Pharmacology of Anesthesia

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Anesthetic Agents

Intravenous Anesthetics

Drug	MOA	P-kinetics	P-dynamics			Uses	✓ Advantages	✖ Disadvantages
			CNS	CVS	Resp.			
Barbiturates	▪ ↑ GABA ▪ ↓Glutamate ▪ ↓Nicotinic Acetylcholine R.	Hepatic elimination	▪ ↓CMRO2 ▪ ↓ICP ▪ ↓ CBF	▪ ↓ Contractility ▪ ↓ CO ▪ ↓ BP ▪ Baroreceptors intact.	▪ ↓ RR ▪ ↓ TV ▪ Laryngeal reflexes intact.	Induction of Anesthesia	▪ Rapid onset 30-45s ▪ Short duration	▪ Histamine release ▪ Myoclonus & hiccups ▪ Cont. in porphyria ▪ Venous irritation and tissue damage.
Propofol	▪ ↑ GABA	Hepatic and extra-hepatic metabolism	▪ ↓ICP ▪ ↓ CPP ▪ ↓ MAP	▪ ↓ Preload ▪ ↓ Afterload ▪ ↓ Contractility ▪ ↓ CO ▪ ↓ *BP, markedly* ▪ Baroreceptors *blunted.*	▪ ↓ RR ▪ ↓ TV ▪ ↓Ventilatory response	▪ Induction of anesthesia. ▪ Sedative/ hypnotic in OR & ICU. ▪ Maintenance of anesthesia ▪ Day case surgery	▪ Rapid onset ▪ Weak analgesics ▪ Antiemetic ▪ Easy LMA insertion. ▪ Safe in MH & Porphyria ▪ ↓Postoperative hangover and N&V	▪ Venous irritations ▪ Bacterial growth ▪ Cont. in lipid disorders ▪ Myoclonus & hiccups ▪ Propofol infusion syndrome: (MA, HF, RF & Rhabdomyolysis)
Etomidate		Hepatic and circulating esterases	▪ ↓CMRO2 ▪ ↓ICP ▪ ↓ CBF	Minimal change in HR, BP & COP	▪ ↓ RR ▪ ↓ TV ▪ Transient apnea	Induction of Anesthesia in patients with *CVS problems*	▪ Short acting ▪ Potent ▪ Suitable for elderly and shocked patients.	▪ Excitatory phenomena (Involuntary limb twitches ▪ Venous irritation ▪ *Adrenal suppression*
Ketamine	Antagonism of NMDA Rs (Dissociative anesthesia)	Hepatic metabolism	▪ *Amnesia* ▪ ↑ CBF ▪ ↑ CMR ▪ ↑ ICP	▪ ↑ HR ▪ ↑ COP ▪ ↑ BP	▪ Mild ↓ in RR & TV ▪Broncho-dialator ▪ Laryngeal reflexes intact.	▪ Induction of general anesthesia ▪ Sedation ▪ Analgesia	▪ Suitable for shocked patients ▪ Sutiable for: - Radiological interv. - Radiotherapy - Burns & dressing changes.	▪ ↑ Salivation ▪ ↑ PONV ▪ Emotional disturbances ▪ Agitations & hallucinations ▪ Cont. in Head trauma pts

Anesthetic Agents

Benzodiazepines

MOA	P-kinetics	P-dynamics			Uses	Adverse effects
		CNS	CVS	Resp.		
↑ GABA affinity	Hepatic metabolism	▪ Amnesia ▪ Anticonvulsant ▪ Anxiolytic ▪ Sedative hypnotic ▪ No analgesia	▪ Mild vasodilator ▪ ↓ CO ▪ HR unchanged	▪ Mild ↓ RR & TV	▪ Premedication ▪ Adjunct to G.A. ▪ With opioids for depression	▪ Drug interactions with anticonvulsant (valproate) ▪ Pregnancy and labor : Risk of cleft lip and palate in the first trimester. ▪ CNS depression in the neonate. ▪ Superficial thrombophlebitis and injection pain by diazepam and lorazepam. ▪ They cause mild respiratory depression but can be marked in elderly leading to apnea.

Drugs

Midazolam (Dormicum)	**Diazepam** (Valium)	**Lorazepam** (Ativan)
▪ Water soluble = suitable IV administration ▪ More rapid onset and more rapid elimination ▪ The most potent amnestic	Water-insoluble = IV use can cause local irritation/pain	

Antidote: Flumazenil

MOA	Antagonist at the benzodiazepine binding site
Contraindications	▪ In patients receiving benzodiazepines for the control of seizures or elevated ICP.

Analgesics & Anesthetic Agents

Opioids (Moderate sedation & Profound analgesia)

MOA	Uses	✓ Advantages	✖ Disadvantages
Binds to opioid receptors μ (mu), κ (kappa), and δ (delta)	▪ *Principally provides analgesia* and some degree of sedation. ▪ Large doses can produce general anesthesia.	▪ Minimal cardiac effects ▪ No myocardial depression	▪ Miosis ▪ N&V, slow gastric emptying & constipation ▪ Urinary retention & biliary colic ▪ Drowsiness or sedation ▪ Chest wall rigidity & respiratory depression ▪ Bradycardia in large doses ▪ Some peripheral vasodilation and histamine release – hypotension ▪ Itching

Drugs

Morphine <	Fentanyl <	Sufentanil citrate (Sufenta) <	Alfentanil <	Remifentanil (Ultiva)
▪ Histamine-releasing action: hypotension and bronchoconstriction. ▪ Poor choice for a patient with renal failure.	▪ Used for induction and maintenance of G.A ▪ Supplement regional and spinal anesthesia. ▪ Ability to maintain cardiac stability.	▪ Rapid elimination ▪ Relatively more rapid recovery as compared with fentanyl.	Shorter duration of action compared to fentanyl and sufentanil.	Ultra short acting and rapidly cleared widespread extrahepatic metabolism by blood and tissue nonspecific esterases.

Antidote: Naloxone

MOA	Opiate receptor antagonist
Adverse effect	▪ Reversal of analgesia ▪ Nausea & vomiting ▪ Increased sympathetic nervous system activity, (tachycardia, hypertension, pulmonary edema, and cardiac dysrhythmias)

Anesthetic Agents

Inhalational Anesthetics

MOA: Work on 3 G's: GABAA, Glycine, and Glutamate receptors

MAC	• Inhalational anesthetics' potency is measured by MAC • The minimum alveolar concentration (MAC) is the amount of vapor (%) needed to render 50% of spontaneously breathing patients unresponsive to a standard painful surgical stimulus • Less MAC means higher potency	
P-kinetics	• 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 • Predominant route of elimination: Exhalation (logic)	
Toxicity	▪ **CNS**	Unconsciousness, amnesia and ↑ cerebral blood flow (CBF)
	▪ **CVS**	Myocardial depression & systemic vasodilation HR tends to be unchanged, except desflurane **MCQ:** Sensitize the myocardium to the arrhythmogenic effects of catecholamines
	▪ **Respiratory**	▪ Dose-dependent respiratory depression ▪ Airway irritation → may precipitate coughing, laryngospasm, or bronchospasm (sevoflurane makes it more suitable) ▪ Bronchodilator (with the exception of desflurane). ▪ Inhibit hypoxic pulmonary vasoconstriction
	▪ **Renal**	↓ renal blood flow
	▪ **Neuromuscular**	↓ skeletal muscle tone. Malignant hyperthermia → dramatic increase in body temperature, acidosis, electrolyte imbalance and shock. Management: removal of triggering agent, 100% Oxygen, active cooling measures & Dantrolene
	▪ **Hepatic**	↓ hepatic perfusion

Anesthetic Agents

Inhalational Anesthetics

MOA: Work on 3 G's: GABAA, Glycine, and Glutamate receptors

	✓ Advantages	✖ Disadvantages
Desflurane سريع سريع	• Rapid onset and recovery of anesthesia • outpatient procedures • least metabolized to toxic byproducts	• Requires a special vaporizer • Pungent smell irritating to the airway (coughing, laryngospasm) • ↑ BP & HR (in high concentrations)
Sevoflurane سريع سريع	• Low blood solubility → rapid induction and emergence • Pleasant smelling (suitable for children) • Bronchodilation properties • Agent of choice in asthma, bronchitis, and COPD. • little effect on the HR • Mild respiratory and cardiac suppression	• CO_2 absorbents in anesthesia machines degrade sevoflurane to Compound A (nephrotoxic compound)
Isoflurane مو سريع مو سريع	• Peripheral vasodilation and increased coronary blood flow	• Moderate solubility → delayed recovery from anesthesia • Sensitize the heart to circulating catecholamines
Halothane Hello babies	• Sweet pleasant odor (induction in children)	• Sensitize the heart to circulating catecholamines • Very soluble in blood and adipose tissue → prolonged emergence • Halothane → Hepatitis

Nitrous Oxide (Laughing gas)

MOA: NMDA receptors antagonist

CNS	CVS	Respiratory	Other side effects
▪ Weak anesthetic ▪ Analgesic ▪ Combined with other anesthetics ▪ Used alone e.g. dental procedures	▪ Mild myocardial depressant ▪ Mild sympathetic stimulant. ▪ HR and BP are usually unchanged. ▪ ↑ pulmonary vascular resistance.	Little effect	▪ Nausea/vomiting. ▪ Risk of bone marrow depression ▪ Inhibits vitamin B-12 metabolism ▪ Expansion of closed gas spaces ▪ Contraindicated in air embolus, pneumothorax, Middle Ear Surgery ▪ Diffuse into the cuff of ETT ▪ Diffusion hypoxia

Anesthetic Agents

Local Anesthetics

MOA: Reversibly blocking sodium channels to prevent depolarization

Applications	• 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) • 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)	
Drugs (Amides)	**Lidocaine**	▪ The most commonly used amide type local anesthetic ▪ Rapid onset and a duration "extended with epinephrine" ▪ Contraindicated in patients with a known sensitivity ▪ Has antiarrhythmic action
	Bupivacaine	▪ Onset of action is slower than lidocaine and anesthesia is long acting "extended with epinephrine" ▪ More cardio-toxic than lidocaine, difficult to treat. ▪ Contraindication: known hypersensitivity
	Ropivacaine	▪ Less toxic ▪ Long-lasting LA. ▪ Ropivacaine is slightly less potent than bupivacaine.
Toxicity	▪ **CNS**	▪ **Initially:** circumoral numbness, 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 reaction**	Rare (less than 1%) rash, bronchospasm
Prevention & Treatment	All Cases: Assure adequate ventilation & administer supplemental Oxygen. • Seizures→ Midazolam • Hypotension→ **1.** Trendelenburg position (head down , legs up) **2.** IV fluid bolus (Isotonic Saline or LR) **3.** Vasopressor (Dopamine if refractory to above). • Dysrhythmias→ As per ACLS protocol (but do not administer further Lidocaine)	

Muscle Relaxants

Neuromuscular Blocking Agents

Primary Uses

1-Perform tracheal intubation 2-Facilitate ventilation 3-Provides optimal surgical operating conditions

Depolarizing (Succinylcholine) AKA Suxamethonium

General Characteristics

- Structurally similar to acetylcholine → activate the acetylcholine receptors (Ach) → depolarization of post junctional membrane.
- Very short duration of action (onset 60 seconds/ duration 10 minutes)
- For short time intubation (Rapid sequence induction)
- Metabolized very quickly by plasma cholinesterase **MCQ**
- Characterized by transient muscle fasciculations followed by relaxation.
- Acetylcholine esterase (AChE) inhibitors potentiate rather than reverse the block.

Adverse Effects

1. 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.
2. Hyperkalemia → burns, RF, muscular dystrophies & paraplegia
3. A transient increase in intraocular pressure
4. Increase in intracranial & intragastic pressure
5. Myalgia : abdomen, back, and neck.
6. Histamine release
7. Dual block

Succinylcholine apnea:

- Low levels of plasma cholinesterase (severe liver or kidney disease)
- A drug-induced inhibition of its activity, a genetically atypical enzyme
- Management: supportive, especially to avoid awareness
- Anaphylaxis
- Malignant hyperthermia (MH)

Non-depolarizing

MOA

competitively blocking the binding of ACh to its receptors and inhibit muscular contraction

Charact-eristics

- Absence of fasciculations
- Potentiation by other nondepolarizing NMBDs and volatile anesthetic agents
- Reversal by AChE inhibitors

Muscle Relaxants

Neuromuscular Blocking Agents				
Non-depolarizing				
Drug	**Mivacurium**	**Atracurium**	**Cisatracurium**	**Rocuronium**
Onset & Duration of action	Short-acting	intermediate	Relatively slow onset of action	Most Rapid onset! intermediate duration of action
Metabolism	rapidly hydrolyzed by plasma cholinesterase	▪ Hofmann degradation and ester hydrolysis in the plasma (good for RF patients) ▪ Duration of action is independent of renal and hepatic function.	Hofmann degradation and does not accumulate in renal failure	———
Histamine release	✓	✓	✖	✖
Other effects	Histamine release causes a transient hypotension and tachycardia	▪ No direct cardiovascular effects ▪ Breakdown product of atracurium, (laudanosine) may accumulate and cause seizures	▪ Isomer of atracurium ▪ Less laudanosine	▪ Rapid sequence induction (RSI) when Suxamethonium is CI ▪ Anaphylactic Reaction.
Choice of NMBD	1. Urgency for tracheal intubation 2. Duration of the procedure 3. Coexisting medical conditions that may affect the NMJ. 4. Side effects & metabolism 5. Cost-effectiveness Suxamethonium → good choice for rapid intubation Rocuronium → 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.			
Peripheral nerve stimulator	• Check the depth of neuromuscular blockade • Determine that neuromuscular blockade is reversed • At least 4 twitches on a train of four should be detected before attempting reversal			

Muscle Relaxants

Neuromuscular Blocking Agents	
Antidote: **Anticholinesterases (Neostigmine)**	
MOA	Inhibit action of acetylcholinesterase enzyme at the NMJ by increasing the concentration of Ach at NMJ
Notes	• Intravenous injection • Clinical tests of adequate resolution of neuromuscular block include the ability to lift the head from the bed for 5 seconds • 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