TEAM ANESTHESIA

435

Pharmacology of Anaesthesia

{Color index: **Important★** | **Notes** | **433 Notes** | Extra | **Editing File**}

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.

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Doctor:" No need to memorize doses for the exam."

Special thanks to Noura ALTawil for her awesome notes!

Clarifying some concepts

What is an anesthetic agent?

The word anesthesia comes from the Greek anaisthēsia, from an- without aisthēsis-sensation. So an anesthetic agent is a medication that completely blocks ANY sensation, including pain.

How is it different than an analgesic?

Analgesia[1] is the relief of pain without total loss of feeling or muscle movement, and most analgesics reduce pain but not completely block it.

Now, why are there many drugs given in general anesthesia?

General anaesthesia always involves a **hypnotic agent** to knock the patient unconscious, an **analgesic** to both reduce the dose for induction and to minimize the sympathetic response elicited by the stress of the surgery (yes, it occurs even when the patient is unconscious), and may also include **muscle relaxation** to intubate for the most part.

What are the types of anesthesia?

Local: blocking nerve transmission, whether the patient is awake or sedated, by one or more of several means **1.** Local anaesthetic field block **2.** Peripheral nerve block **3.** Nerve plexus block **4.** Central neuraxial block, e.g. spinal or epidural or combined.

General: A reversible state of unconsciousness is achieved. It can be divided into three stages:

- Induction: Refers to the transition from an awake to an anaesthetized state.
- Maintenance: Refers to keeping a patient unconscious and can be achieved using inhaled volatile agents (mostly used) or continuous infusion of intravenous agents[2].
- Emergence: Refers to switching off maintenance agents when anesthesia is no longer required. Before emergence, adequate analgesia and anti-emesis should be ensured and NMJ function restored if a muscle relaxant has been used.

Recovery: At the end of surgical procedure administration of anaesthetic is stopped and consciousness regain

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[1] Interestingly, opioids (fentanyl) in great dosages produces anesthesia. This method is widespread for major surgical operations, especially in patients with cardiovascular disease because unlike other anesthetics, opioids don't cause cardiac depression. However the enormous load usually cause prolonged recovery from anesthesia with the risk of postoperative ventilatory depression.

[2] Total intravenous anaesthesia (TIVA) is often used in day surgery, neurosurgery or if patients get severe postoperative nausea and vomiting as it avoids emetogenic volatiles and enables rapid recovery with minimal hangover effect.

[3] AKA: Pethidine.

General Anaesthetics:

- Drugs Which Produce Reversible Loss of
- consciousness and all sensation
- Loss of sensation – Pain
- Unconsciousness and amnesia
- Immobility and Muscle relaxation
- Loss of reflexes

Mechanism of action:

Main Sites of action are Cortex, Thalamus and Hippocampus Can also act at Peripheral Sensory Nerves, Spinal Cord, Brain Stem

Molecular Mechanism:

- Chloride Channel GABA-A Receptor
- Complex
- Glycine gated chloride channel
- Neuronal Nicotinic receptors
- Antagonizing NMDA receptors

Minimum Alveolar Concentration (MAC)

➢ Measures of Potency of inhalational General anaesthetic agent
➢ Lowest Concentration in alveoli
➢ To produce immobility in 50 % subjects In
➢ response to painful stimuli.
➢ Correlation with oil/gas partition Coefficient
➢ Reflect capacity of anaesthetic to enter into CNS

Practically

Alveolar concentrations can be monitored continuously by measuring end-tidal anesthetic concentration using spectrometry

❏ Premedication with CNS depressant lowers MAC
❏ When combination is used MAC is additive
❏ DRC of inhaled anesthetic is steep
❏ Concentration exceeding 1.5 MAC are not used , 2-3 MAC is lethal
❏ Patient wakes up when concentration falls to 0.4 MAC

Pharmacokinetics:

❖ Depth of anaesthesia depends on Potency of the agent (MAC) and Partial Pressure (PP) attained in the brain.
❖ Induction and recovery depends on rate of change of PP in brain

Factors affecting PP of anaesthetic:

1. PP of anaesthetic in the inspired gas

Higher the inspired gas tension more anaesthetic will be transferred to the blood. Induction can be hastened by administering the GA at high concentration in the beginning

2. Pulmonary Ventilation Delivery of GA to alveoli depends on ventilation

Hyperventilation – More delivery per minute

Hypoventilation – Opposite effects

3.Alveolar Exchange

The GAs diffuse freely across alveoli, but if alveolar ventilation and perfusion are mismatched the attainment of equilibrium between alveoli and blood delayed Induction and recovery both are slowed

Ideal Anaesthetic

Ideal For Patient:

*Pleasant, nonirritating, no nausea or vomiting.

*Induction and recovery should be fast with no after effects

Ideal for Surgeon

*Adequate analgesia, immobility and muscle relaxation.

*Noninflammable and nonexplosive

Ideal for Anaesthetic

*Easy, Controllable and Versatile

*Wide margin of safety.

*Potent so that low concentrations are needed.

*Rapid adjustments in depth of anaesthesia should be possible.

*Cheap, stable and easily stored.

*Not react with rubber tubing or soda lime

The previous one and a half pages are from doctor jumana's slides

Intravenous Anesthetics

1. Barbiturates	
Example	Thiopental (thiopentone sodium) is a thiobarbiturate.
Mechanism of action	1. Facilitate inhibitory neurotransmission by enhancing GABAA receptor function. 2. Inhibit excitatory neurotransmission via glutamate and nicotinic acetylcholine receptors.
Pharmacokinetics	• Metabolism and elimination is hepatic. • Multiple doses or prolonged infusions may produce prolonged sedation or unconsciousness.
Pharmacodynamics	CNS • Dose-dependent CNS depression. • ↓ in (CMRO2) Cerebral metabolic Rate of O2. • ↓ in ICP and (CBF) Cerebral Blood Flow. This considered as advantages (can be used for trauma Pt). Cardiovascular system • Depress myocardial contractility, leading to dose-dependent ↓ in BP and CO

	• Baroreceptor reflexes remain largely intact Respiratory system • Dose-dependent decrease in RR and TV (Tidal Volume) • Apnea may last for 30 to 90 seconds after induction dose. So be careful! • Laryngeal reflexes remain more intact compared to propofol so higher incidence of cough and laryngospasm. You'll have to give muscle relaxants to intubate
Primary Use	**Induction of anesthesia**
Advantages	• Rapid onset (30 - 45 sec), ultra short duration (5 – 8 min) initial dose; redistributed from brain to muscle resulting in return of consciousness. • It has potent anticonvulsant properties. Sometimes it's the best for status epilepticus, because it cause CNS depression.
Adverse Effects	• Dose dependent histamine release. • Myoclonus and hiccups. • Absolutely contraindicated in Porphyria. The only contraindication. • Venous irritation and tissue damage cannot be given subcutaneously • If injected subcutaneously or intra-arterially, it causes tissue necrosis and severe pain. This drug is highly alkaline (pH=11) so it damages arteries ↳ In which case, heparin, vasodilators, and regional sympathetic blockade may be helpful in treatment.
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.
2. Propofol (2, 6- diisopropylphenol)	
What is it?	It is the most widely used induction agent. 1% isotonic oil-in- water emulsion, which contains egg lecithin, glycerol, and soybean oil.
Mechanism of Action	Facilitates inhibitory neurotransmission by enhancing the function (GABAA) receptors in CNS. similar to thiopental sodium
Pharmacokinetics	Hepatic and extrahepatic metabolism leads to inactive metabolites which are excreted by renally
Pharmacodynamics	CNS Induction: rapid onset of unconsciousness (30 to 45 seconds), followed by a rapid termination of effect by redistribution, so emergence is rapid. • Weak analgesic effects. Analgesics should be given to prevent ↑ HR and BP • ↓ (ICP) and ↓ (CPP) due to markedly ↓ (MAP). • Anticonvulsant. • Less Postoperative nausea and vomiting (PONV) occurs. Cardiovascular System • Dose dependent ↓ in preload, afterload, and contractility lead to ↓ in (BP) and COP. • Hypotension may be marked in hypovolemic, elderly, or hemodynamically compromised patients. So we reduce dose in these Pts.

	• 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 Uses	• **A sedative/hypnotic in OR & ICU. Antiemetic effect** • Induction of anesthesia. As a single dose. • Maintenance of anesthesia Total Intravenous Anesthesia (TIVA).
Advantages	• Produces Laryngeal & pharyngeal muscle relaxation, allowing LMA insertion. Absent laryngeal reflexes • Safe in Malignant hyperthermia (MH) & Porphyria patients. • Antiemetic properties. • Suitable for day case surgery to avoid prolonged postoperative hangover (drowsiness, ataxia). More rapid recovery (TIVA) and nausea and vomiting are less. • Situations where volatile anesthetics cannot be used (MH, transfer of sedated patients, airway surgery). • Bronchodilation (safe in asthmatics)
Adverse Effects	• Venous irritation. Lidocaine is given to reduce it • Bacterial growth. Propofol is good media for bacteria growth. Don't use it after opening it for hours • Lipid disorders. used cautiously in disorders of lipid metabolism (e.g. hyperlipidemia and pancreatitis). • Myoclonus and hiccups. • May cause bradycardia, we should be careful with patients with DM or CV, we may not use it. • **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). Shouldn't be used for multiple days (like the ICU)
Dosage and Administration	Induction: IV 1-2.5mg/kg Sedation: IV 25-100 µ/kg/min Titrate with incremental doses in hypovolemic, elderly, or hemodynamically compromised patients or if administered with other anesthetics.
3. Etomidate (carboxylated imidazole)	
Mechanism of Action	Facilitates inhibitory neurotransmission by enhancing the function (GABAA) receptors. Same as propofol
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. • ↓ (CBF), cerebral metabolic rate, (CMR), and (ICP). used for patients with raised ICP and head trauma Cardiovascular System Minimal changes in HR, BP, and COP. preferred in the 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 and shocked patients.**
Adverse Effects	• Excitatory phenomena (Involuntary limb twitches), myoclonus. • Nausea and vomiting. • Venous irritation and superficial thrombophlebitis. • Adrenal suppression, (Inhibits 11β & 17 α hydroxylase). 'Addisonian crisis' • A single dose suppresses adrenal steroid synthesis for up to 24 hours. Repeated doses /infusion is associated with increased mortality in ICU patients. Contraindicated for sedation in ICU patients
Dosage and Administration	Induction: IV 0.2-0.5 mg/kg
4. Ketamine	
What is it?	It is phencyclidine derivative causing 'dissociative anesthesia[4]' patient's eyes could be open but they're anesthetized and not talking or feeling any pain
Mechanism of Action	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 active metabolite). Weak anesthesia! • Elimination half-life is 2 to 3 hours
Pharmacodynamics	CNS • Amnesia and profound analgesia. So no need to give another drugs for analgesia. • ↑ (CBF), ↑ (CMR) Cranial Metabolic Rate, and ↑ (ICP) pressure. So it is a contraindication in pt with head injury! Cardiovascular System • ↑ HR, COP, and BP . • **Used in hemodynamically compromised patients.** Good for trauma patients in shock (Bleeding, hypovolemia) given that they don't have raised ICP

[4] Meaning, the patient may be unaware and detached from his/her surrounding but not completely unconscious

	Respiratory system • Mild depression of (RR) and (TV). • Potent bronchodilator. Special about ketamine • Laryngeal protective reflexes are maintained. So if the patient regurgitates, they will cough and won't aspirate
Primary Uses	• Induction of general anesthesia. • Sedation and analgesia.
Advantages	• CVS stability makes it suitable for shocked patients • Preservation of airway reflexes & less respiratory depression makes it suitable for short procedures like: radiological interventions, radiotherapy, burns & dressing changes.
Adverse Effects	• ↑ salivation, PONV. • Emotional disturbance • Agitation & hallucinations
Contraindication	Patients with head trauma Increase in ICP Don't use it in patients with CVD, because it increases the cardiac output
Dosage and Administration	Induction: IV 1-2 mg/kg , IM 3-5 mg/kg Useful for IM induction in patients with **no IV access** (e.g., children). 5 mg/kg for pediatric patients with a sip of juice, should put them to sleep in 10 min

Inhalational Anesthetics[56]

Characteristic of the ideal inhaled anesthetic

- Non-toxic, non-allergenic, non-irritant, non–flammable.
- No extra specialist equipment required, stable in storage.
- Low solubility in blood and tissues (fast induction and recovery) High solubility = stays within the body for a longer duration.
- Resistance to physical and metabolic degradation.
- Analgesic.
- No CVS effect or respiratory depression.
- Environmentally inert.
- No reaction to soda lime/ breathing circuit.
- Not a malignant hyperthermia (MH) trigger.

What's a volatile anesthetic?

They are liquids at room temperature and pressure and vaporized into gases for administration.

[5] Common uses include pediatric patients, cases of difficult airway, difficult venous access or inhaled foreign body where maintaining spontaneous ventilation is preferable.

[6] Intubation of the trachea can be achieved under deep inhalational anesthesia without muscle relaxation

The Minimum Alveolar Concentration (MAC)[7][8]

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

- Halothane 0.75%
- Isoflurane, 1.15%
- Sevoflurane, 1.85%
- Desflurane 6.0% at one atmosphere

All the inhalational anesthetics discussed share the following properties	
Mechanism of Action	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: the predominant route of elimination
Pharmacodynamics	CNS • Unconsciousness and amnesia. • ↑ cerebral blood flow (CBF). Respiratory System • Dose-dependent respiratory depression • Airway irritation and, during light levels of anesthesia, may precipitate coughing, laryngospasm, or bronchospasm seen with desflurane (sevoflurane is more suitable) • Bronchodilator (with the exception of desflurane). • Inhibit hypoxic pulmonary vasoconstriction. Renal system • ↓ renal blood flow Cardiovascular System • Myocardial depression & systemic vasodilation. • HR tends to be unchanged, except with desflurane • Sensitize the myocardium to the arrhythmogenic effects of catecholamines. Neuromuscular system • Dose-dependent ↓ in skeletal muscle tone. • May precipitate **malignant hyperthermia:** A dramatic increase in body temperature, metabolic acidosis, electrolyte imbalance and shock.

[7] In other words, it is the alveolar concentration of of a volatile agent which, when given alone, prevents movement in 50% of volunteers in response to a standard stimulus (a surgical incision).

[8] MAC is inversely proportional to potency.

	• Management is removal of triggering agent, 100% Oxygen, active cooling measures & **Dantrolene**[9] (1 to 10 mg/kg). Also, you have to maintain BP, cooling the pt, correct electrolyte imbalance. Hepatic System • ↓ hepatic perfusion.
1. Desflurane	
Advantages	• Rapid onset and recovery of anesthesia (outpatient procedures) • Good for obese patients, used in laparoscopic gastric sleeve surgeries • One of least metabolized to toxic byproducts
Disadvantages	• Requires a special vaporizer • Pungent and irritating to the airway (leading to more coughing, laryngospasm) • High inspired gas concentrations lead to a significant ↑ in the patient's BP & HR.
2. Sevoflurane	
Advantages	• Low solubility in blood (produces rapid induction and emergence) • Pleasant smelling (suitable for children) • Has good bronchodilating properties. • **Agent of choice in asthma, bronchitis, and COPD.** It has little effect on the heart rate**.** Bronchodilator + ↓ Secretions • Mild respiratory and cardiac suppression
Disadvantages	• Carbon dioxide absorbents in anesthesia machines degrade sevoflurane to Compound A which is toxic • Cannot be used for long durations.
3. Isoflurane	
Advantages	It causes peripheral vasodilation and increased coronary blood flow.
Disadvantages	• Moderate solubility, so recovery from anesthesia may be delayed. • Isoflurane can make the heart "more sensitive" to circulating catecholamines (like epinephrine).
4. Halothane	
Primary Use	Induction in children (sweat pleasant odor) very good drug
Properties	Prolonged emergence (very soluble in blood and adipose tissue)

[9] A skeletal muscle relaxant used in malignant hyperthermia and congenital neuroleptic syndrome.
Congenital neuroleptic syndrome: life-threatening, idiosyncratic reaction to neuroleptic medications that is characterized by fever, muscular rigidity, altered mental status, and autonomic dysfunction
Although its clinical picture is similar to that of MH, neuroleptic malignant syndrome (NMS) is caused by the central effects of drugs with dopamine antagonist properties, including antipsychotics (eg, haloperidol) and antiemetics (eg, metoclopramide and droperidol). The onset of the syndrome occurs hours to days after initiation of treatment with the drug.

Adverse Effect	• Sensitize the myocardium to the arrhythmogenic effects of catecholamines arrhythmias in 50% of patients • Blood pressure usually falls. • **Halothane hepatitis** (rare) autoimmune hepatitis, usually with repeated doses
5. Nitrous Oxide	
Properties	MAC is 104% at one atmosphere[10]
Pharmacodynamics	CNS • Antagonism of NMDA receptors in CNS. • Weak anesthetic, produce analgesia. Cardiovascular system • Mild myocardial depressant & a mild sympathetic HR and BP are usually unchanged. • ↑ pulmonary vascular resistance. Respiratory system • Little effect on respiration.
Uses	• Usually combined with other anesthetics. • Used alone in dental procedures.
Adverse Effects	• Nausea/vomiting. • Risk of bone marrow depression. • Inhibits vitamin B-12 metabolism. • Expansion of closed gas spaces (nitrous oxide is 35 times more soluble in blood than nitrogen) • Diffuse into the cuff of ETT. increasing pressure in the cuff and compromising vascularity • 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) you already have 79% of nitrogen in the blood along with 21% O2. When the surgery is done, NO will leave the body through the lungs with the already present nitrogen leading to the dilution of O2 so Tx is with O2.
Contraindications	• Air embolism. • Pneumothorax. • Middle ear surgery.

[10] The least potent of all inhalational anesthetics.
You need to supplement them with 21% O2.
Since 104 cannot be achieved without being in hyperbaric chamber (i.e. cannot be achieved at normal atmospheric pressure). Because MAC reflects an adequate dose for only 50% of patients, successful clinical anesthesia may require 0.5 to 2.0 MAC for individual patients. For example, administering a mixture of 52% nitrous oxide with 2% sevoflurane will provide 1.5 MAC.

Local Anesthetics

All the local anesthetics discussed share the following properties		
What are they?	LAs are drugs that reversibly prevent the transmission of pain stimuli locally at their site of administration.	
Mechanism of Action	Reversibly blocking sodium channels to prevent depolarization.	
Properties	• Lipid solubility → Determines potence • Plasma protein binding → Determines duration of action	
Choice of LA	Onset (it should be fast onset), Duration, Sensory (Postoperative) Vs Motor (both sensory & motor during surgery), Potential for toxicity.	
Addition of a vasoconstrictor	Prolongation of anesthetic action, decreased risk of toxicity and decrease in bleeding from surgical manipulation (adrenaline)	
Application	1. Nerve block: Dental and other minor surgical procedures. 2. Topical application: To skin for analgesia (e.g., benzocaine) or mucous membranes (for diagnostic procedures) 3. Spinal & epidural anesthesia 4. Local infiltration: At end of surgery to produce long-lasting post-surgical analgesia (reduces need for narcotics) 5. I/V infusion: For control of cardiac arrhythmias (e.g., lidocaine for ventricular arrhythmias)	
Toxicity	CNS: with increased doses or IV injection • 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 "Always give O2 to your pt."	• All Cases: Assure adequate ventilation & administer supplemental Oxygen. • Seizures: Midazolam in the OR, propofol can be given • 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)	
Types	**Esters (metabolized by plasma cholinesterase)**	**Amides (metabolized by cytochrome p-450)**
	↳ Cocaine (out of date) ↳ Benzocaine ↳ Procaine ↳ Tetracaine	↳ Lidocaine short acting ↳ Bupivacaine ↳ Mepivacaine ↳ Prilocaine ↳ Ropivacaine

	Not available in the hospital. Also, not used anymore, we use Amides instead.	
1. Lidocaine (the most commonly used amide LA)		
Onset and Duration	Rapid onset and a duration of 60-75 minutes, extended with epinephrine for up to 2 hours.	
Metabolism	Metabolized by the liver and excreted by kidneys	
Advantage	It has an antiarrhythmic effect	
Contraindication	In patients with known sensitivity	
2. Bupivacaine		
Onset and Duration	Onset of action is slower than lidocaine and anesthesia is long acting - 2-4 hours, extended with epinephrine for up to 7 hours also commonly used	
Metabolism	Metabolized by the liver and excreted by kidneys	
Disadvantage	More cardiotoxic than lidocaine and ropivacaine and difficult to treat.	
Contraindication	In patients with known sensitivity Careful not to administer it in the vein, should be next to the nerve or epidural	
3. Ropivacaine		
In general	Less potent and less toxic with long standing local anesthesia	
Metabolism	Undergoes extensive hepatic metabolism, with only 1% of the drug eliminated unchanged in the urine.	

Opioids[11]

All the opioids discussed share the following properties	
What do they do?	Opioids produce moderate sedation and profound analgesia.
Mechanism of Action	They exert their effects by binding with opioid receptors in CNS 3 major opioid receptors μ (mu), κ (kappa), and δ (delta).
Primary Uses	1. They mimic endogenous compounds: Endorphins, enkephalins & dynorphins. 2. Principally provides analgesia and some degree of sedation. 3. Large doses can produce general anesthesia.
Advantage	Minimal cardiac effect (myocardial depression)

[11] Intraoperatively, very potent and ultra short acting opioids are used
Postoperatively, long acting opioids are used (such as morphine).

Adverse Effects	• Miosis • Nausea & vomiting, slow gastric emptying which can cause aspiration pneumonia in emergency cases, constipation • Drowsiness or sedation • Chest wall rigidity[12] & **respiratory depression.** In large dose the pt will be apeanic. • Bradycardia in large doses • Some peripheral vasodilation and histamine release causing hypotension but generally cardiac activity is maintained. • Itching • Urinary retention & biliary colic.
1. Fentanyl[13]	
Properties	A potent synthetic opioid with x100 the analgesic potency of morphine
Primary Use	Used for induction and maintenance of G.A and to supplement regional and spinal anesthesia
Advantage	Ability to maintain cardiac stability
2. Sufentanil Citrate (Sufena)	
Properties	• 10 times as potent as fentanyl • Rapidly eliminated from the body • More rapid recovery than fentanyl
3. Alfentanil	
Properties	Shorter duration of action compared to fentanyl and sufentanil more potent
4. Remifentanil (Ultiva)	
Properties	Ultra short acting and rapidly cleared **the MOST potent**
Metabolism	Widespread extrahepatic metabolism by blood and tissue nonspecific esterases
Advantage	Excellent cardiac stability. Used in scoliosis correction surgeries (since it's rapidly cleared, spinal or nerve damage can be quickly noticed)
5. Morphine	
Disadvantages	• May produce hypotension and bronchoconstriction as a consequence of its histamine-releasing action (poor choice for asthmatics and RF patients). • Morphine may be a poor choice for a patient with **renal failure** and asthmatic.
Naloxone!	

[12] Very rare in the OR but if it does happen, you wouldn't be able to intubate.
[13] Short duration 20-30 min

What is it?	A specific opiate receptor antagonist, binding the receptor.
Dosage and Duration	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
Adverse Effects	• Reversal of analgesia narcotics shouldn't be reversed entirely, otherwise pt will experience pain! • Nausea and vomiting • Increased sympathetic nervous system activity (tachycardia, hypertension, pulmonary edema, and cardiac dysrhythmias) could lead to cardiac failure

Neuromuscular Blocking Agents

All the following NMBAs discussed share the following properties			
Primary Uses	• Perform tracheal intubation • Facilitate ventilation and provide optimal surgical operating conditions		
Types	Depolarizing	Non Depolarizing	
	Short acting	Short Acting	Intermediate Acting / Long Action
	Succinylcholine	Mivacurium	Atracurium, Cisatracurium, Vecuronium, Rocuronium / Doxacurium, Pancuronium, Pipercuronium

Depolarizing NMBAs

Succinylcholine (suxamethonium)

Mechanism of Action	• Structurally similar to acetylcholine so it will activate the acetylcholine receptors (Ach) causing depolarization of post junctional membrane persistent partial depolarization with no repolarization • Characterized by transient muscle fasciculations followed by relaxation.
Duration of Action	Very short duration of action (onset 60 seconds/ duration 10 minutes)

Metabolism	• Metabolized very quickly by plasma cholinesterase AKA pseudocholinesterase[14] • Acetylcholinesterase (AChE) inhibitors potentiate their effect whereas they reverse the NM blockade of nondepolarizing drugs
Primary Use	**For short time intubation (Rapid sequence induction)** in patients with full stomach
Adverse Effects "Repeating dose will cause cardiac arrest"	• 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** ↳ Reconsider in burns, renal failure, muscular dystrophies[15] & paraplegia. • A transient increase in intraocular pressure. • Increase in intracranial & intragastric pressure. So it is contraindicated in pt with perforated eye (eye injury)! • Myalgia in the abdomen, back, and neck. • Histamine release. • Dual block[16] • Anaphylaxis[17] (over 50% of anaphylactic reactions to NMBD) • Malignant hyperthermia. • **Succinylcholine apnea** ↳ Low levels of plasma cholinesterase (severe liver or kidney disease) ↳ A drug-induced inhibition of its activity, a genetically atypical enzyme. ↳ Management is supportive, especially to avoid awareness. You give them analgesics and sedatives
Nondepolarizing NMBAs	
Mechanism of Action	They act by competitively blocking the binding of ACh to its receptors and inhibit muscular contraction.
Advantages	• Absence of fasciculation • Potentiation by other nondepolarizing NMBDs and volatile anesthetic agents • Reversal by AChE inhibitors (neostigmine)
1. Mivacurium	
Properties	Short-acting, rapidly hydrolyzed by plasma cholinesterase
Adverse Effects	Histamine release causing a transient hypotension and tachycardia

[14] Pseudocholinesterase (plasma cholinesterase) Vs. true cholinesterase (acetylcholinesterase):
Pseudocholinesterase (butyrylcholinesterase): cholinesterase found in the plasma that degrades many choline containing drugs (such as, succinylcholine, mivacurium, cocaine, lidocaine, heroin) Caution must be taken in patients with pseudocholinesterase deficiency.
Acetylcholinesterase: is a cholinesterase found in RBCs and NMJs, it breaks down acetylcholine and other choline containing neurotransmitters.

[15] Incidence of MH is higher, especially with Duchenne MD.

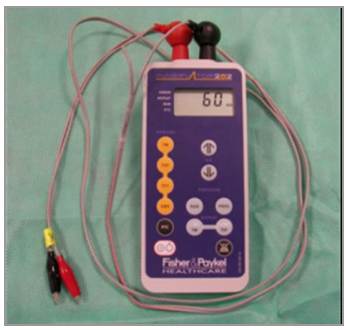
[16] It happens when the drug is given for long times, it'll act as a nondepolarizing agent.

[17] Highest risk is seen with suxamethonium, followed by rocuronium.

2. Atracurium	
Metabolism	Metabolized by **Hofmann degradation**[18] and ester hydrolysis in the plasma.
Extra Advantage	Suitable for patients with hepatic or renal failure since its metabolism is independent of the kidneys and liver. No direct cardiovascular effects.
Adverse Effect	• **Laudanosine** (a breakdown product) may accumulate and cause seizures. • Histamine release.
3. Cisatracurium (isomer of atracurium)	
Properties	• Slow onset of action • No histamine release
Metabolism	Hoffman degradation (does not accumulate in renal failure)
Advantage	Less laudanosine production.
4. Rocuronium	
Properties	• The most rapid onset of the clinically available non-depolarizing NMBDs
Uses and Dosage	• 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
Disadvantage	Higher incidence of **anaphylactic reactions**
Anti Acetylcholinesterase (Neostigmine!)	
Mechanism of action	They inhibit the action of the acetylcholinesterase enzyme at the NMJ resulting in increase in the concentration of Ach at NMJ
Testing Efficacy	Clinical tests of adequate resolution of neuromuscular block include the ability to lift the head from the bed for 5 seconds.
Dosage	Intravenous injection at a dose of 0.05 mg/kg (maximum 5mg)
Adverse Effects	Bradycardia, miosis, GI upset, nausea, bronchospasm, increased sweating, salivation & bronchial secretions ↳ An an antimuscarinic such as glycopyrronium 0.01 mg/kg or atropine 0.02 mg/kg must be administered along with the anticholinesterase

Choice of NMBA depends on

- Urgency for tracheal intubation.
- Duration of the procedure
- Coexisting medical conditions that may affect the NMJ



[18] Anatomically degraded by the body's pH.

- Side effects & metabolism
- Cost-effectiveness

Remember

- **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 its vagolytic effects may be appropriate in pediatrics.
- ER C-sections/ full stomach Suxamethonium.
- Suxamethonium is contraindicated? Use rocuronium.

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.\

Antimuscarinics Drugs such Atropine, Glycopyrollate, Hyoscine

- Decrease salivary and bronchial secretions
- Prevents laryngospasm, bronchospasm, Nausea and
- Vomiting
- Prevent Vasovagal attack, Prevent Bradycardia, Hypotension, Cardiac arrhythmia and arrest
- Used to reverse muscarenic effect of cholinesterase inhibitors
- Hyoscine – Sedation, amnesia, Antiemetic They ↑ body temperature Produce Pupillary dilation – alter pupil sign

Benzodiazepines

All the opioids discussed share the following properties	
Mechanism of Action	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 • Diazepam clearance is reduced in the elderly
Pharmacodynamics	CNS • Amnesic, anticonvulsant, anxiolytic, and sedative- hypnotic (dose-dependent manner). • **No analgesia** Cardiovascular System • Mild systemic vasodilation and ↓ in cardiac output • HR is usually unchanged Respiratory system • Mild dose-dependent ↓ in RR and tidal volume • Respiratory depression may be more if administered with an opioid
Primary Uses	• Sedation, amnesia, anxiolytic use

	• As premedication or as adjunct to GA to calm the patient before going to the OR
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 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. So if you are not able to control airway **don't** give the IV Benzodiazepines.
1. Midazolam (Dormicum)	
Properties	• Water soluble, so drug of choice for IV administration • More rapid onset and more rapid elimination • The most potent amnestic used in the OR. • Cause no pain during injection.
2. Diazepam (Valium)	
Properties	• Water-insoluble (IV use) long acting • Can cause local irritation/pain
3. Lorazepam (Ativan)	
Properties	Water insoluble used as a premedication, it is longer acting
Flumazenil!	
Duration	Reversal of sedative effects occurs within 2 min; peak effects at 10 min. Half-life is shorter than the benzodiazepine
Mechanism of Action	A competitive antagonist at the benzodiazepine binding site of GABAA receptors in the CNS
Metabolism	Metabolized to inactive metabolites in the liver
Dosage	• 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
Contraindication	In patients receiving benzodiazepines for the control of seizures or elevated ICP

Complication of Anaesthesia:

During Anaesthesia

Bradycardia, Cardiac arrhythmia, Cardiac arrest
Hypotension
↑ Salivary and bronchial secretion
Respiratory depression, Hypercapnia , Aspiration pneumonia
Delirium, Convulsions ,Hypoxia
Awareness and recall of events , Fire and explosion

After Anaesthesia

Nausea and Vomiting
Delayed recovery, Persistent sedation
Atelectasis and pneumonia
Liver and Kidney damage
Delirium
Nerve palsy

Extra read:

- In certain circumstances, extubation may be performed ‘deep’ i.e. with the patient still under anesthesia. Under anesthesia, airway reflexes will remain suppressed, reducing the risk of coughing, laryngospasm and HTN associated with extubation. This may be preferable in certain neurosurgical and cardiac patients in whom surges in intracranial or systemic BP should be avoided.

Have you heard of twilight anesthesia?

It’s puting the pt in a state where they are not unconscious, but sedated. The patient would be relaxed and "sleepy", able to follow simple directions by the doctor, and is responsive. Generally, twilight anesthesia causes the patient to forget the surgery and the time right after.

TEAM MCQs

435

1. Which of the following is the fastest acting inhalational agent?
    a. Halothane
    b. Isoflurane
    c. Ether
    d. Sevoflurane

2. A 65 year old patient and a known case of ESRD for PD catheter insertion, which of the following is the muscle relaxant of choice for this patient?
    a. Suxamethonium
    b. Pancuronium
    c. Atracurium
    d. Rocuronium

3. Which of the following inhalational anesthetic agents is used as an induction agent choice in children?
    a. Methoxyflurane
    b. Sevoflurane
    c. Desflurane
    d. Isoflurane

4. Which of the following has an association with hepatotoxicity?
    a. Diethyl ether
    b. Thiopentone
    c. Propofol
    d. Halothane

5. Which of the following in the most significant risk factor for postoperative nausea and vomiting?
    a. Morphine
    b. Breast surgery
    c. Smoking
    d. NSAIDs

6. Which of the following is the morphine antagonist?
    a. Flumazenil
    b. Neostigmine
    c. Intralipid
    d. Naloxone

7. At which of the following receptors do barbiturates act?

a. GABA
b. NMDA
c. A2
d. Nicotinic

8. Which of the following IV anesthetics have bronchodilator effect?
    a. Etomidate
    b. Propofol
    c. Barbiturates
    d. Midazolam

9. A 45 year old lady who underwent craniotomy for posterior fossa tumor in sitting position, intraoperatively the patient developed air embolism. Which of the following inhalational agents should be stopped to prevent expansion of embolism?
    a. Sevoflurane
    b. Nitrous Oxide
    c. Isoflurane
    d. Desflurane

10. Which of the following is the muscle relaxant for rapid sequence induction?
    a. Cisatracurium
    b. Suxamethonium
    c. Vecuronium
    d. Pancuronium

Q1: D | Q2: C | Q3: B | Q4: D | Q5: A| Q6: D | Q7: A | Q8: B | Q9: B | Q10: B