neuromuscular blockade secondary to benzylisoquinoline relaxants
Dosage	Dose is 2, 4 and 16 mg/kg.

succinylcholine will metabolize itself with plasma cholinesterase. So, no need to give a reversal .

Local Anesthetics

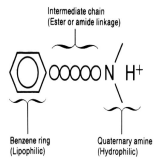
Local anesthetics (LAs)

LAs are 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 [1]	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)

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



Esters are Not used these days because of the higher complication rate

Amides (metabolized by cytochrome p-450)

- **Lidocaine**
- **Bupivacaine**
- Mepivacaine
- Prilocaine
- **Ropivacaine**

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
- The most commonly used amide type local anesthetic. - 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	- Less toxic - Undergoes extensive hepatic metabolism, with only 1% of the drug eliminated unchanged in the urine. - Ropivacaine is slightly less potent than bupivacaine. - Superior in terms of cardio toxicity to bupivacaine - But less motor block than bupivacaine

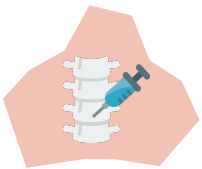
1- ↑ lipid solubility → ↑ potency / ↑ plasma protein binding → ↑ duration of action

Local Anesthetics

Applications of local anesthesia

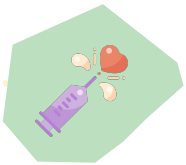
Nerve block:
(e.g., dental and other minor surgical procedures)

Topical application:
To skin for analgesia (e.g., benzocaine) or mucous membranes (for diagnostic procedures)



Plexus block [1], 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 [2], 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 [3] 20%.

Dysrhythmias: As per ACLS protocol (but do not administer further Lidocaine)

1- Used in regional anesthesia of limbs and post operative anesthesia
2- Anesthesia around the tongue
3- (Very life saving) will bind to the local anesthetic and decrease its cardio toxicity

Lecture Quiz

Answers: 1(E) 2(E) 3(A) 4(B) 5(D)

Question 1: What is the most frequent complaint made by patients in whom suxamethonium (succinylcholine) has been used?

A. Pain at the site of injection
B. Prolonged action in those with pseudocholinesterase deficiency
C. Diplopia
D. An increase in body temperature
E. Diffuse muscle pains.

Question 2: Lidocaine can be injected intravenously, but what is the main reason why bupivacaine should not be injected into a vein during local anaesthesia?

A. It lasts longer.
B. It is often used with adrenaline.
C. It can cause methemoglobinemia
D. It may cause convulsions.
E. It is cardiotoxic.

Question 3: Which of the following should be avoided for pain control in malignant conditions?

A. Remifentanil.
B. Fentanyl.
C. Pethidine.
D. Codeine.
E. Methadone.

Question 4: A 74-year-old woman with a history of a previous total abdominal hysterectomy presents with abdominal pain and distention for 3 days. She is noted on plain films to have dilated small-bowel and air-fluid levels. She is taken to the operating room for a small-bowel obstruction. Which of the following inhalational anesthetics should be avoided because of accumulation in air-filled cavities during general anesthesia?

A. Diethyl ether
B. Nitrous oxide
C. Halothane
D. Methoxyflurane
E. Trichloroethylene

Question 5: A 56-year-old man undergoes a left upper lobectomy. An epidural catheter is inserted for postoperative pain relief. Ninety minutes after the first dose of epidural morphine, the patient complains of itching and becomes increasingly somnolent. Blood-gas measurement reveals the following: pH 7.24, $PaCO_2$ 58, PaO_2 100, and HCO_3 28. Which of the following is the most appropriate initial therapy for this patient?

A. Endotracheal intubation
B. Intramuscular diphenhydramine (Benadryl)
C. Epidural naloxone
D. Intravenous naloxone
E. Alternative analgesia

Explanation File

Good Luck

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