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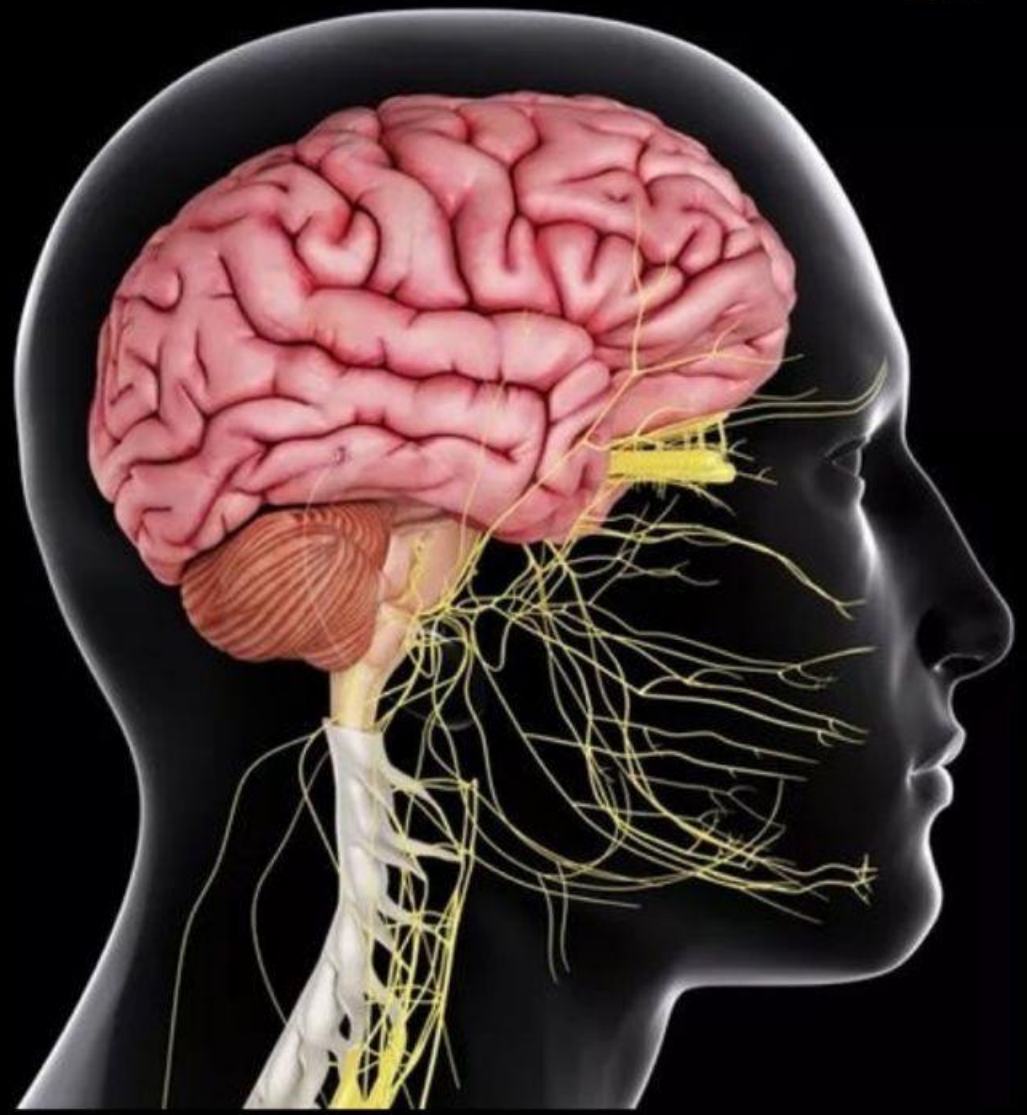


النادي الطبي

CENTRAL NERVOUS SYSTEM

SUBJECT : Pharma

LEC NO. : Lec 8 anesthetics

DONE BY : Enas wail hantash

Anesthetics

General Anesthesia is a *reversible* state of CNS depression → loss of responses to and perception of stimuli.

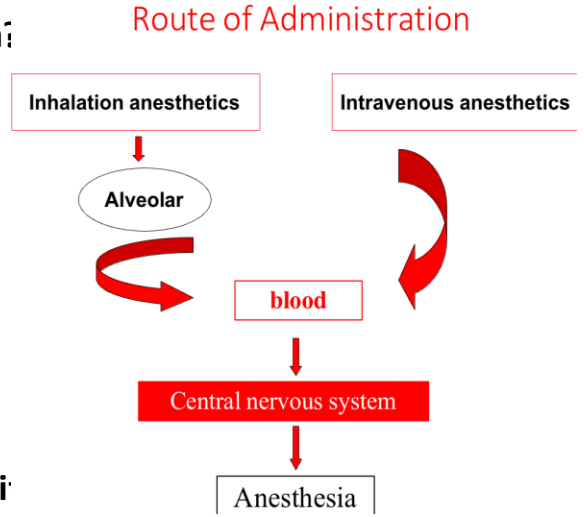
Why are they "general"?

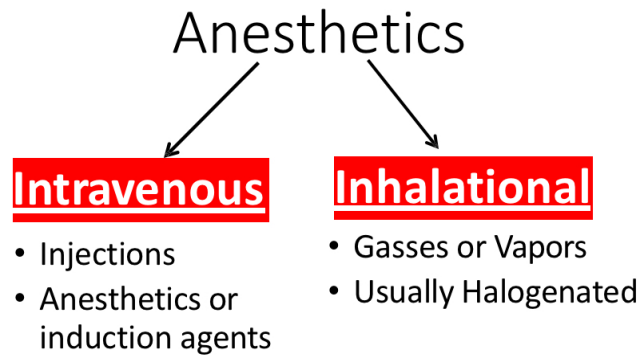
- **Sensory**
  - -Absence of intraoperative pain
- **Cognitive**:
  - -Absence of intraoperative awareness
  - -Absence of recall of intraoperative events
- **Motor**:
  - -Absence of movement
  - -Adequate muscular relaxation
- **Autonomic**:
  - -Absence of hemodynamic response
  - -Absence of tearing, flushing, sweating, and gastric secretions

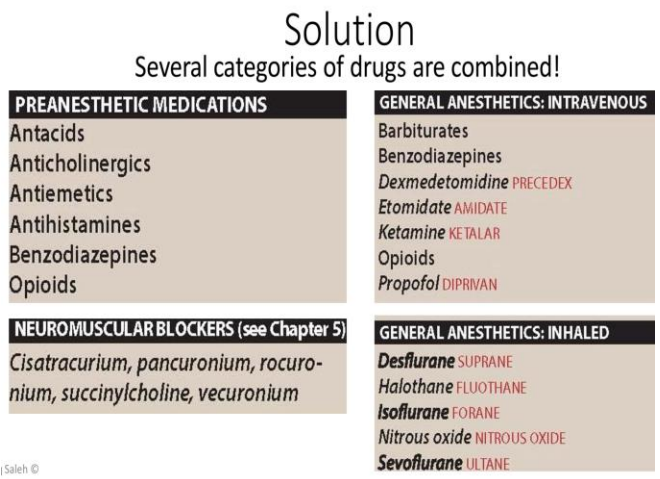
- **What are the benefits of anesthesia?**
- **Sedation and reduction of anxiety**
- **Lack of awareness and amnesia**
- **Analgesia**
- **Skeletal muscle relaxation**
- **Suppression of undesirable reflexes**

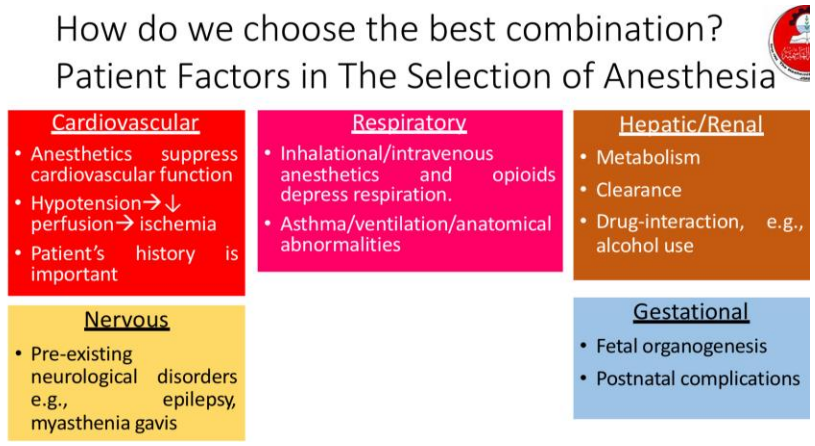
- **What is the "perfect" anesthetic?**
- **chemical stable with low flammabili**
- **produces "reversible" loss of consciousness**
- **produces analgesia, suppresses reflexes and produces muscle relaxation**
- **minimal cardiovascular and respiratory side effects**
- **cheap and easy to manufacture and administer**

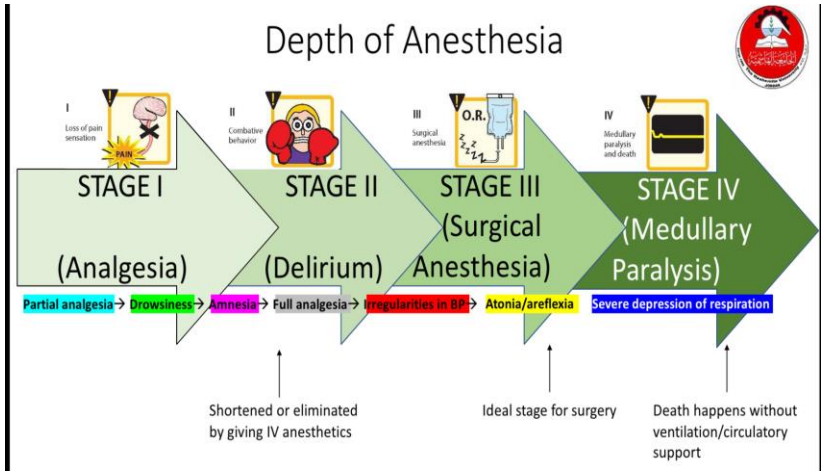
NO SINGLE DRUG HAS ALL THESE CHARACTERISTICS!



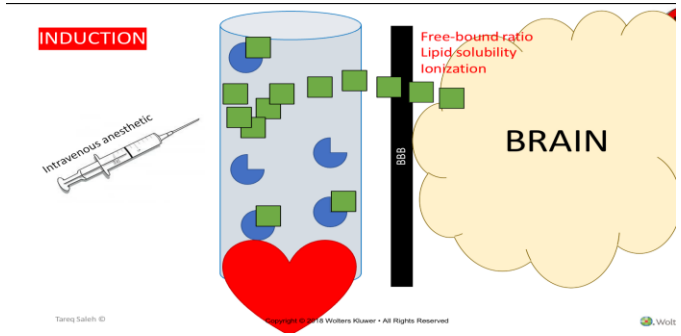


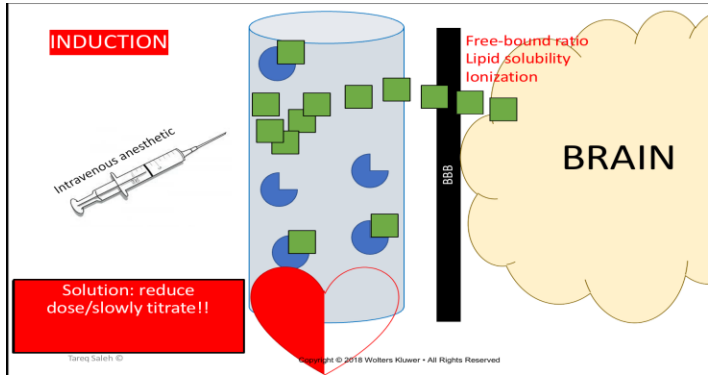


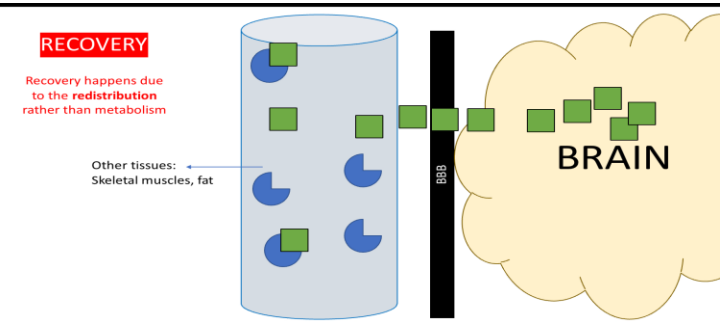




- Rapid induction of anesthesia "*arm-brain circulation time*"
- Could be used for maintenance – short surgeries – TIVA
- At low doses → sedative/hypnotic
- Mechanism of action is <u>unknown</u>







<u>Intravenous Anesthetics</u>

- I. **<u>Propofol</u>** IV sedative/hypnotic
- <u>First choice</u> for <u>induction of general anesthesia</u> and sedation
- "mill-like appearance"
- Induction: 30-40 seconds Redistribution: 2-4 minutes
- No analgesia ‘‘‘ No postoperative nausea/vomiting
- Decreases BP and ICP

- II. **<u>Barbiturates (thiopental)</u>** Ultra-short acting barbiturate
- Induction ~ 1 minute Potent anesthetic – weak analgesic
- Largely replaced by propofol (no longer used in the US)

<u>III. Benzodiazepines (midazolam, diazepam)</u>

- Used in adjunct with other anesthetics for their sedative/amnestic effects

IV. Opioids (fentanyl)

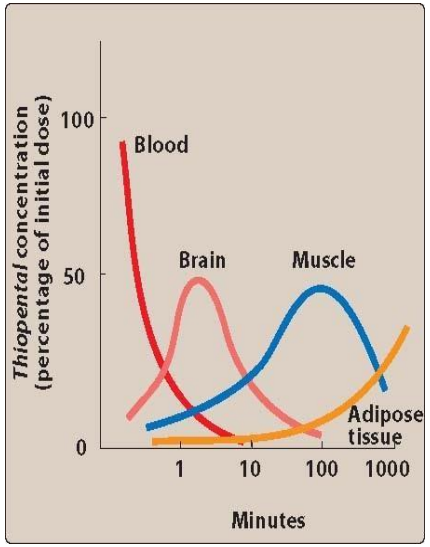
V Ketamine Short-acting, non-barbiturate

- NMDA receptor antagonist
- Induces ***dissociative anesthesia*** + **analgesia**
- <u>Cardiovascular effects</u>: ↑ blood pressure ↑ cardiac output and bronchodilator

--- good for hypovolemic, cardiogenic shock, asthmatics

--- contraindicated in hypertensive, stroke

- May induce hallucinations/dream-like state



Inhalational Anesthetics

- **Primarily used for <u>maintenance</u> of anesthesia following induction by IV agents.**
- **Depth of anesthesia correlates with inhaled concentration.**
- **Less risk of cardiac/respiratory depression than IV agents.**
- **No antagonists.**

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

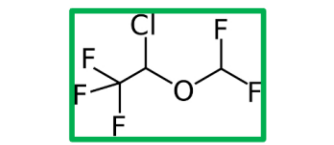
* **Halothane**
* **Isoflurane**
* **Desflurane**
* **Sevoflurane**

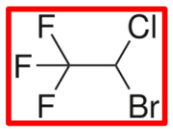
2 Gases: Nitrous oxide

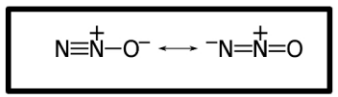
Mechanism of Action of Inhalational Anesthetics is UNKNOWN!

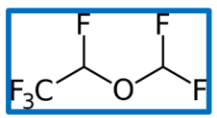
<u>Possible mechanisms:</u>

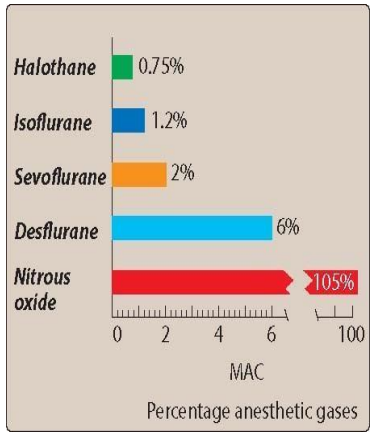
Increase the sensitivity of $GABA_A$ receptors to GABA
(nitrous oxide, ketamine have no effect on GABA)
Inhibition of NMDA receptors
Increase the activity of glycine receptors in the spinal chord
Block excitatory postsynaptic currents of nicotinic receptors

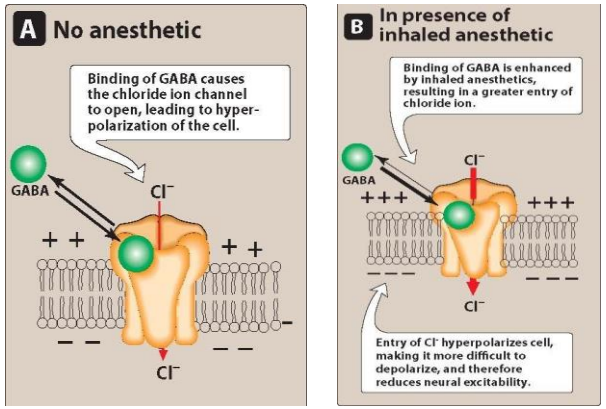


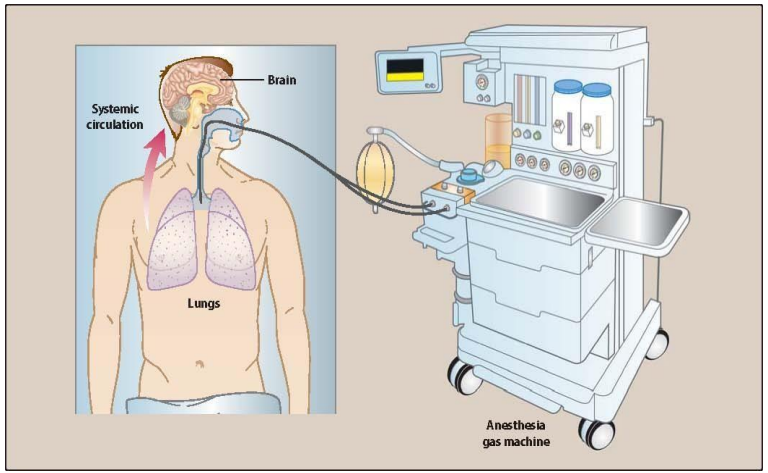












Potency: MAC

Minimum Alveolar Concentration (MAC)

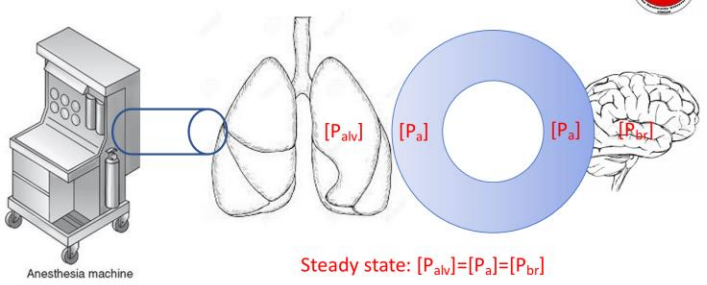
- The end-tidal concentration of an inhalational anesthetic needed to eliminate movement in 50% of patients stimulated by a standardized incision.
- MAC = ED_{50} of an anesthetic
- MAC is expressed as percentage of alveolar gas mixture/ partial pressure as % of 760 mm of Hg.

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

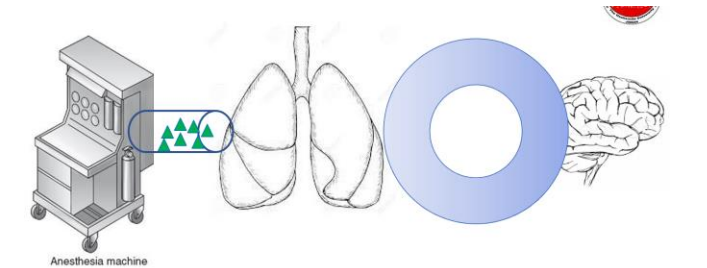
- **↓ MAC**
- Increased age
- Hypothermia
- Pregnancy
- Sepsis
- Concurrent use of an IV anesthetic
- α_2 agonists

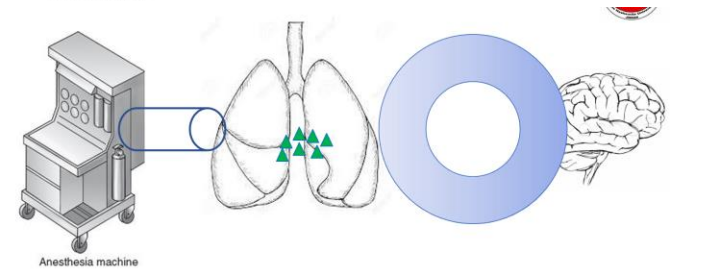
<u>Distribution</u>

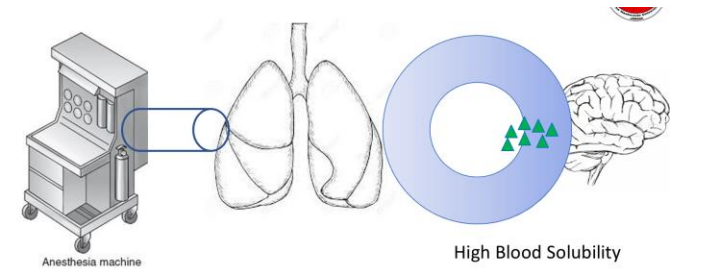
The pharmacologic effect of an inhalation agent is determined by the partial pressure of the anesthetic in the brain [P_{br}]
[P_{br}] depends on alveolar partial pressure [P_{alv}] which is controlled by pressure at the origin of the respiratory pathway.



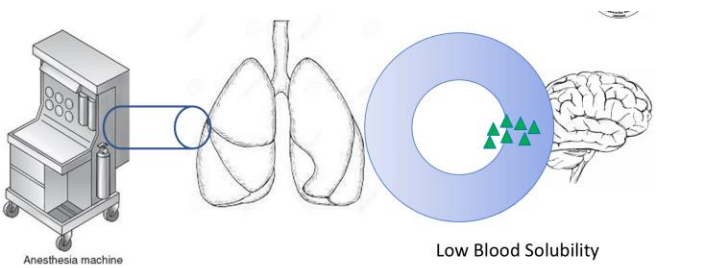
Steady state: $[P_{alv}]=[P_a]=[P_{br}]$





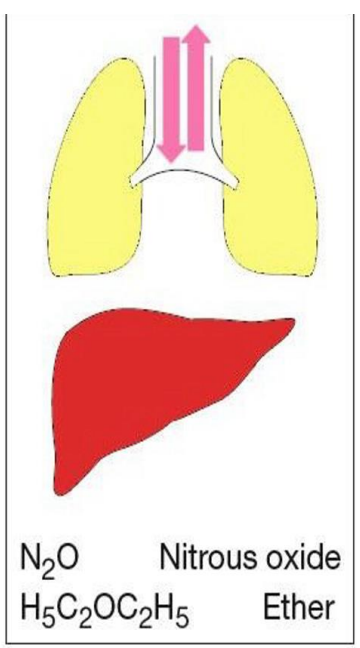


High Blood Solubility



Low Blood Solubility

All inhaled anesthetics are eliminated mainly through lungs



N_2O Nitrous oxide

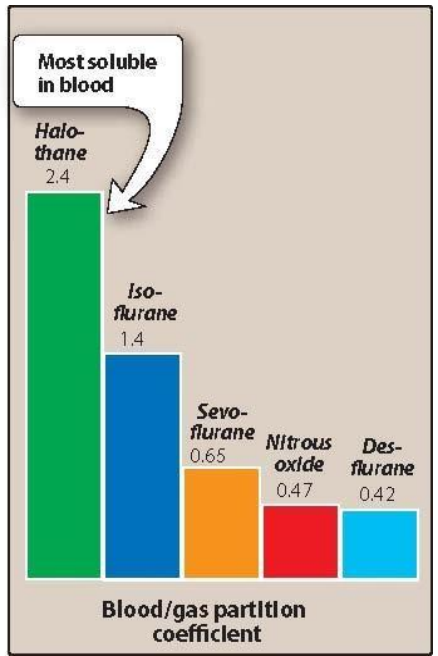
$H_5C_2OC_2H_5$ Ether

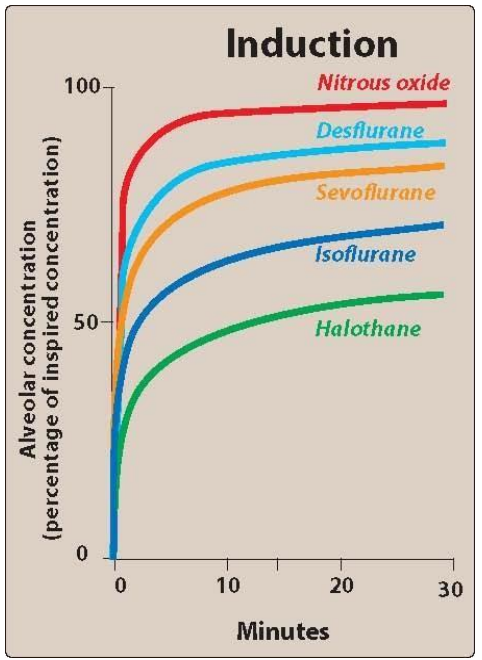
- Recovery
- The duration of exposure to the anesthetic can have a marked effect on the time of recovery. If exposure to the anesthetic is short, recovery may be rapid.

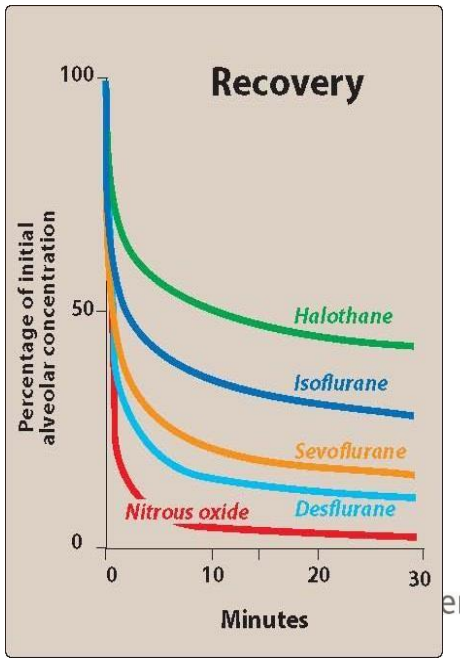
- Clearance of inhaled anesthetics by the lungs into the expired air is the major route of their elimination from the body

leh ©

Elimination routes of different volatile anesthetics







Isoflurane

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

Desflurane

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

Sevoflurane

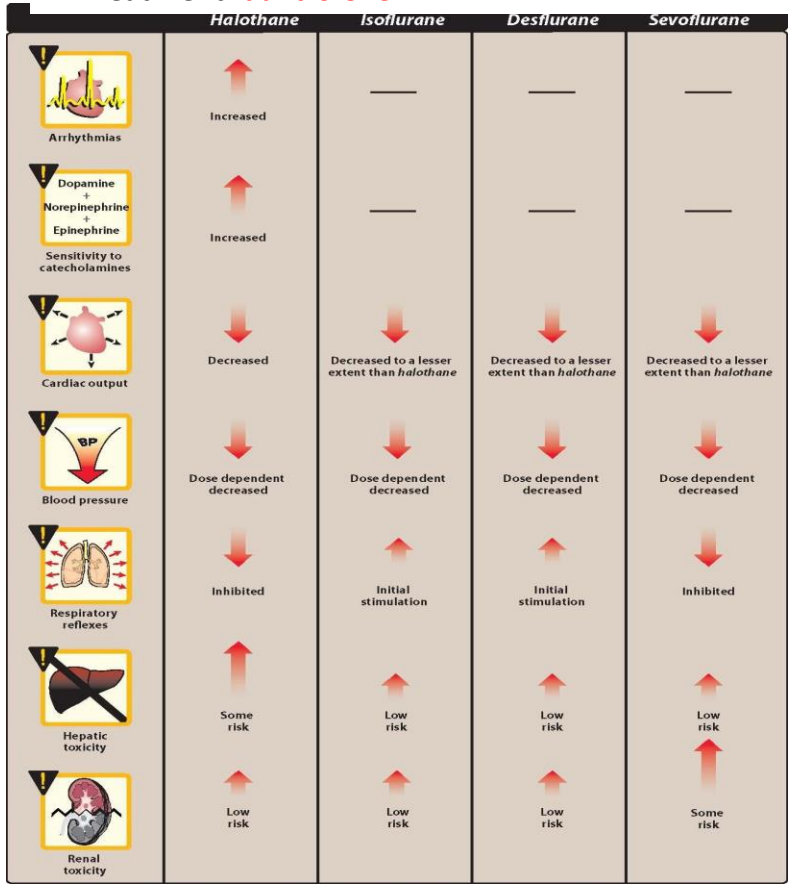
- Low pungency and respiratory irritation → <u>can be used for inhalational induction</u>
- Low solubility

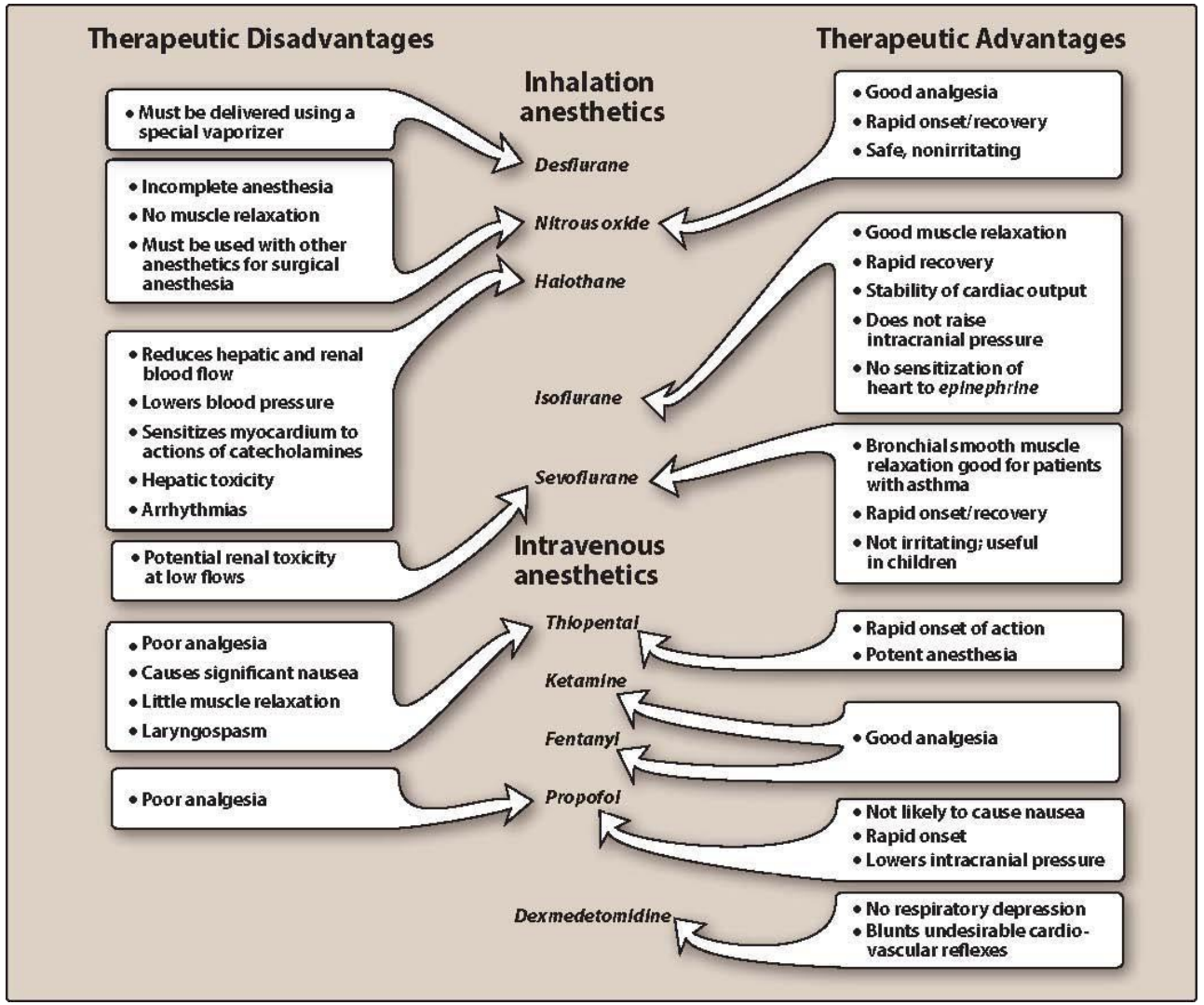
Nitrous Oxide

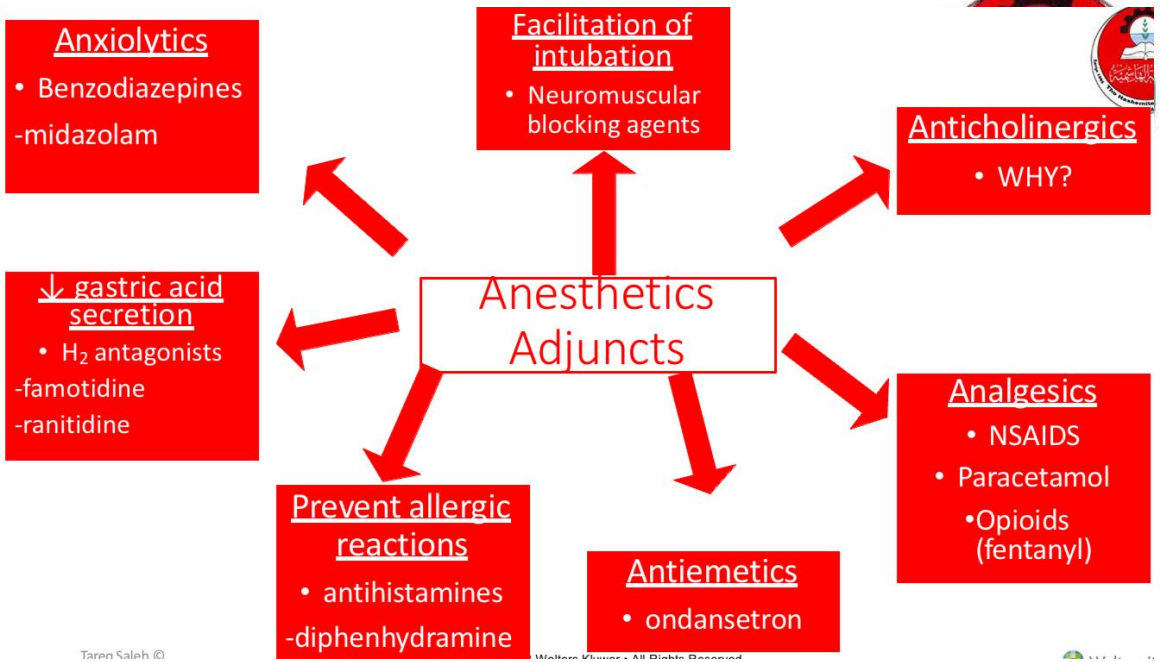
- **Gas**
- **Very rapid induction and recovery.**
  - **Why?**
- **least potent, highest MAC value.**
- **Poor anesthetic, good analgesic**
- **Administered with O_2 to avoid diffusion hypoxia (to produce sedation dentistry)**
- **Administered with other inhalational agents for general anesthesia**

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







Stages of Anesthesia

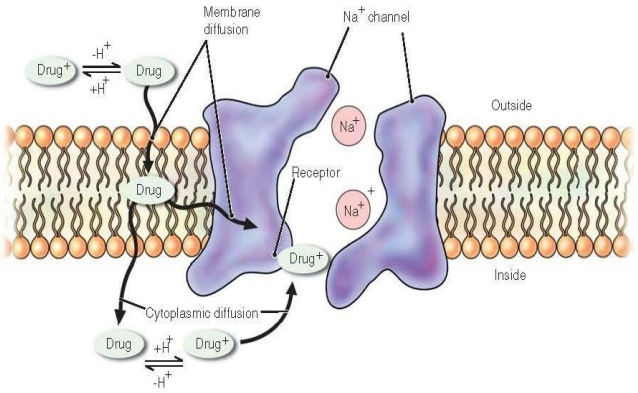
INDUCTION	MAINTENANCE	RECOVERY
• Mostly using intravenous anesthetics *-propofol* • Produce unconsciousness in 30-40 seconds • Could use an inhalational agent e.g., pediatric	• Mostly using inhalational agents • Combined with fentanyl to produce analgesia	• Recovery happens due to the **redistribution**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

Local Anesthetics

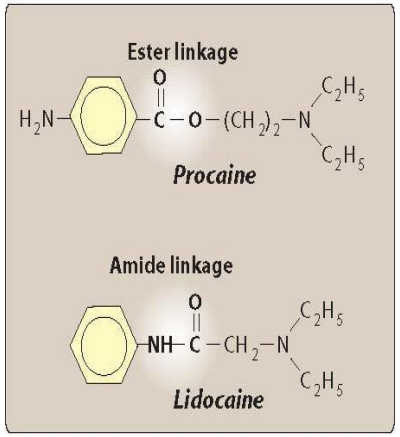
- Low doses: block sensory conduction
- High doses: block motor impulses
- **Mechanism of action:** "Sodium channels blockade"

Delivery Options

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



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



LOCAL ANESTHETICS: AMIDES

Bupivacaine MARCAINE
Lidocaine XYLOCAINE
Mepivacaine CARBOCAINE
Ropivacaine NAROPIN

LOCAL ANESTHETICS: ESTERS

Chloroprocaine NESACAINE
Procaine NOVOCAINE
Tetracaine PONTOCAINE

Local anesthetic

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
   - What happens if the tissue is infected?

Hepatic metabolism does NOT affect duration of action of local anesthetics

- **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)

CHARACTERISTIC	ESTERS • *Procaine* • *Chloroprocaine* • *Tetracaine* • *Cocaine*	AMIDES • *Lidocaine* • *Bupivacaine* • *Ropivacaine* • *Mepivacaine* • *Prilocaine*
Metabolism	Rapid by plasma cholinesterase	Slow, hepatic
Systemic toxicity	Less likely	More likely
Allergic reaction	Possible- PABA derivatives form	Very rare
Stability in solution	Breaks down in ampules (heat, sun)	Very stable chemically
Onset of action	Slow as a general rule	Moderate to fast
pK_a's	Higher than physiologic pH (8.5–8.9)	Close to physiologic pH (7.6–8.1)

DRUG	POTENCY	ONSET	DURATION
Procaine	Low	Rapid	Short
Chloroprocaine	Low	Rapid	Short
Tetracaine	High	Slow	Long (spinal)
Lidocaine	Low	Rapid	Intermediate
Mepivacaine	Low	Moderate	Intermediate
Bupivacaine	High	Slow	Long
Ropivacaine	High	Moderate	Long