Hashemite University
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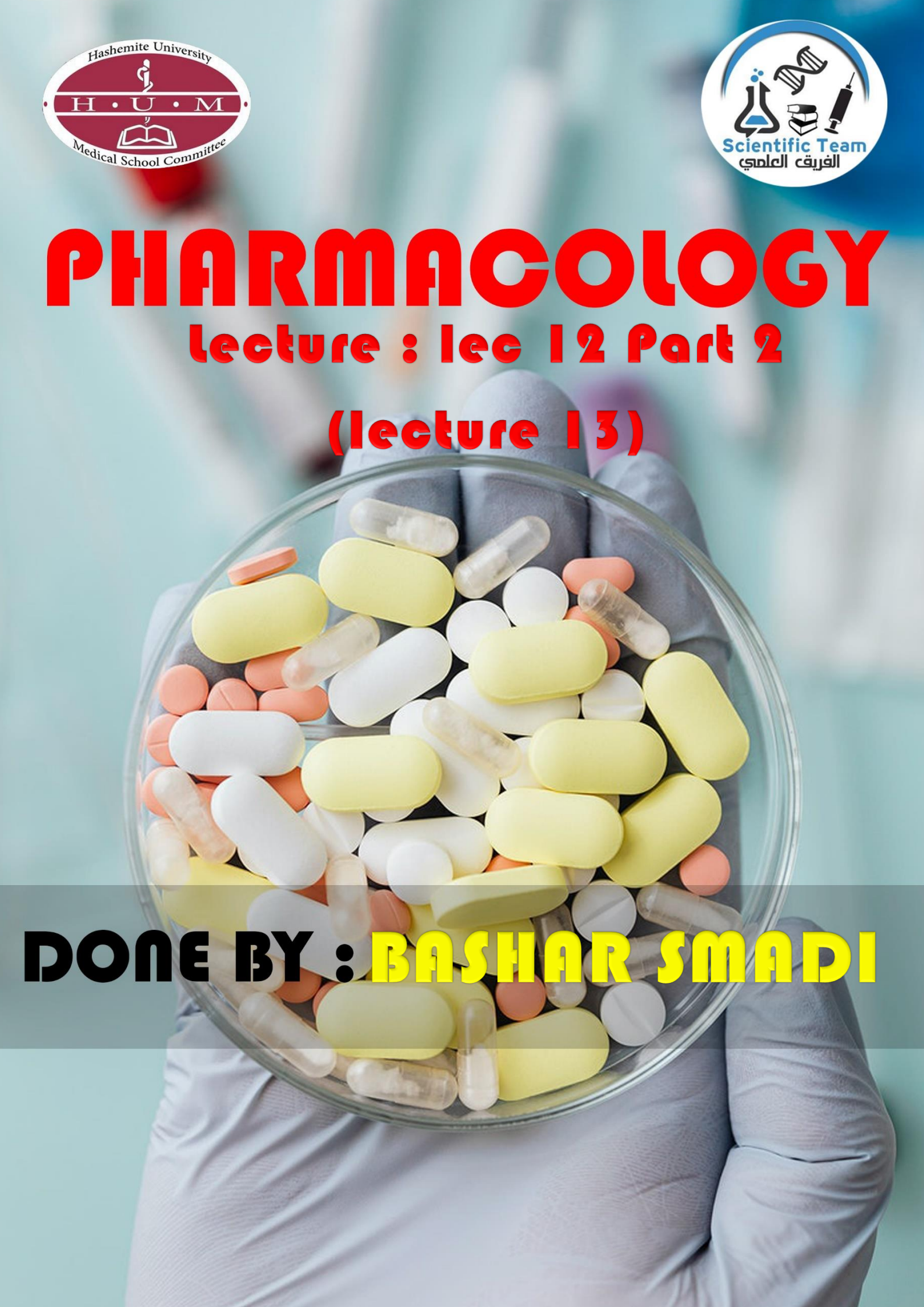
Medical School Committee

Scientific Team
الفريق العلمي

PHARMACOLOGY

lecture : lec 12 Part 2

(lecture 13)



DONE BY : BASHAR SMADI

Lecture 12 part 2 (13)

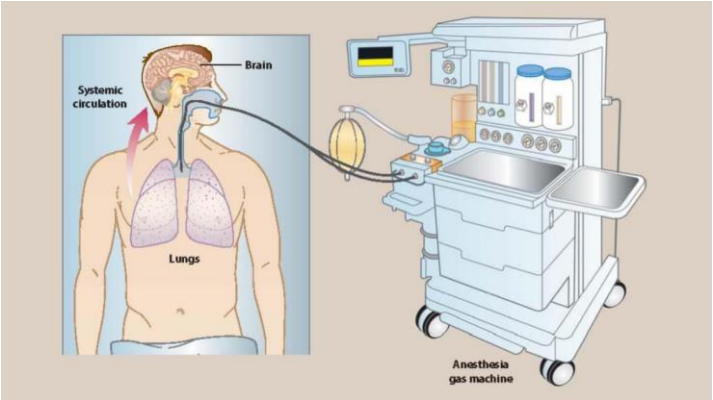
Inhalational Anesthetics

• Primarily used for maintenance of anesthesia following induction by IV agents (like propofol)

• Depth of anesthesia correlates with inhaled concentration.

• Less risk of cardiac/respiratory depression than IV agents.

• No antagonists.



Inhaled anesthetics

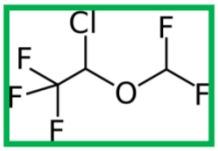
1- Halogenated(with Cl- ,F- ,I-) Volatile liquids:

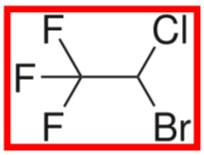
* Halothane

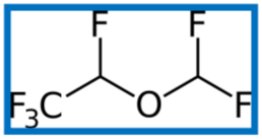
* Isoflurane

* Desflurane

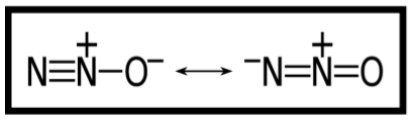
* Sevoflurane







2- Gases: Nitrous oxide



Mechanism of Action of Inhalational Anesthetics is UNKNOWN!

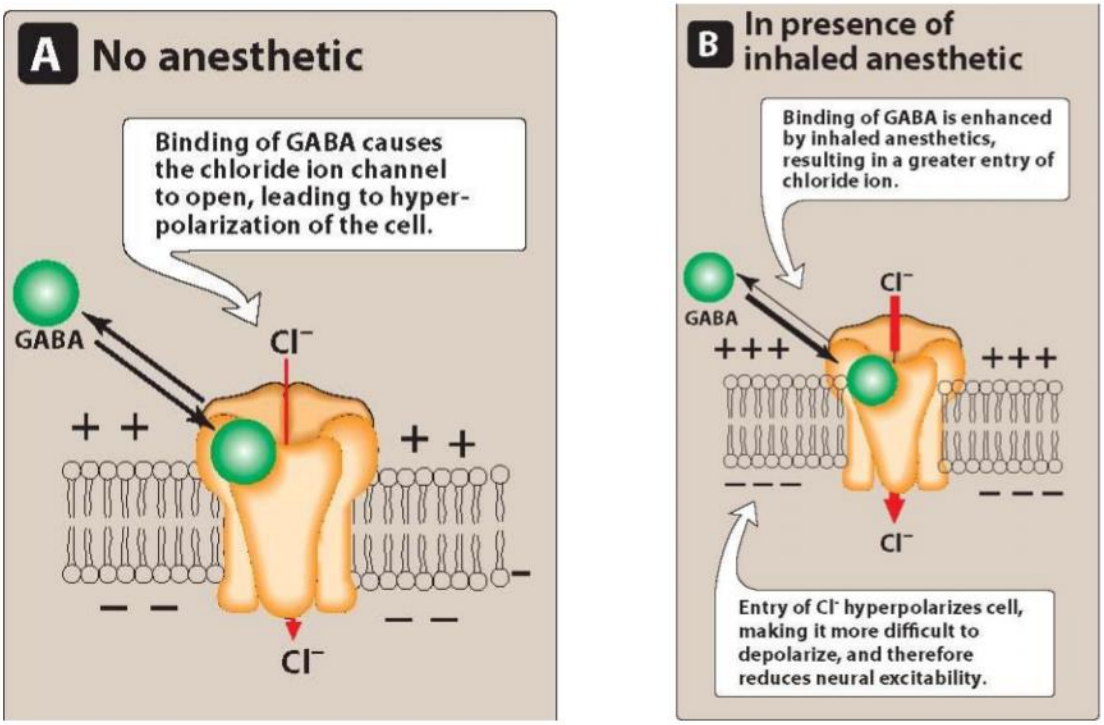
Possible mechanisms:

- Increase the sensitivity of GABAA receptors to GABA

(nitrous oxide, ketamine have no effect on GABA)

- Inhibition of NMDA receptors
- Increase the activity of glycine receptors in the spinal chord
- Block excitatory postsynaptic currents of nicotinic receptors

brief revision of GABA receptor:



This increases chloride ion influx and hyperpolarization of neurons

مهم Potency: MAC

Minimum Alveolar Concentration (MAC)

• The end-tidal concentration of an inhalational anesthetic needed to eliminate movement in 50% of patients stimulated by a standardized incision.

• MAC = ED_{50} of an anesthetic

• MAC is expressed as percentage of alveolar gas mixture/ partial pressure as % of 760 mm of Hg.

↑ MAC
- Hyperthermia
- Chronic alcohol abuse
- ↑CNS catecholamines

↓ MAC
- Increased age
- Hypothermia
- Pregnancy
- Sepsis
- Concurrent use of an IV anesthetic
- α_2 agonists

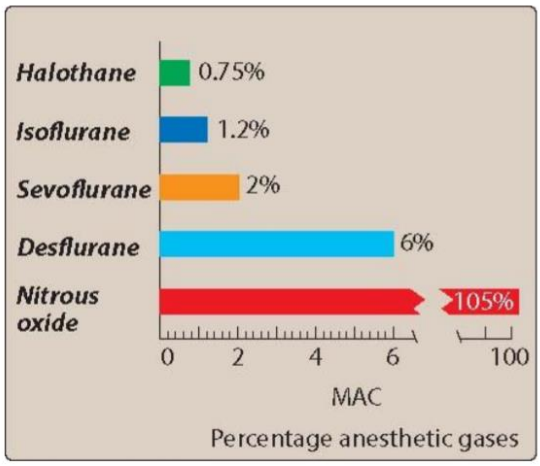


Figure 13.5
Minimal alveolar concentrations (MAC) for anesthetic gases are used to compare pharmacologic effects of different agents (high MAC = low potency).

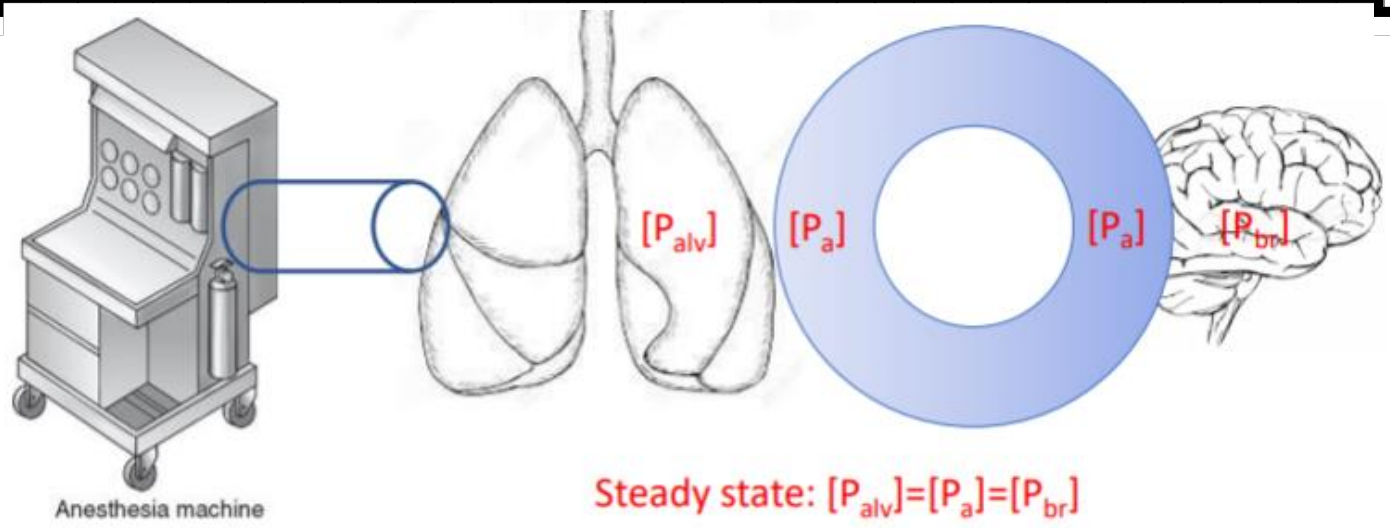
So Halothane is the most potent

And Nitrous Oxide is the least

Distribution

The pharmacologic effect of an inhalation agent is determined by the partial pressure of the anesthetic in the brain [P_{br}] P_{br} = partial pressure in the brain

[P_{br}] depends on alveolar partial pressure [P_{alv}] which is controlled by pressure at the origin of the respiratory pathway.



it all starts with the Anesthesia Machine which starts delivering the gas through the lungs (which makes partial pressure in the alveoli).. and then the gas defuses into the plasma (which makes partial pressure in the arteries) .. and then blood supply is delivered to the brain (which makes partial pressure in the brain)

we can control the [Pbr] by controlling [Palv]
if we have equilibrium state ([Palv] = [Pa] = [Pbr])

so our goal is to reach the Steady state = full Anesthesia

Factors affecting equilibrium/steady state

I. Alveolar Wash-In
"Replacement of normal lung gases with inspired anesthetic mixture"

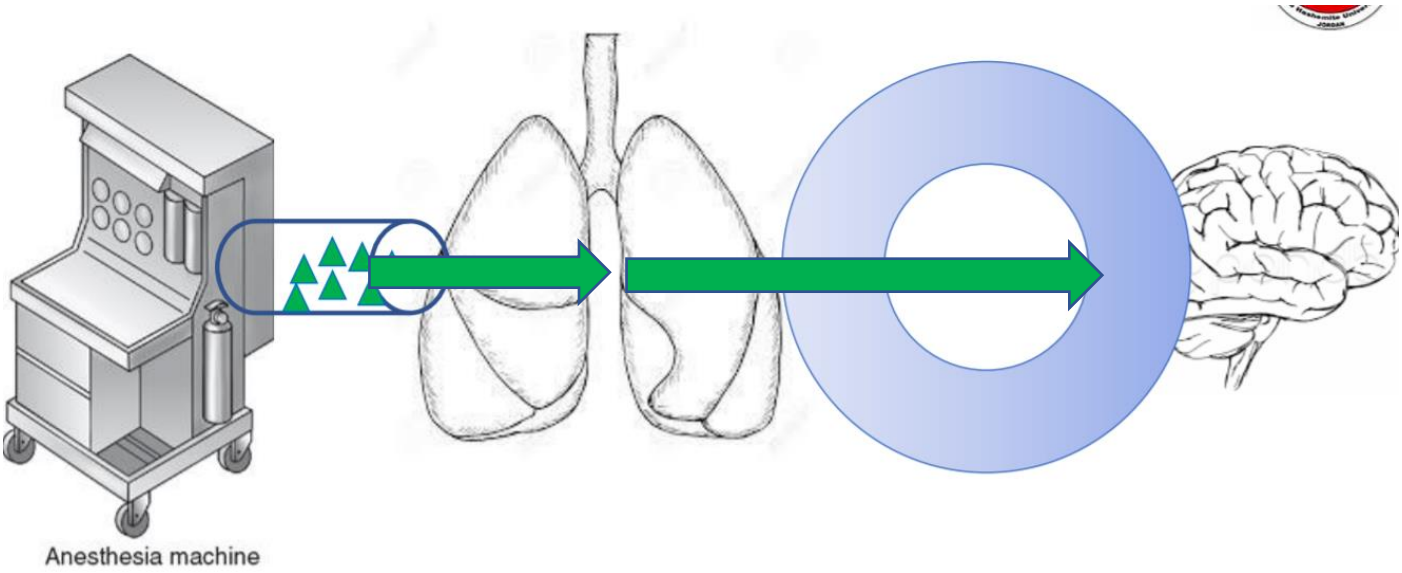
II. Anesthetic Uptake (to the bloodstream)

a. Solubility in blood
b. Cardiac output
c. Tissue type
d. Alveolar:venous gradient

Solubility

• Determined by **blood:gas partition coefficient** [the ratio of the concentration of the anesthetic in the blood to the concentration of the anesthetic in the gas phase=solubility of an anesthetic in blood]
• **Low** blood solubility → **few** anesthetic molecules are required to raise [Pa] → **Less** time for induction and recovery
• **High** blood solubility → **more** anesthetic molecules are required to raise [Pa] → **more** time for induction and recovery

كل ما **زاد** ال coefficient كل ما كان concentration تبع الDrug في الدم **اعلى** وبالتالي ال solubility **اعلى**

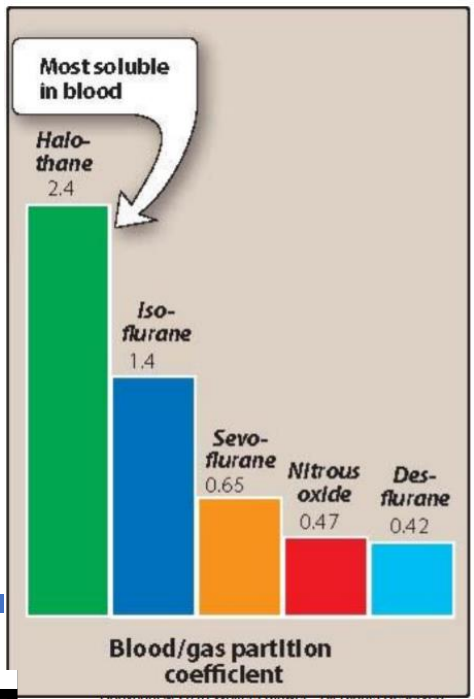


Anesthetics passes through the Anesthesia machine → it passes through the trachea -airway to the lungs (in the alveolar space) → ability there to wash out the natural gases in the alveoli (so the drug has alveolar partial pressure [Palv]) → it goes from high blood pressure space (alveolar space) into low pressure (the bloodstream) →

→ if the drug has high solubility in the plasma it will stay in the circulation for a longer period of time and it will need more drug molecules to raise arterial partial pressure of the gas → more time for induction and recovery

→ if the drug has low blood solubility and low (blood:gas partition coefficient) a larger percentage of the drug molecules will diffuse from the blood circulation to the brain → so they will raise [P_{br}] at a faster rate

So the low solubility drug will reach the steady state faster



The fastest to induce anesthesia is Desflurane because it is least soluble

The slowest is Halothane

the most potent is Halothane because of MAC (في صفحة 3) as we said before

Cardiac Output

• CO affects washing the anesthetic to peripheral tissue (NOT the site of action)

High CO → ↑pulmonary blood flow (more removal to the periphery) → **slow** rise in [P_{alv}] → **slow** induction

Low CO → ↓ pulmonary blood flow (less removal to the periphery) → fast rise in [P_{alv}] → **faster** induction

Differences in Tissue Type on Uptake

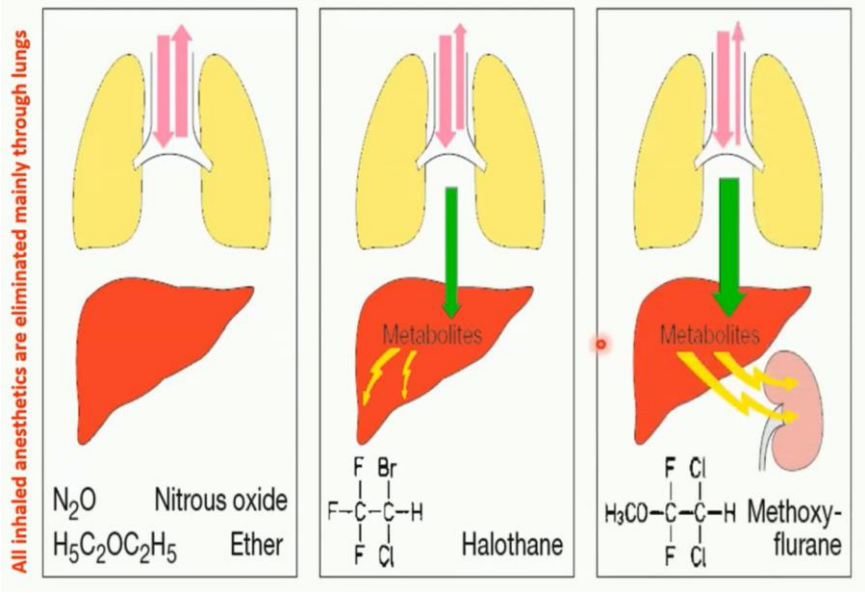
$$\text{Steady State} \sim \frac{\text{Blood flow to the tissue}}{\text{Capacity of tissue to store the anesthetic (proportional to tissue volume)}}$$

Tissue Type	Perfusion (Blood Flow)	Capacity
Brain, heart, liver , kidney, endocrine glands	Good	low
Skeletal muscles	Poor	Large
Adipose tissue	Poor	Large
Bone, cartilage	Poor	Low

Elimination

• The time to recovery from inhalation anesthesia depends on the rate of elimination of anesthetics from the brain after the inspired concentration of anesthetic has been decreased.

• Inhaled anesthetics that are relatively insoluble in blood (low blood: gas partition coefficient) and brain are eliminated at faster rates than more soluble anesthetics.



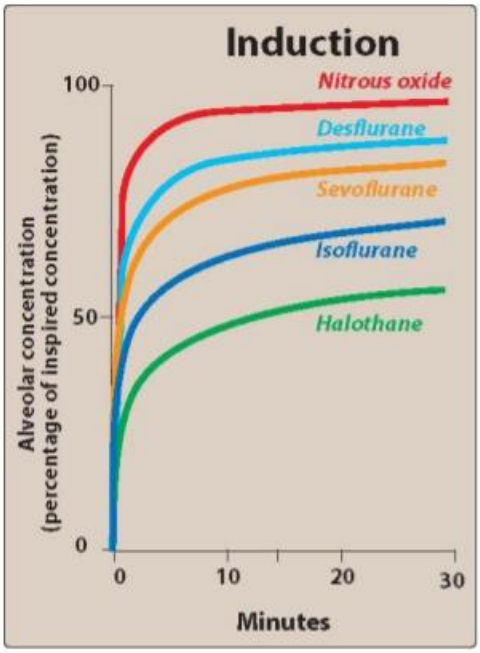
Recovery

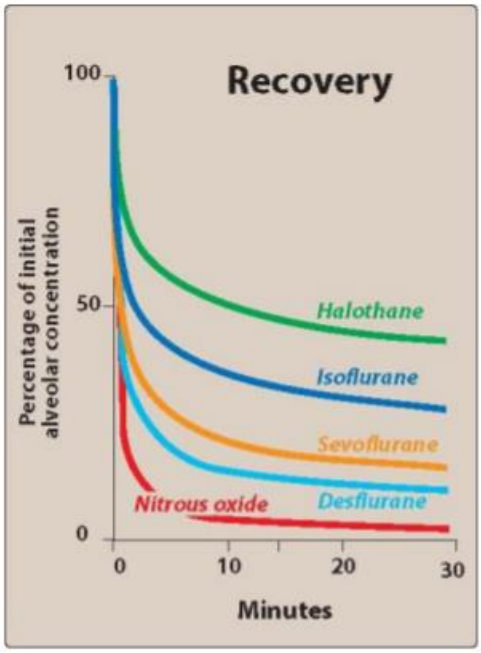
• The duration of exposure to the anesthetic can have a marked effect on the time of recovery. If exposure to the anesthetic is short, recovery may be rapid.

• Clearance of inhaled anesthetics by the lungs into the expired air is the major route of their elimination from the body

Changes in the alveolar blood concentrations of some inhalation anesthetics over time. →

nitrous oxide exits the body faster than does Halothane





Isoflurane

• Has a pungent smell → stimulates the respiratory reflexes → NOT used for inhalational induction
• Causes hypotension
• Solubility? Induction time? In the graphs above
• Low cost
• Longer surgeries

Desflurane

• Respiratory irritant → NOT used for inhalational induction
• Causes hypotention
• Low blood solubility
• Higher cost
• Better for short surgeries

Sevoflurane

• Low pungency and respiratory irritation (we often use it to induce anesthesia) → can be used for inhalational induction

• Low solubility

Nitrous Oxide

(We rarely use it induce anesthesia)

• Gas

• Very rapid induction and recovery.

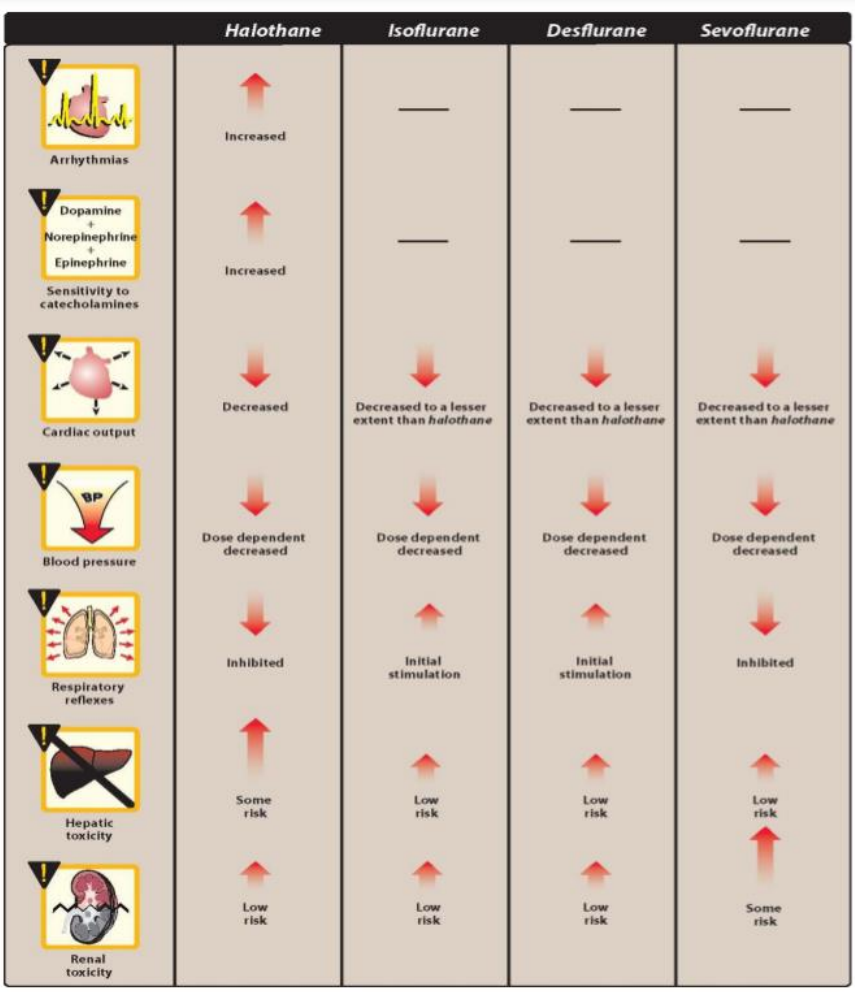
• least potent, highest MAC value.

• Poor anesthetic, good analgesic

• Administered with O2 to avoid diffusion hypoxia (to produce sedation-dentistry)

• Administered with other inhalational agents for general anesthesia

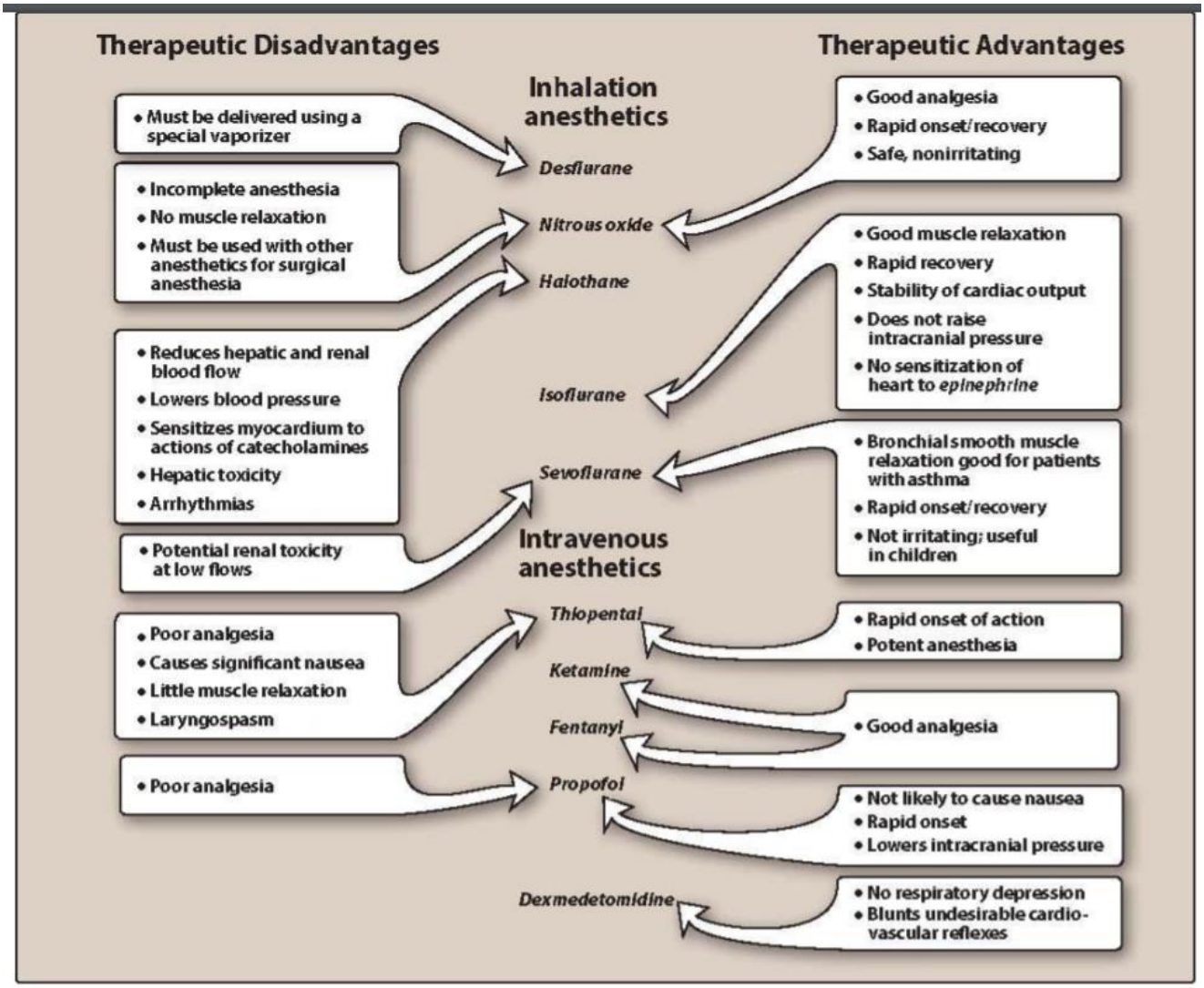
Summary for the characteristics of Inhalational Anesthetics →



Malignant Hyperthermia

- Rare anesthesia complication (only in susceptible patients; autosomal dominant)
- Exposure to: halogenated anesthetics, succinylcholine
- Life threatening
- Due to uncontrolled, excessive increase in skeletal muscle oxidative metabolism
- Treatment: dantrolene

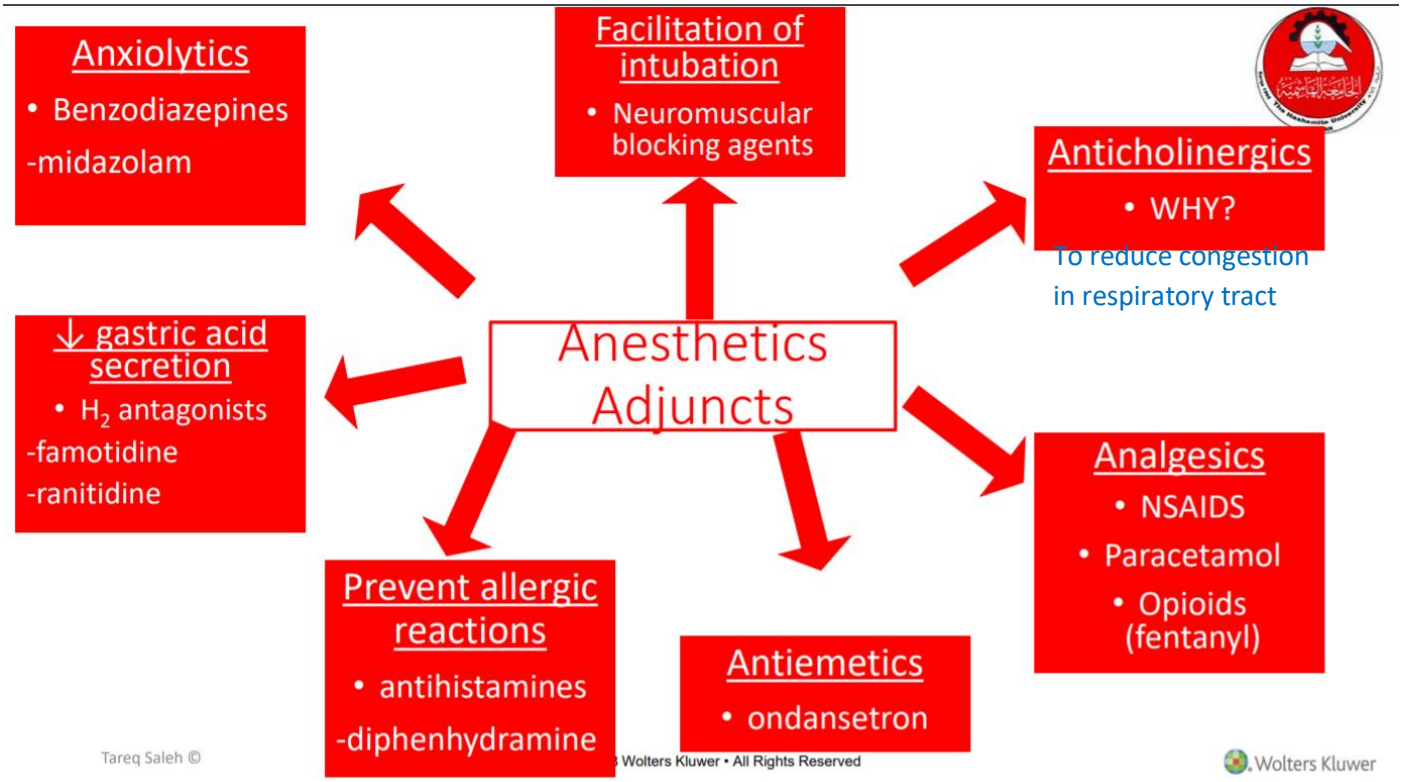
Summary for the characteristics of Inhalational Anesthetics



Anesthetic Adjuncts

In order to solve the lack of the perfect Anesthetic,,

we need combination of drugs to do so



Stages of Anesthesia

INDUCTION	MAINTENANCE	RECOVERY
• Mostly using intravenous anesthetics *-propofol* • Produce unconsciousness in 30-40 seconds • Could use an inhalational agent e.g., pediatric	• Mostly using inhalational agents • Combined with fentanyl to produce analgesia	• Recovery happens due to the **redistribution** rather than metabolism

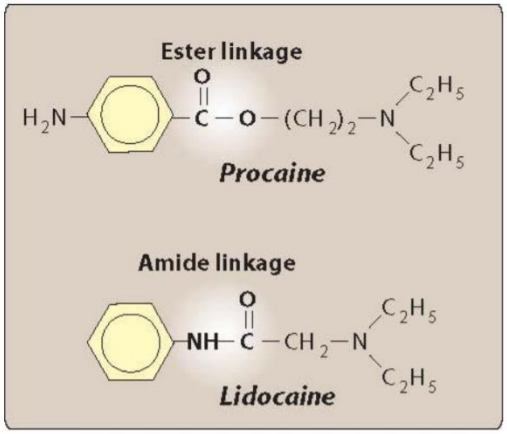
Local Anesthetics

for minor surgeries (locally)

- Low doses: block sensory conduction
- High doses: block motor impulses
- **Mechanism of action**: "Sodium channels blockade

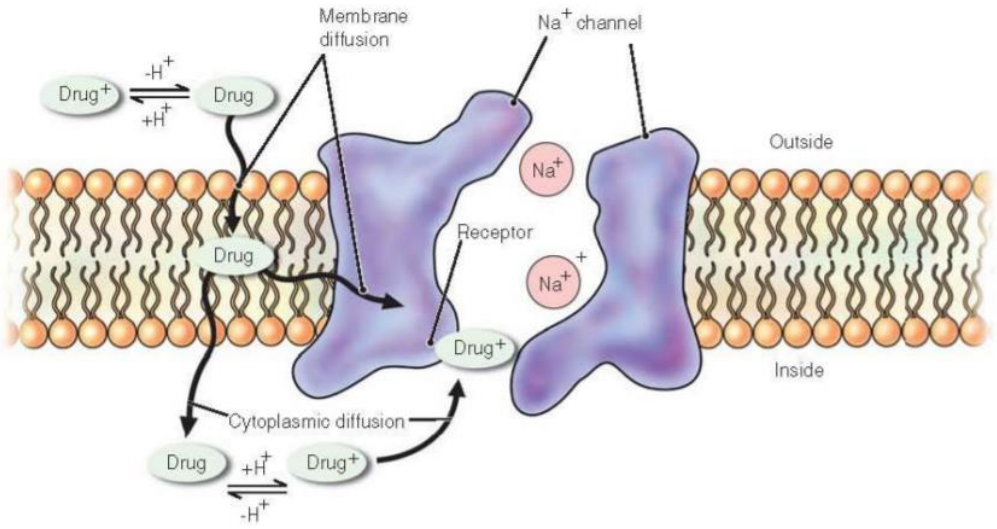
we have 2 types of local Anesthetics : AMIDES + ESTERS

depending on the chemical group



LOCAL ANESTHETICS: AMIDES
Bupivacaine MARCAINE
Lidocaine XYLOCAINE
Mepivacaine CARBOCAINE
Ropivacaine NAROPIN
LOCAL ANESTHETICS: ESTERS
Chloroprocaine NESACAINE
Procaine NOVOCAINE
Tetracaine PONTOCAINE

GAs appear to act by depressing synaptic transmission (unlike local anesthetics which act primarily by blocking axonal conduction)



Delivery Options

- Topical
- Infiltration
- Perineural
- Neuraxial
  - Spinal
  - Epidural
  - Caudal

Actions:

• **Vasodilation**
- leads to rapid diffusion → short duration of action
- overcome by adding a vasoconstrictor e.g., *epinephrine*

• **Antiarrhythmic**

- e.g., lidocaine

Duration of actions:

• **Factors affecting the duration of action**:

1. Tissue pH
2. Nerve morphology
3. Concentration
4. Lipid solubility
5. pKa (most important)
- lower pKa → more ionized at physiologic pH → faster

Hepatic metabolism does NOT affect duration of action of local anesthetics

What happens if the tissue is infected?
The infection makes the pH lower . and makes the action of the anesthetic slower

Systemic Toxicity

• What if a local anesthetic was administered frequently or inadvertently in the vein (IV)?

❑ Local Anesthetic Systemic Toxicity (LAST)

1. Altered mental status
2. Seizures
3. Cardiovascular instability

Treatment: Lipid Rescue Therapy (20% lipid emulsion infusion)

THANK YOU AND GOOD LUCK