GENERAL ANESTHETICS

By

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BY THE END OF THIS LECTURES YOU SHOULD BE ABLE TO:

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. List the factors that influence inhalation anesthetic biodisposition
4. Describe the main pharmacokinetic and pharmacodynamic characteristics of the intravenous anesthetics

GENERAL ANESTHESIA

General anesthesia is a reversible state of unconsciousness produced by anesthetic agents and characterized by loss of the body sensations, analgesia and amnesia.

It is used almost exclusively in surgery.

Used also in other painful invasive procedures.

No one anesthetic agent can produce analgesia, muscle relaxation and amnesia, **so:**

- A combination of agents is used in the three clinical stages of surgical general anesthesia:
    * Premedication
    *Induction
    * Maintenance

Premedication

- **(pre-anethetic medication)**

- Relief from anxiety and produce amnesia; benzodiazepines

- Reduction of PS bradycardia & secretions; Atropine-like drugs

- Analgesia – to stop physiologic stress to pain; Opioids/NSAIDs

- Prevention of postoperative emesis; metoclopramide

INDUCTION

- patient goes from state of consiousness to a state of unconsiousness

  - Intravenous propofol, thiopental or etomidate produce a fast and smooth why??? induction
  - Prevention of acid aspiration in emergency and obstetric operations is crucial; H2-receptor antagonist /PPI prior to induction
  - Neuromuscular blocking agents decrease movement and provide muscle relaxation
  - Local anesthetics decrease pain and sensory transmission

×Maintenance

- Inhalation anesthetics are used to maintain a state of general anesthesia after induction (most cases).

- IV agents can be used via a continuous pump.

Four stages of anesthesia: (described in 1930s): modern anaesthetics improved speed of onset,recovery and safety

- Stage I (analgesia): loss of sensation but patient is still alert and speaking.
- Stage II (Excitement): CNS excitation+ BP (irregular) + respiratory rate irrigular + release of subconscious emotions.
- Stage III (surgical anesthesia): regular respiration + relaxed skeletal muscles + progressive decrease in eye reflexes till eye movement stops and pupil is fixed
- Stage IV (Medullary paralysis): over dose?? **fatal depression of RC and VMC**

STAGES OF ANESTHESIA

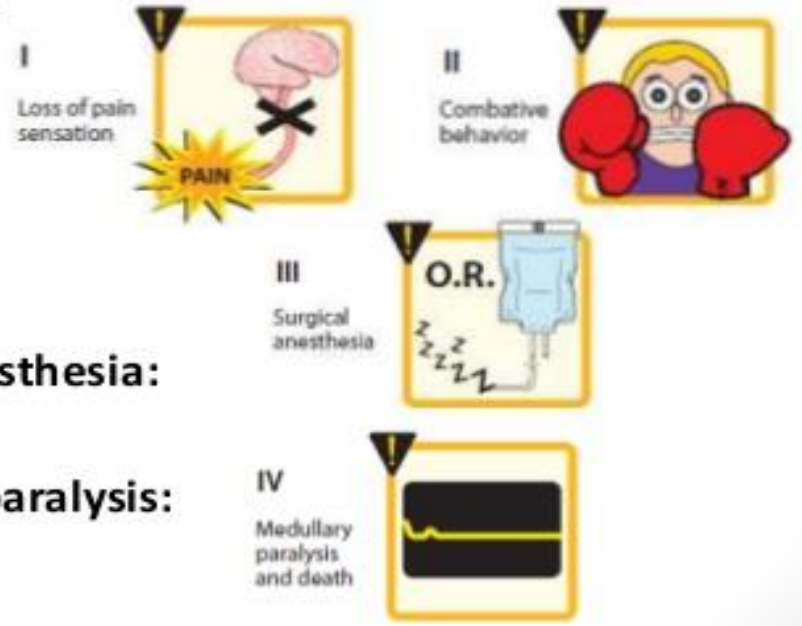
A. Induction

B. Maintenance of anesthesia

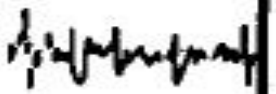
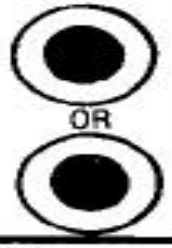
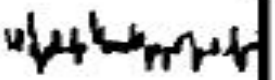
C. Recovery

D. Depth of anesthesia:

- Stage I—Analgesia:
- Stage II—Excitement:
- Stage III—Surgical anesthesia:
- Stage IV—Medullary paralysis:



STAGES OF GENERAL ANESTHESIA

STAGE	PUPIL		RESP.	PULSE	B.P.
	USUAL SIZE	REACTION TO LIGHT			
1 ST INDUCTION				IRREGULAR	NORMAL
2 ND EXCITEMENT	 OR			IRREGULAR & FAST	HIGH
3 RD OPERATIVE				STEADY SLOW	NORMAL
4 TH DANGER				WEAK & THREADY	LOW

GENERAL ANESTHETIC AGENTS

They depress all excitable tissues including CNS neurons, cardiac muscle and smooth and striated muscle .

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

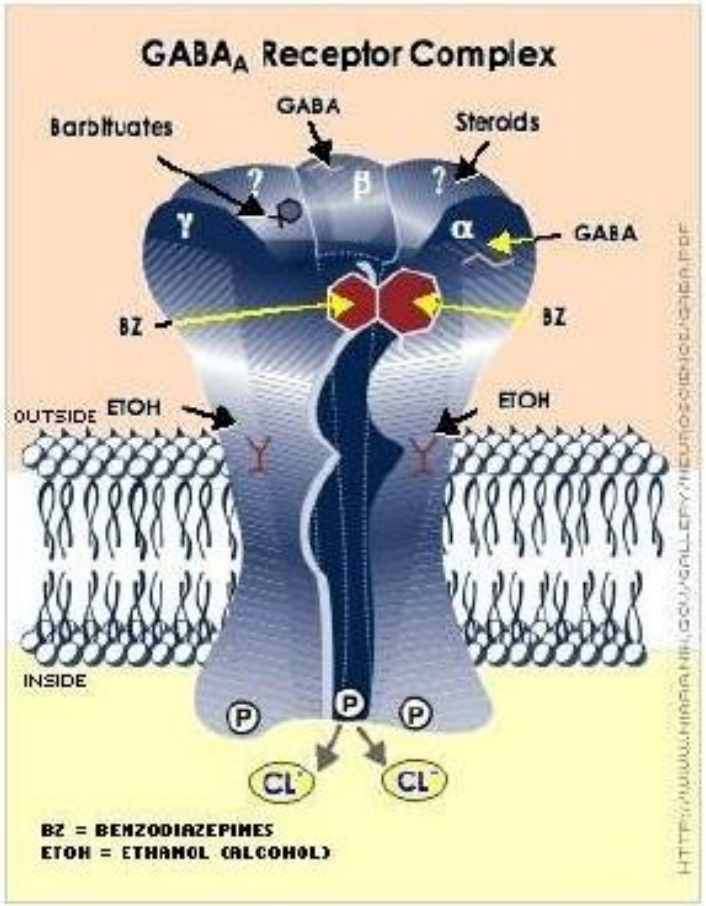
* The medullary centers are less sensitive to the general anesthetics than other parts of the CNS.

MECHANISM OF ACTION

1. Earlier theories suggested interaction with lipid membrane bilayer
2. Recent work favors interaction with ligand-gated membrane ions; to

enhance the action of $GABA_A$ and glycine receptors and inhibit central actions of acetylcholine, serotonin, and glutamate.

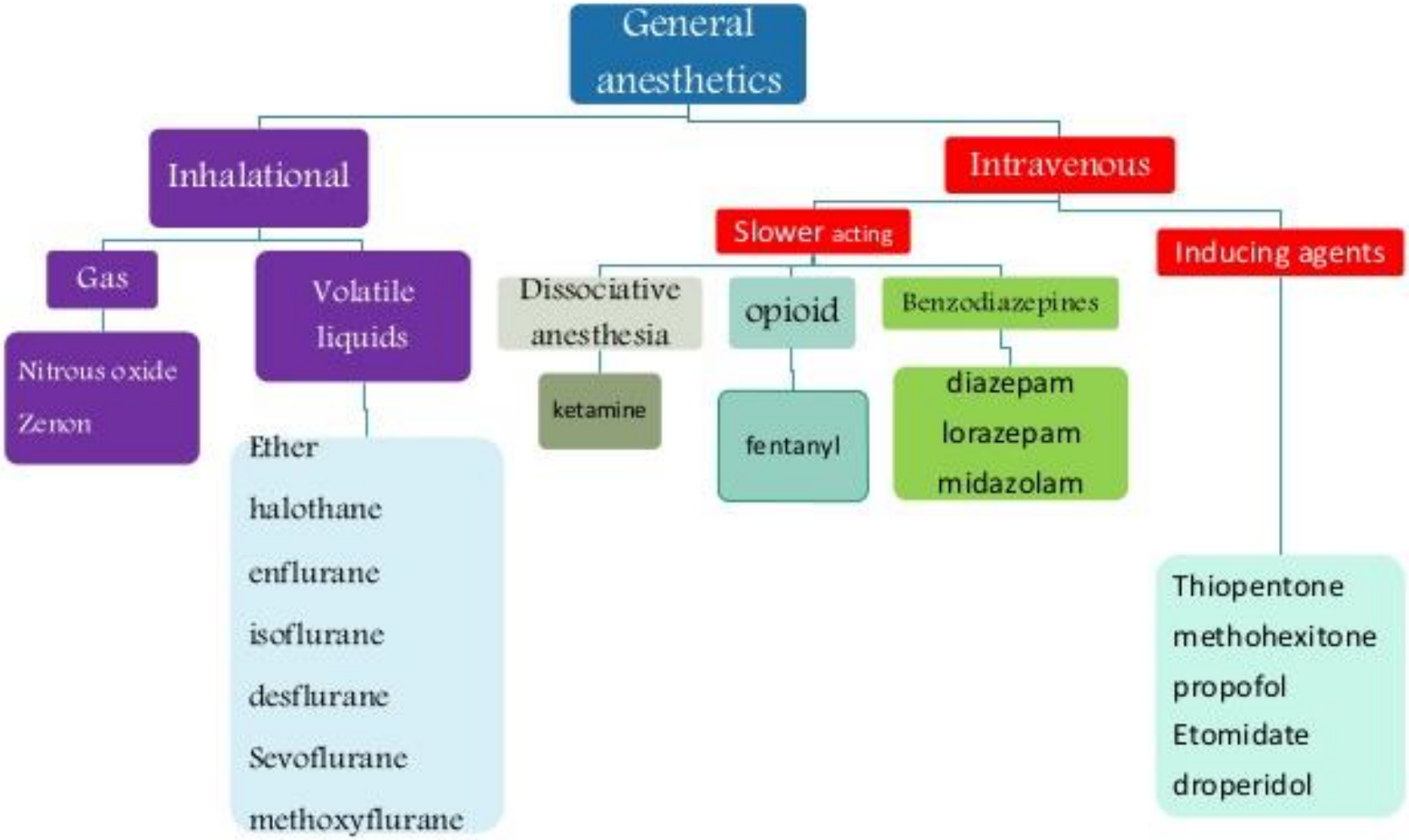
Molecular Action: $GABA_A$ Receptor



- Receptor sits in the membrane of its neuron at the synapse
- **GABA**, endogenous compound, causes GABA to open
- Receptor capable of binding 2 GABA molecules, between an alpha and beta subunit
  - Binding of GABA causes a **conformational change** in receptor
    - Opens central pore
    - Chloride ions pass down electrochemical gradient
  - Net inhibitory effect, reducing activity of the neuron

- **Mechanism of action at macroscopic level:**
- Reticular activating system: reversible loss of consiousness.
- Hippocumpus, amygdala and prefrontal cortex: amnesia
- Spinal cord: immobility and analgesia

CLASSIFICATION



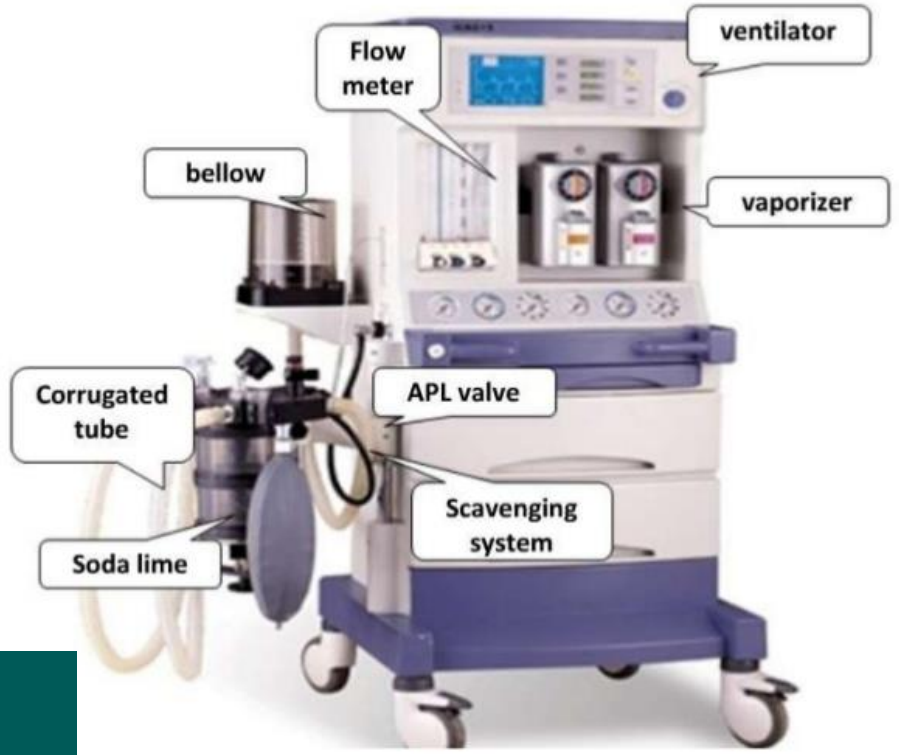
INHALATION ANESTHESIA

This method of administration is unique to anesthesia.

They are given with oxygen to avoid hypoxia during anesthesia.

Following induction with an intravenous anesthetic, an inhalational agent can be used to maintain anesthesia.

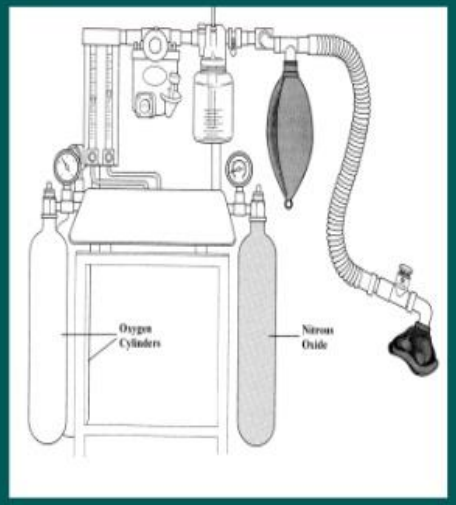
Drugs are introduced into the respiratory system by means of an anesthetic machine with the use of vaporizers.



Continuous flow (Boyle's) anaesthetic machine

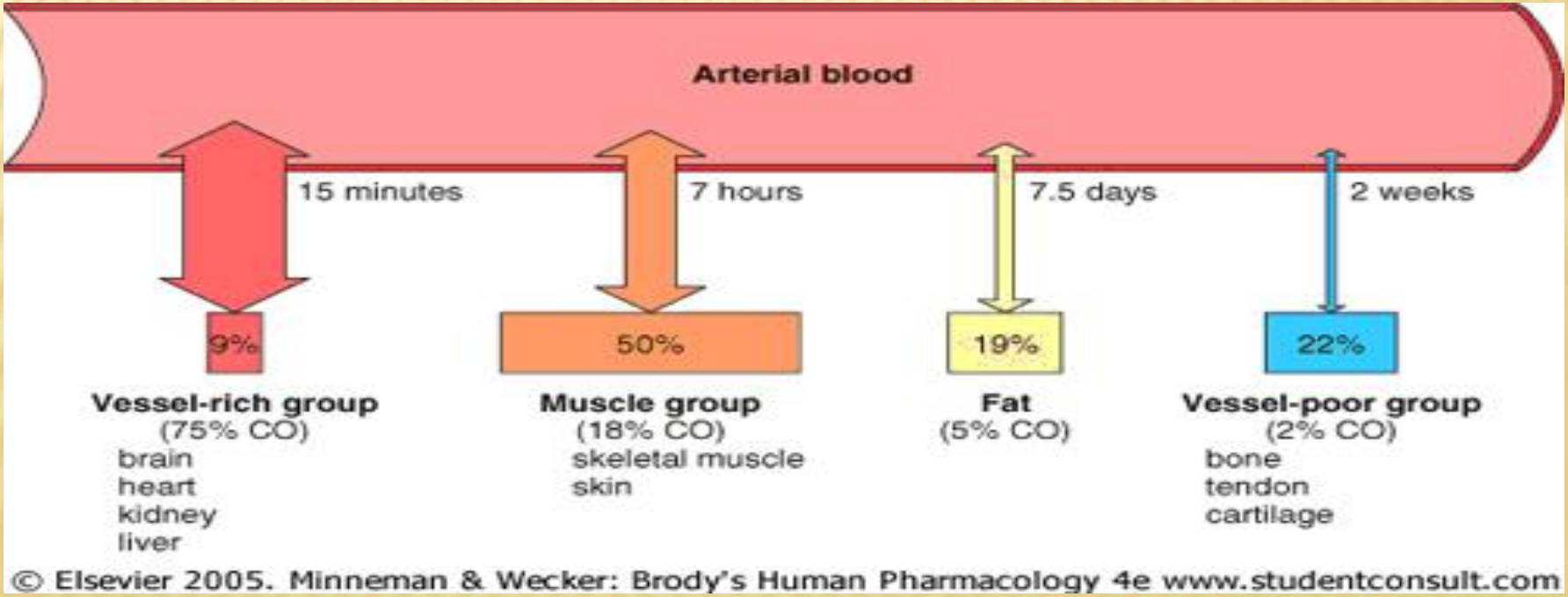
Anaesthetic Machine (Boyle's equipment)

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

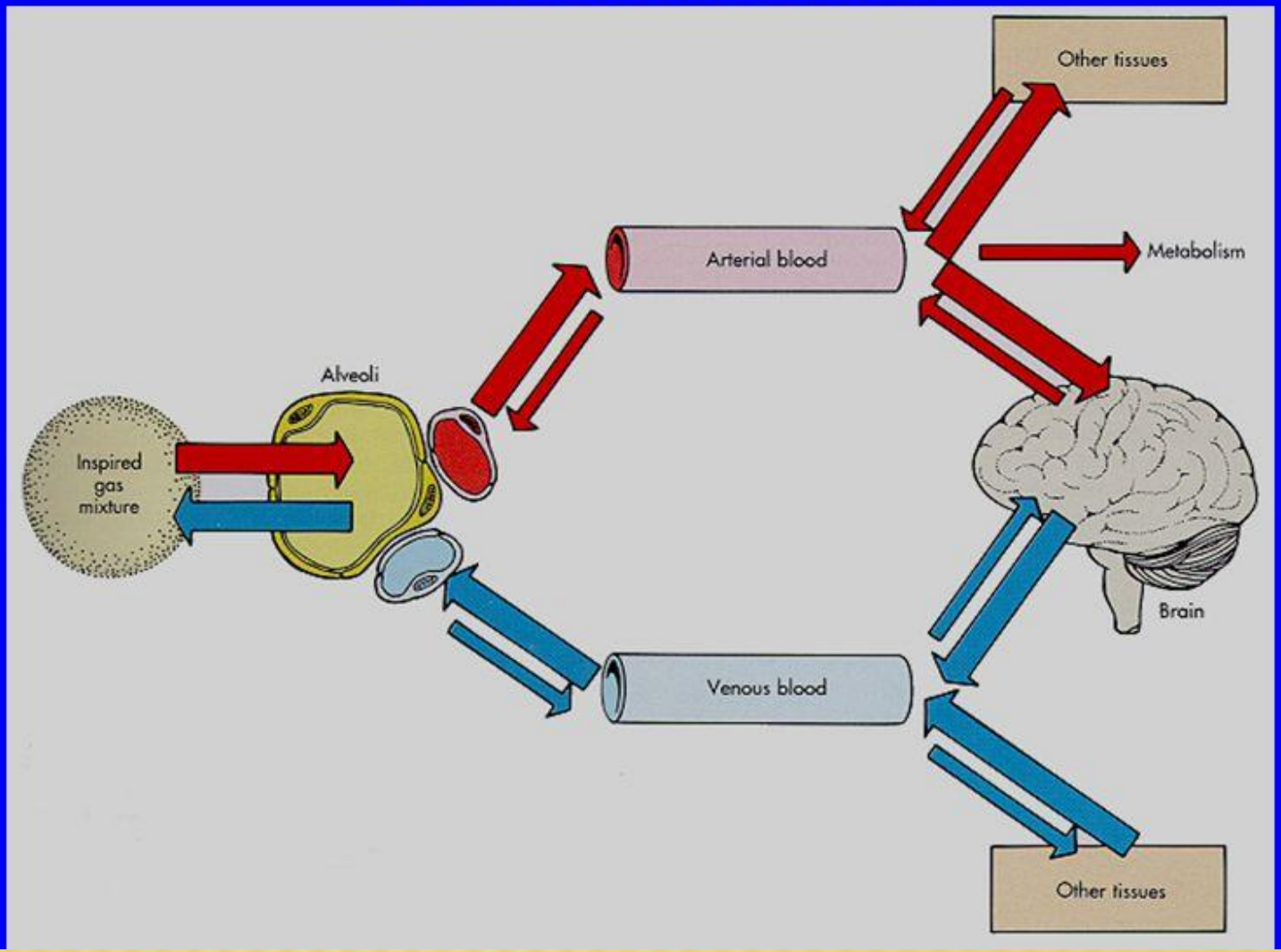


- The rate at which an inhalational anesthetic agent is taken up by a tissue depends on the fraction of the cardiac output (CO) that the tissue receives.

- The approximate time for halothane to equilibrate between blood and tissues is indicated to the arrows; the percentage of body mass that the tissue represents is shown in the boxes

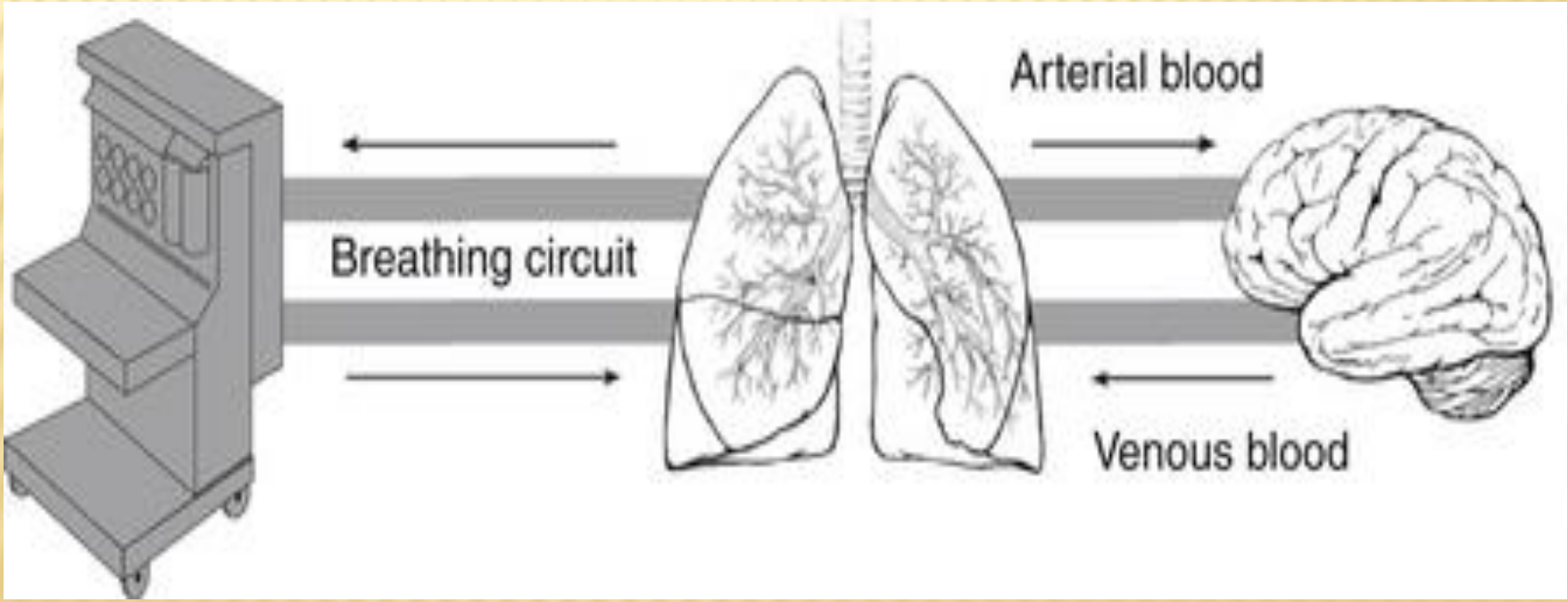


Pathway for General Anesthetics



PHARMACOKINETICS OF INHALATION AGENTS

The depth of anesthesia →directly related to partial pressure of the agent in the blood, as this determine the conc. Of anesthetic in the CNS



- The blood conc. of anesthetic is in turn depend on:

1-The concentration of anesthetic in the inspired gas (alveolar concentration)

2- The solubility of the agent in blood (blood/gas partition coefficient)

3 - Cardiac output

4 -Alveolar ventilation

* Rapid induction and recovery are important properties of an anesthetic agent → allowing flexible control over the arterial tension (and hence brain tension) →depth of anesthesia

The speed of anesthesia is determined by:

1- The solubility of the anesthetic in the blood (blood/gas partition coefficient)

2- It's solubility in the fat (lipid solubility)

- Agents of low blood solubility (e.g., nitrous oxide, desflurane) produce rapid induction and recovery because relatively small amounts are required to saturate the blood, and so the arterial tension (and hence brain tension) rises and falls quickly
- Agents of high blood solubility (e.g., halothane) have much slower induction and recovery times because much more anesthetic solution is required before the arterial tension approaches that of inspired gas

N.B. High lipid solubility agents accumulate in the body fat during prolonged anesthesia & may induce hangover

RECOVERY FROM ANESTHESIA

- Elimination of inhaled anesthetics is done mainly by ventilation through the lungs

- The rate of reduction of alveolar partial pressure determines the rate of recovery from the anesthetic

- Long duration of anesthesia is an important factor slowing the rate of recovery (lots of anesthetic dissolved in low perfusion tissue)

Factors decreasing the length of recovery:

- Reduction of the inspired concentration
- High alveolar ventilation
- Low blood gas solubility
- Duration of anesthesia.

ANESTHETIC POTENCY

- **Minimum alveolar concentration: (MAC)**
- MAC was proven the most useful index and is defined as that alveolar partial pressure of an inhaled anesthetic, at one atmosphere which prevents movement in response to a standard noxious stimulus in 50% of patients (ED 50).
- The dose of inhalation anesthetics that produces surgical anesthesia is higher than 1 MAC (expressed in partial pressure). Usually 1.2-1.4 MAC.

PROPERTIES OF INHALATION ANESTHETICS

	Halothane	Isoflurane	Nitrous oxide
	Volatile hydrocarbons		Gaseous anesthetic
Potency	High	High	Week
Induction & recovery	Slow	Rapid	Very Rapid
CVS	↓BP & COP↓		Minimal
Arrhythmia	1. ↑ risk 2. ↑ sensitivity to catecholamines	No risk	No risk
Hepatotoxicity	↑ risk (but not in children)	No risk	No risk
Therapeutic advantages	1- Of choice in children (pleasant odour) 2. Good for asthmatic (bronchodilataion)	1. good muscle relaxation. 2. Rapid recovery 3. No sensitization to catecholamines	1. Rapid onset & recovery. 2. Good analgesia.

- **Halothane : an old but still used inhalational agent for mask** induction in children, because it is the least irritant volatile agent.
- **Enflurane: old and not recommended because of its powerful cardiac and** respiratory depressant actions.
- **Isoflurane has largely replaced halothane and enflurane because it offers the** most rapid induction and recovery and has little organ toxicity but produces laryngospasm
- **Desflurane has partly replaced isoflurane because it permits more rapid** induction and recovery from anesthesia. It can cause laryngospasm (i.e. irritant) in children and was not approved for pediatric induction .

- **Sevoflurane is widely used for children as it has a pleasant odor, an** advantage when using it for induction by mask, but can cause laryngospasm
- **Nitrous oxide is not sufficiently potent to be used alone, but it has the** advantage of producing analgesia and is often used in combination with other anesthetics, thus reducing the required dose of the other agent.

ADVERSE EFFECTS OF INHALATIONAL ANESTHETICS

- **Cardiovascular system:**
- **Most agents, particularly halothane, depress** myocardial contractility and produce **bradycardia** by interfering with transmembrane calcium flux.
- This decreases cardiac output and blood pressure. ***Halothane also sensitizes the heart to catecholamines, which*** can lead to arrhythmias.
- Inhaled anesthetics often increase cerebral blood flow, which can exacerbate an elevated intracranial pressure.

- **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. This is because of interaction of reactive metabolites with cellular proteins, which initiate an autoimmune reaction. Hepatotoxicity has resulted in the decreased use of ***halothane, and avoidance of repeat use*** within 3 months

- **Respiratory system:**
- **All agents depress the response of the respiratory** centre in the medulla to carbon dioxide and hypoxia. Some agents can cause laryngospasm???

- **Kidney: Both renal blood flow and renal vascular resistance decrease,** resulting in a reduced glomerular filtration rate

- **Uterus: There is 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

- **Skeletal muscle:**
- **Most agents produce some muscle relaxation, which** enhances the activity of neuromuscular blocking drugs.
- **Chemoreceptor trigger zone: Inhalational anesthetics trigger** postoperative nausea and vomiting. This may be most pronounced with nitrous oxide.
- **Postoperative shivering: This occurs in up to 65% of those recovering** from general anesthesia. The etiology is unclear.
- **Malignant hyperthermia.**

Malignant Hyperthermia

- Malignant hyperthermia (MH) is a pharmacogenetic hypermetabolic state of skeletal muscle induced *in susceptible individuals* by inhalational anesthetics and/or succinylcholine (and maybe by stress or exercise).

Malignant Hyperthermia

- Genetic susceptibility-Ca^{+} channel defect or RYR1 (ryanodine receptor)
- Excess calcium ion leads to excessive ATP breakdown/depletion

Malignant Hyperthermia

- Signs: tachycardia, tachypnea, metabolic acidosis, hyperthermia, muscle rigidity, sweating, arrhythmia
- May be fatal
- Treated with dantrolene

IV ANESTHETIC DRUGS

- **Can be used for**

  -short surgical procedures

  - Longer procedures

  - Rapid induction followed by an inhalational agent

- They produce anesthesia by relatively selective depression of the reticular activating system in the brain.

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

Thiopental	Ketamine	Propofol
Pharmacological properties		
1. IV barbiturate. 2. Short duration of anaesthesia (about 2-5 min). 3. Rapid induction but slow recovery (sedation up to 24 hs) 4. Potent anesthetic but no analgesic	1. Slower onset & recovery than other IV anesthetics. 2. It produces **dissociative anaesthesia** (i.e. patient appears awake but unconscious and doesn't feel pain. In addition, there is sedation, amnesia and immobility. **3. Good analgesia.** 4. Associated with a **bronchodilator effect due** to ↑ sympathetic outflow.	1. Rapid induction. 2. Rapid & more pleasant recovery with propofol than with other IV anesthetics. 3. Postoperative nausea and vomiting are less than with other agents. Propofol has an anti-emetic action. 4. It can be used by IV infusion for total intravenous anaesthesia or for up to 3 days in conscious patients requiring controlled ventilation (for sedation) in intensive care unit.
Disadvantages		
1. No analgesia 2. Little Sk.m.relaxation 3. ↓↓ BP & bradycardia 4. Laryngospasm, apnea, cough, bronchospasm	1. ↑ **sympathetic outflow** →cardiac stimulation & ↑BP. (contraindicated in hypertensives or those with stroke) 2. **↑ cerebral blood flow →** post-operative hallucinations & nightmares.	· No analgesic action & causes pain at injection site that may be minimized by injection into large veins or by first injecting lidocaine. · Dose-related respiratory depression, bradycardia, and hypotension may occur.

Neuroleptanalgesia

- Method of i.v. anesthesia which combines the use of neuroleptic drug with an opioid analgesic.
- Subject is conscious & able to co-operate during surgery.
- most favoured combination- droperidol + fentanyl
- After administering nitrous oxide with oxygen neuroleptanalgesia can be converted to neuroleptanesthesia.
- C/I - patients receiving MAO inhibitors, abuse drugs or alcohol, with Parkinson disease.

Thank you