Pharmacology of general anesthesia

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JORDAN 2025/2026

Objectives

1. Identify the main inhalation anesthetic agents and describe their pharmacodynamic properties and side effects
2. Describe the relationship of the blood: gas partition coefficient of an inhalation anesthetic with its speed of onset of anesthesia and its recovery time
3. Describe the main pharmacokinetic and pharmacodynamic characteristics of the intravenous anesthetics

Introduction

- General anesthesia is (a combination of medicines) administered before surgeries which induces a deep sleep-like state: patient is completely unconscious and doesn't feel any pain during surgeries
- It is given in stages – just before the surgery begins and then throughout the surgery to keep the pateint in that sleep state.
- General anesthesia is given by an anesthesiologist: a doctor who specializes in anesthesiology.
- The anesthesiologist remains in the operating room throughout the surgical procedure

General Anesthesia

- General anesthesia is a Reversible State of CONTROLLED unconsciousness produced by anesthetic agents and characterized by loss of the body sensations, analgesia, amnesia and skeletal muscle relaxation, maintenance of physiological stability and reduced response to surgical stress.
- It is used almost exclusively in surgery.
- Used also in other painful invasive procedures.
- No one anesthetic agent can produce analgesia, muscle relaxation, loss of body sensations and amnesia with safe therapeutic window, so:

Balanced Anesthesia

• **Multimodal anesthesia**, uses a mix of drugs and techniques to achieve anesthesia, aiming for optimal surgical conditions (calm, pain-free, immobile) while minimizing side effects from any single agent, often through a hypnotic, analgesic, and muscle relaxant combination.

•**Benefits of balanced anesthesia:**

•**Minimized Side Effects:** Lower doses of each

•**Improved Patient Safety:** Better control

•**Enhanced Recovery:** Faster, smoother awakening and reduced postoperative pain.

Premedication (pre-anesthetic drugs)

- **(Premeds) are drugs given before surgery to:**
- Calm patients and reduce anxiety (anxiolysis)
- Analgesia
- Minimize the amount of general anesthetic needed
- Prevent side effects like nausea
- Decreasing secretions (saliva)

Premedication (pre-anesthetic drugs)

- **Benzodiazepines**: anxiolytic
- **Antihistamines** to prevent anaphylactic reactions
- **Anticholinergics** prevent reflex bradycardia
- **H_2-antagonists, antacids**, **prokinetics**: prevent reflux and subsequent aspiration pneumonia
- **Neuroleptics** together with opioids serve to induce **neuroleptanalgesia**, a state of sedation, analgesia and amnesia, but **NOT** unconsciousness - the patient is able to cooperate
- **Opioids**: for painful injuries.

Phases of general anesthesia

- Phase 1: induction
- Phase 2: maintenance
- Phase 3: recovery

Phase of Induction

- **Transitioning a patient from consciousness to unconscious, pain-free state using IV drugs or inhaled gases**
- **Goal:**
- Rapid, smooth loss of consciousness, amnesia, analgesia, and muscle relaxation.
- **Methods:**
  - **Intravenous propofol, thiopental or etomidate** produce a fast and smooth induction. **Most common method**

  - **Inhalation method**: **for special patients**: **difficult air ways** and **children** (mask or hand introduced gradually from the side)
- **Involves**: securing the airway (intubation/laryngeal mask) and starting continuous monitoring (heart rate, blood pressure, oxygen saturation).

Phase of Maintenance

- **Continuously administering inhaled (most cases) or intravenous drugs to keep patients unconscious, pain-free, and immobile throughout surgery.**
- **IV agents can be used via:**

1- Continuous pump (Total intravenous anesthesia (TIVA): example: continuous infusions of propofol (hypnotic) and remifentanil (opioid)

2- Balanced Anesthesia: Combination of inhaled agents with IV opioids (fentanyl) and muscle relaxants

- **Monitoring of:**
- HR
- BP
- Pupil size, lacrimation
- Movement

Phase of recovery

- Requires careful monitoring because of risk of complications:
- **Nausea and vomiting**: 10-15%
- **Spasm of airways**: 7-10 %
- **Urinary retention**: over 50 years old: 3-4%
- **Hypotension** : 3-4 %
- **Hypothermia**: in immediate post-operative period due to lack of muscle movement (shivering): 2-3%

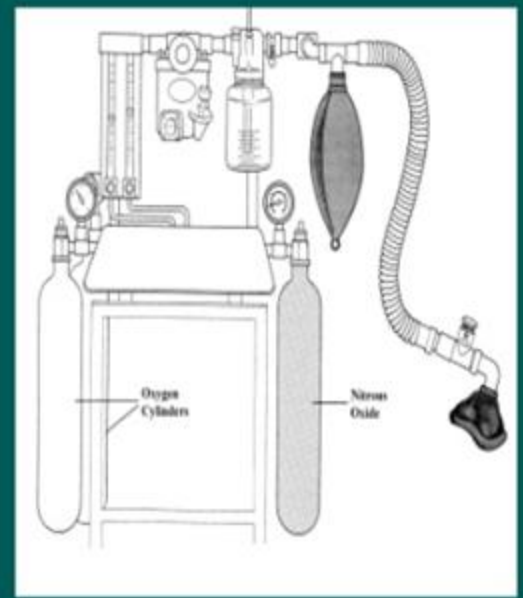
Anesthetic Machine

- An anesthesia machine is a sophisticated medical device that delivers **precise** mixtures of medical gases (like oxygen, nitrous oxide) and anesthetic vapors.

Continuous flow (Boyle's) anaesthetic machine

Anaesthetic Machine (Boyle's equipment)

- The anaesthetic machine
- Gas source- either piped gas or supplied in cylinders
- Flow meter
- Vaporisers
- Delivery System or circuit



Stages Of Anesthesia

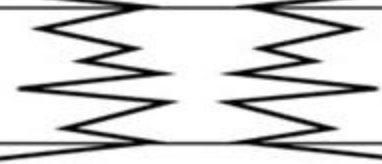
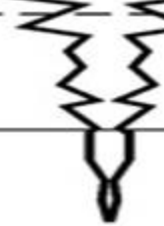
- **Described in 1930s (Guedel's classification)**
- We can observe these stages when using inhalation anesthetics, although they were only really visible during anesthesia using ether, they are not very clear in today's anesthetic procedures - mainly stage II.
- Modern anesthetics improved speed of onset, recovery and safety
- **Stage I (analgesia):** The patient loses consciousness and the perception of pain is reduced.

- **Stage II (Excitement):** The patient is in unconsciousness, but many reflexes are strengthened, motor restlessness
- The risk of death and cardiac arrest is greatest
- Release of subconscious emotions.

Stages Of Anesthesia

- **Stage III (surgical anesthesia):**
- Begins with the reappearance of regular breathing and ends with the cessation of spontaneous breathing
- Muscle tone decreases, spontaneous movements disappear, all reflexes disappear with deepening anesthesia. (pupil is fixed)
- **Stage IV (Medullary paralysis):**
- Spinal depression - depression of the vasomotor and respiratory center, death can occur within minutes

Stages Of Anesthesia

Stage	Muscle tone	Breathing	Eye movement
1 Analgesia	Normal		Slight
2 Excitement	Normal to markedly increased		Moderate
3 Surgical anaesthesia	Slightly relaxed		Slight
	Moderately relaxed		None
	Markedly relaxed		None
	Markedly relaxed		None
4 Respiratory paralysis	Flaccid		None

Mechanism of action of general anethetics

- Anesthetic agents absorbed to blood stream then **pass BBB**
- Enters **specific cells in CNS**, where they act on **specific receptors**
- There effects are **reversible**
- They **depress all excitable tissues** including CNS neurons, cardiac muscle and smooth and skeletal muscle fibers .
- Different parts of the CNS have different sensitivities to these agents, however, the **reticular activating system** (which is responsible for consciousness) is among the most sensitive
- The **medullary centers are least sensitive**

Mechanism of action (macroscopic level)

- **General anesthetics depress the following CNS parts:**
- **Reticular activating system**: reversible loss of consciousness
- **Prefrontal cortex, hippocampus and amygdala:** amnesia
- **Spinal cord**: immobility and analgesia

Mechanism Of Action (molecular level)

- By enhancing inhibitory signals (like GABAergic neurotransmission) and blocking excitatory signals (like glutamatergic transmission), leading to **widespread neuronal depression**

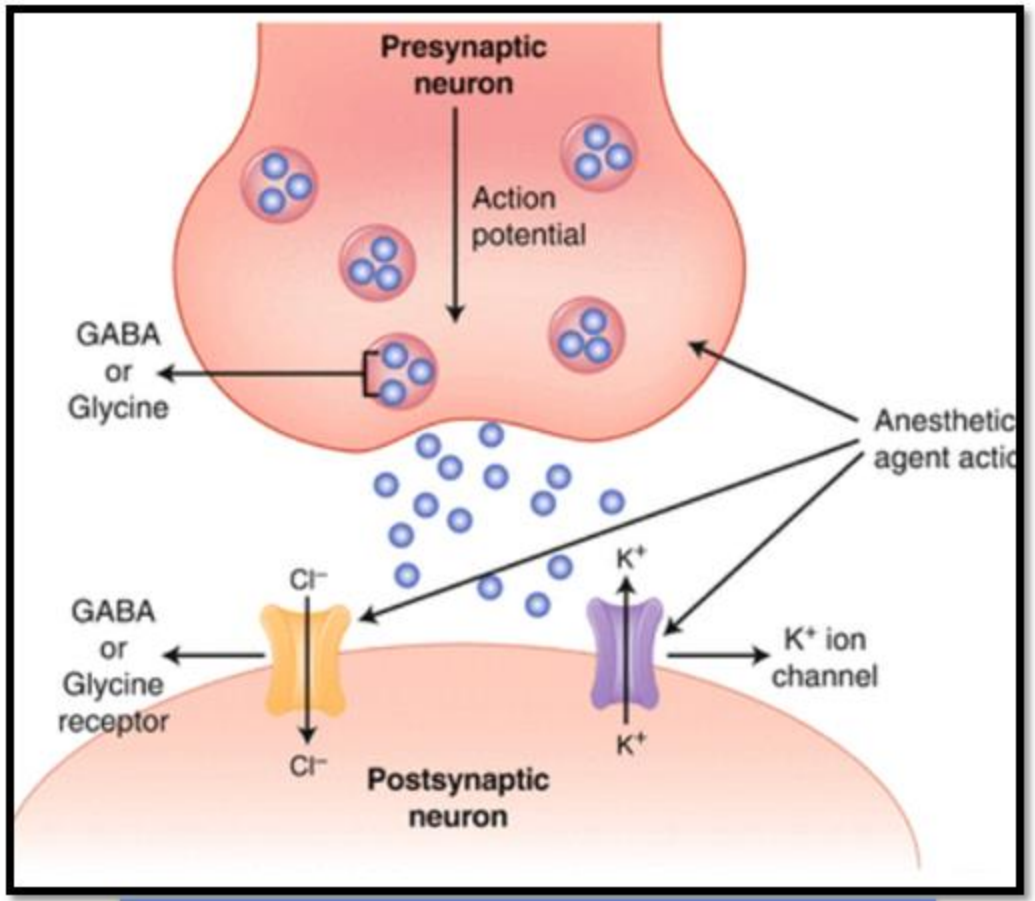
•1- **Activation of $GABA_A$ receptors (inhibitory): increasing the influx of chloride ions, hyperpolarizing neurons, and making them less excitable**

•2- **Blocking of NMDA receptors (excitatory): block these glutamate receptors, preventing excitatory signals from being transmitted**

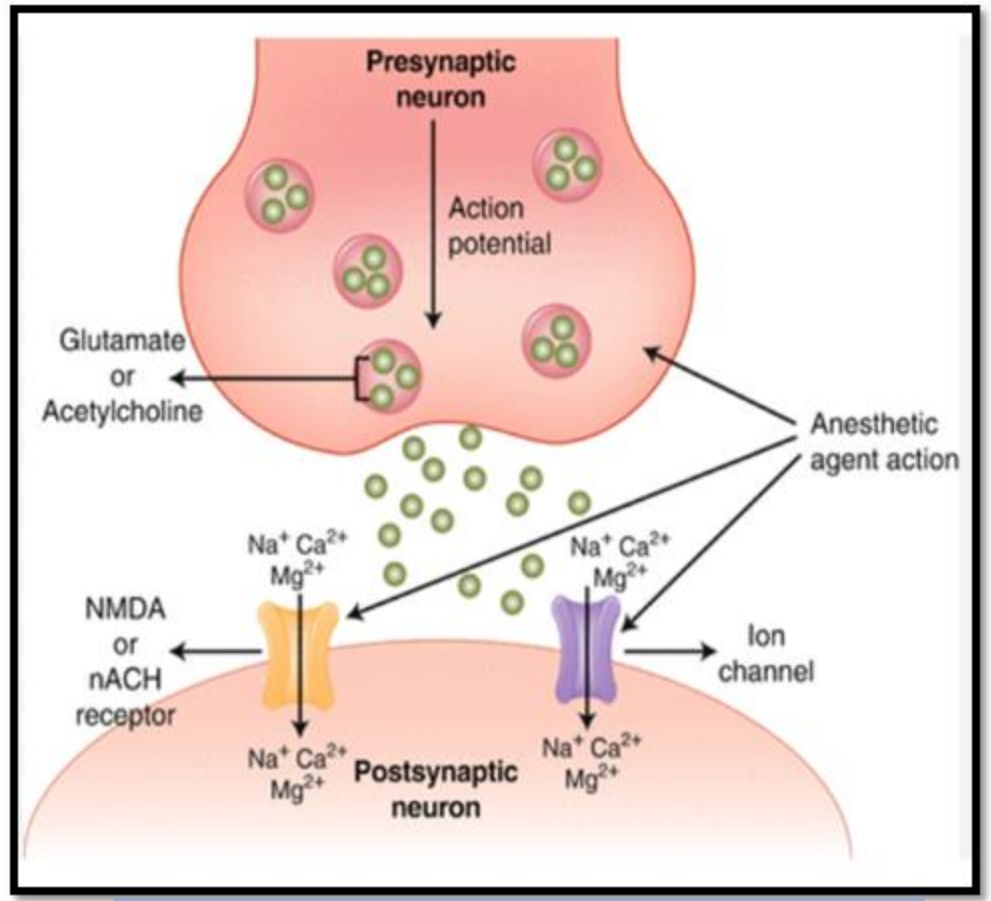
•3- **Opening of two-pore K+ channels (K2P):** Some agents open these "leak" channels, causing a constant outward flow of potassium, further hyperpolarizing neurons and reducing excitability.

•4- **Glycine Receptors (Inhibitory):** Similar to $GABA_A$, enhancing their function to promote inhibition.

Mechanism of action



Inhibitory neurotransmitters



Excitatory neurotransmitters

Classification of general anesthetics

Inhalational Anesthetics:

Administered through mask or tube, they pass from lungs to blood to brain

Often used for maintenance

- **1- Gases:** Nitrous Oxide (N_2O)
- **2- Volatile liquids (vapors):**
- Sevoflurane
- Isoflurane
- Desflurane
- Halothane
- Ether (older).

Intravenous (IV) Anesthetics (Injectable)

- **1- Inducing Agents**: Propofol, Etomidate, Thiopental
- **2- Sedatives/Amnestics**: Benzodiazepines (Midazolam, Diazepam)
- **3- Analgesics**: Opioids (Fentanyl, Remifentanil)
- **4- Dissociative Agents**: Ketamine

Pharmacokinetics of Inhalation Agents

- **How these agents move from anesthetic machine to the brain (uptake, distribution, elimination)?**
- **Factors affecting pharmacokinetics (flexible control and depth of anesthesia):**
- **1- Concentration of the anesthetic agent in inspired air:** the greater the inspired concentration, the faster the induction of anesthesia.
- **2- Blood solubility of the agent (speed of induction and recovery)**
- **3- Pulmonary ventilation**
- **4- Cardiac output**

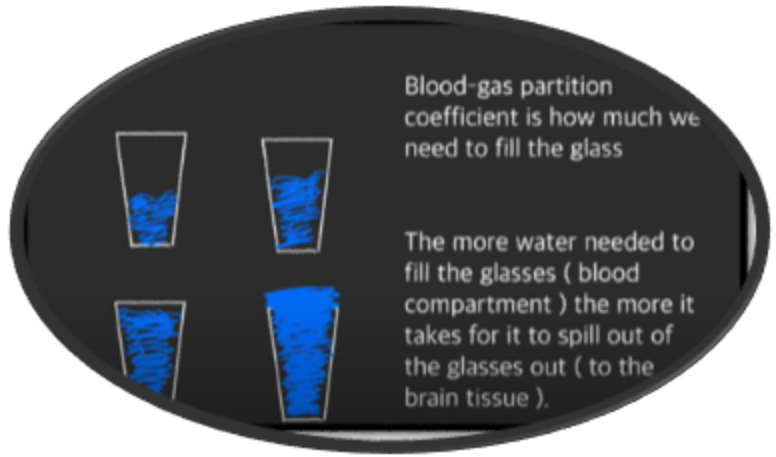
Blood/Gas Partition Coefficient (λb/g)

- The blood/gas partition coefficient reflects solubility of the volatile agent in blood
- It is defined as the **ratio** of volatile agent concentration in blood to alveolar gas when their partial pressures are in equilibrium
- **Example:** Isoflurane has a blood–gas partition coefficient of 1.4, meaning that at equilibrium, when there is no difference in the partial pressures between blood and alveolus, the concentration in blood is 1.4 times the concentration in the gas (alveolar) phase

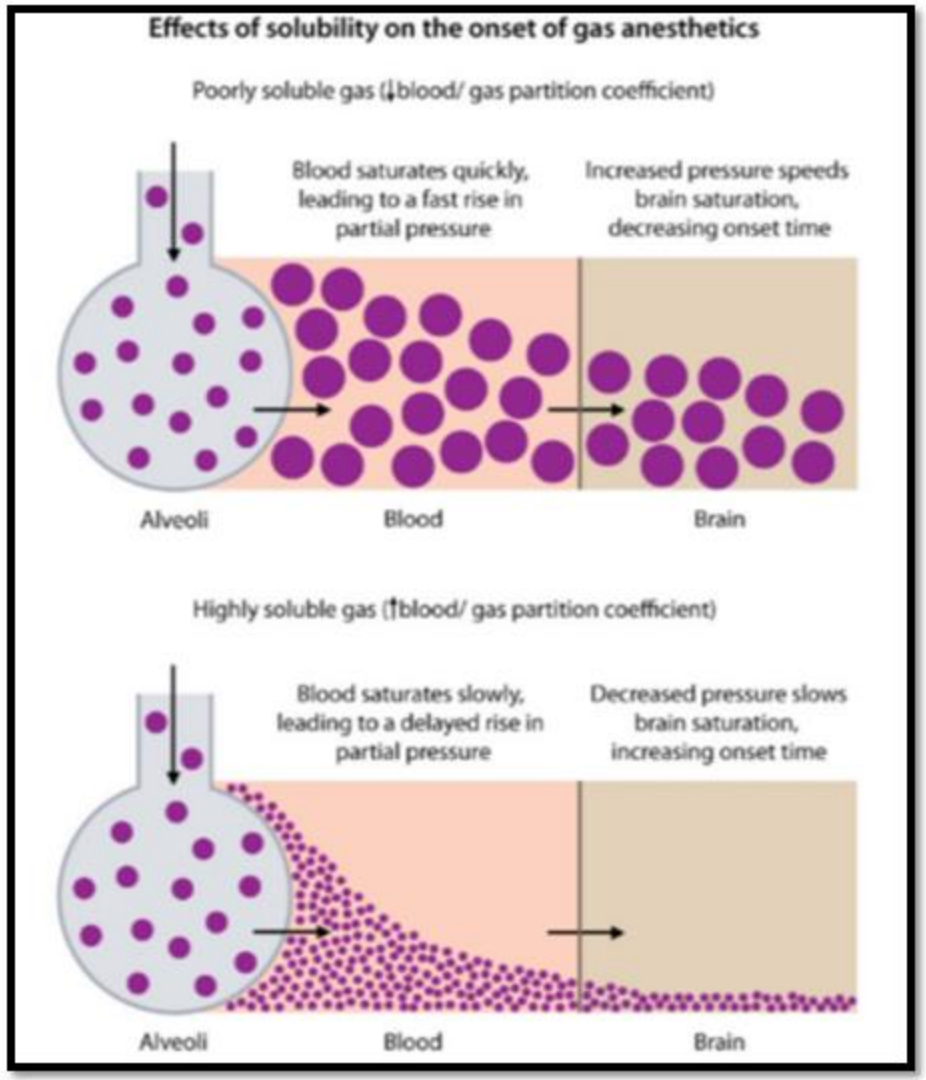
Blood/Gas Partition Coefficient (λb/g)

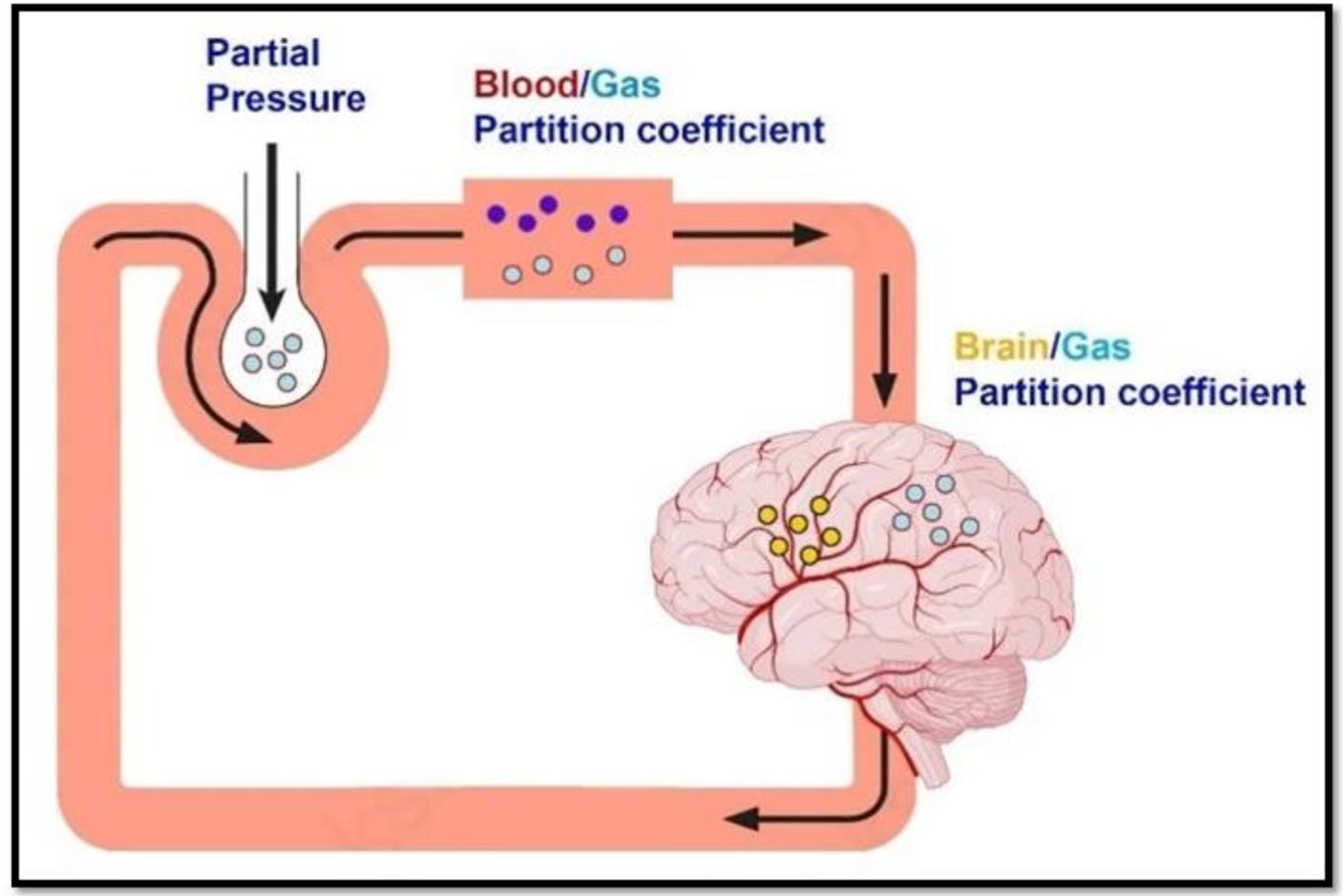
- **Agents of low blood solubility**
- (e.g., nitrous oxide, desflurane): **rapid induction and recovery**
- Because free gas molecules more than bound gas form and so the arterial tension (and hence brain tension) **rises and falls quickly**

- **Agents of high blood solubility**
- Example: halothane: **slow induction and recovery**
- Because free gas molecules are less than bound gas form, so the arterial tension (and hence brain tension) **rises and falls slowly**



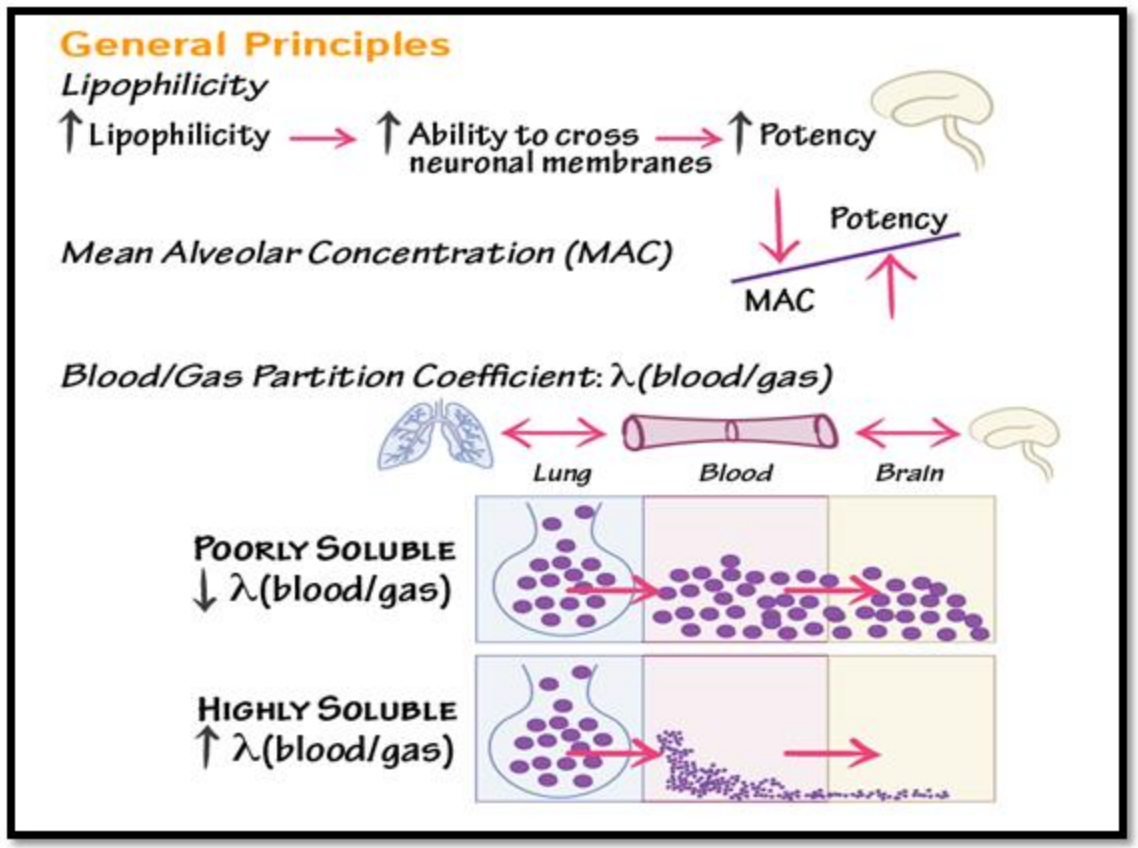
PKs of inhalational anesthesia





PKs of inhalational agents

- **Minimum Alveolar Concentration (MAC)**: (ED50)
- The standard measure of inhaled anesthetic **potency**, defined as the concentration in the alveoli that prevents movement in 50% of patients in response to a painful stimulus.
- A lower MAC value indicates a more potent anesthetic, meaning less is needed to achieve the same effect



Properties of Inhaled Anaesthetics

Minimal Alveolar Concentration (MAC)

- Smaller the MAC value more potent is the anaesthetic and vice versa.

Arteriovenous concentration Gradient(ACG)

- Smaller the ACG value faster will be the onset of action and vice versa.

Blood – Gas partition coefficient

- Smaller the B/G partition coefficient value faster will be the onset of action and vice versa.

Adverse effects of inhaled anesthetics

1- Malignant Hyperthermia

- Malignant hyperthermia (MH) is a **pharmacogenetic hypermetabolic state of skeletal muscle**
- Induced *in* ***susceptible individuals*** by inhalational anesthetics and/or succinylcholine.
- **Etiology:** Genetic Ca+2 channel defect or RYR1 (ryanodine receptor)
- Excess calcium ion release from SR leads to excessive ATP breakdown/depletion
- **Signs:** tachycardia, arrhythmia, tachypnea, metabolic acidosis, hyperthermia, muscle rigidity, sweating
- May be fatal: 75% mortality
- **Treatment**: dantrolene IV: close Ca channels: **LIFE-SAVING**.

Adverse effects of inhaled anesthetics

- **2- CNS**: increased ICT due to VD: headache, blurred vision and vomiting
- **3- CVS**: **Most agents, particularly halothane, depress** myocardial contractility and produce **bradycardia**.
- This decreases cardiac output and blood pressure
- ***Halothane also sensitizes the heart to catecholamines, which*** can lead to arrhythmias
- **4- Respiratory:**
- Broncho-dilatation **except desflurane**: laryngospasm and bronchoconstriction.

Adverse effects of inhaled anesthetics

- **5- Liver:**
- **Most agents decrease liver blood flow.**
- **Mild hepatic dysfunction**
- **Halothane:**
- **About 1 in 30000 people will develop severe hepatic necrosis** following the use of **halothane, especially after repeated exposure within 3-months.**
- **Mechanism**: interaction of reactive metabolites with cellular proteins, which initiate an autoimmune reaction.
- **Hepatotoxicity** has resulted in the decreased use of **halothane, and avoidance of repeated use** within 3 months
- **6- Uterus:**
- Relaxation of the uterus, which may increase the risk of hemorrhage if anesthesia is used in labor.
- Nitrous oxide has less effect on uterine muscle compared with the other agents

IV anesthetic drugs

- **Include:**
- **ketamine, etomidate, fentanyl, propofol, thiopental, midazolam**
- **Indications:**

1-Short surgical procedures: diagnostic endoscopy, cardiac catheterization, abscess removal, episiotomy, etc. …

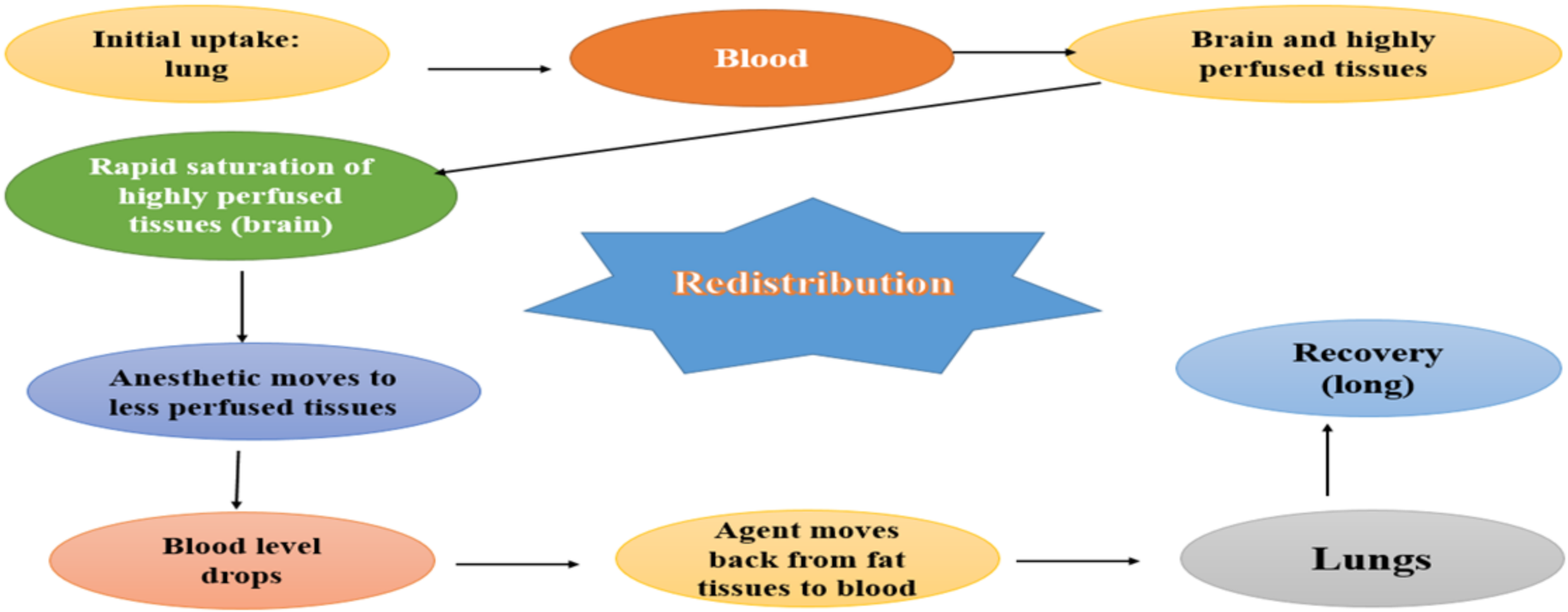
2- Longer procedures: TIVA

3- Rapid induction followed by an inhalational agent

- **PKs:** They are highly lipid-soluble agents and cross the BBB rapidly; (onset <30 seconds), duration of action (minutes) (Redistribution).

Redistribution

- **Redistribution of anesthesia** is the process where the anesthetic, after initial uptake, moves from highly perfused tissues (like the brain) to less perfused areas (like fat), then back into the bloodstream, affecting how fast patients wake up.



	Thiopental	Ketamine	Propofol (milk of amnesia)
Class	IV barbiturate	produces **dissociative anesthesia** (i.e. patient appears awake (nystagmus gaze) and hallucinates but unconscious with analgesia	powerful intravenous **anesthetic and sedative**
Mechanism of action	enhancing the inhibitory effects of GABA	NMDA receptor blocker	enhancing the inhibitory effects of GABA
Indications	Only for Rapid induction (Ultra-Short duration of anesthesia (about 2-5 min) but slow recovery (redistribution) (sedation up to 24 hrs.)	Ketamine is used to **induce and maintain general anesthesia**, either alone or in combination with other agents, particularly for short procedures that do not require skeletal muscle relaxation	**The most common** for rapid induction and recovery
Advantages	Ultra-short duration: rapid induction	1. Good analgesia. 2. Associated with a STRONG bronchodilator effect due to ↑ sympathetic outflow. 3. No depression of respiration 4. More tolerable in children	1. Rapid induction & recovery. 2. Postoperative nausea and vomiting are less than with other agents. Propofol has an anti-emetic action. 3- Anticonvulsant 4- Bronchodilator
Disadvantages	1. CVS depression: ↓↓ BP & bradycardia 2. Respiratory depression 3. Thiopental solution is alkaline, it must be strictly given IV: leakage leads to tissue necrosis and gangrene	1. ↑ Sympathetic outflow →cardiac stimulation & ↑BP. (contraindicated in hypertensive pateints or those with stroke) 2. ↑ Cerebral blood flow → post-operative hallucinations & nightmares. 3. Increased salivation	1- Pain at injection site (lidocaine prior to propofol) 2- Propofol-infusion syndrome: rhabdomyolysis, acidosis, lipemia, kperkalemia, renal failure, arrhythmia, circulatory collapse: (lipid emulsion) milky white appearance Fospropofol: better

IV agents

- **Etomidate: a potent, ultrashort-acting intravenous hypnotic agent used primarily for the induction of general anesthesia**
- **Rapid onset of action (within one minute)**
- **Enhances $GABA_A$ receptor action**
- **Advantages:**
- 1- Less CVS depression: minimal effect on BP 2- No RC depression
- 3- No tissue necrosis if leaked
- **Disadvantages:**
- 1- Acute adrenal suppression if given in presence of sepsis with high mortality rate
- 2- Post-operative nausea and vomiting
- **Midazolam**:
- **short-acting benzodiazepine**: enhances $GABA_A$ receptors
- **Duration: (5-10 min.)** due to drug **redistribution**
- **Advantages: Decreases cerebral blood flow- anticonvulsant**
- **Disadvantages: Mild hypotension- respiratory depression**
- Used for short surgical procedures
- **Antidote**: **flumazenil**

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Thank you