Anesthetic Drugs

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Anesthetic Drugs

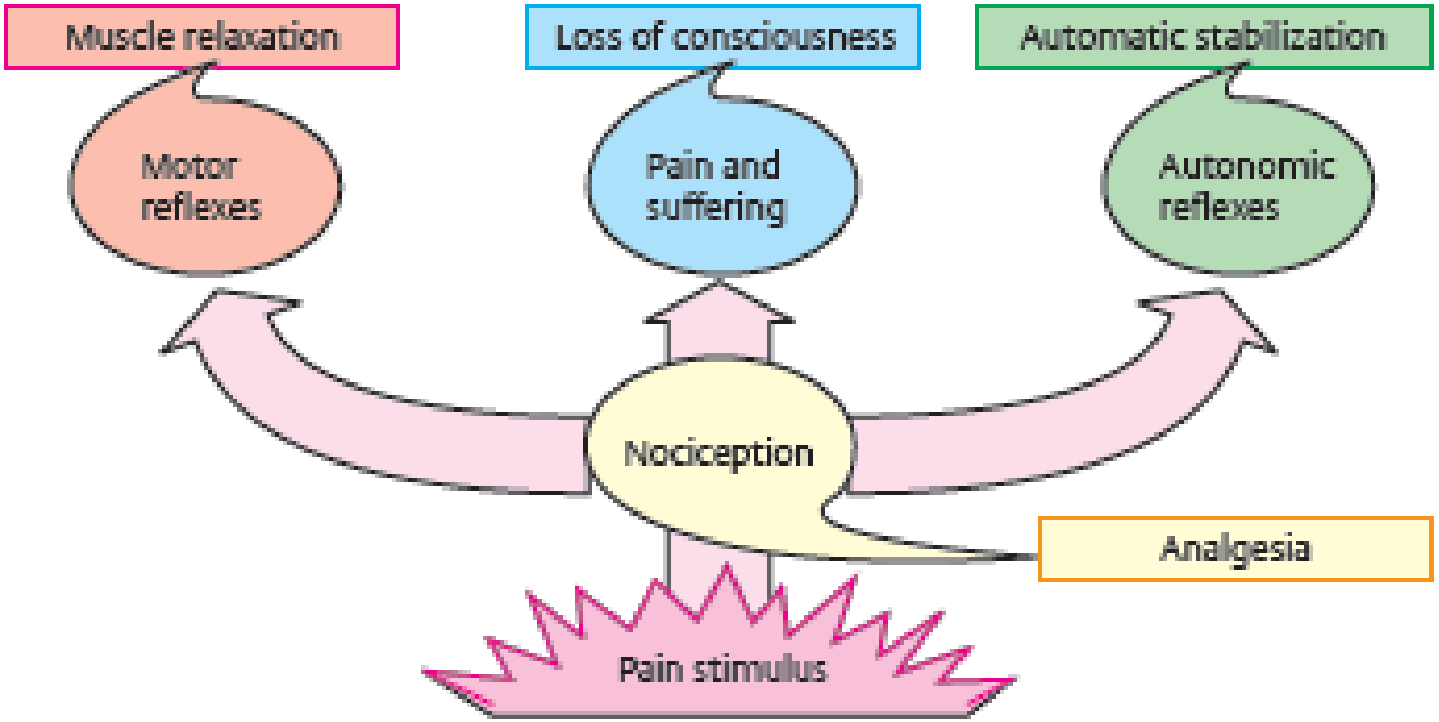
- Anesthesia is defined as the lack of sensation.
- The **ideal** general anesthetic agent would produce:

1. U**nconsciousness**
2. **Analgesia**
3. **Amnesia**
4. **muscle relaxation**

- with no untoward side effects or toxicities

Goals of surgical anesthesia.

- Adjunct drugs to general anesthetics are drugs that produce more selective muscle relaxation, analgesia, loss of consciousness, amnesia, and autonomic stabilization.



- Anesthetics developed to date are not ideal and are administered in combination with numerous other preoperative and postoperative medications in order to achieve the desired effects listed above

Adjunct to Anesthetics

Desired Effect	Drugs Used (Intravenously)	Example(s)
Induction of anesthesia	Ultra short-acting barbiturate	Thiopental, thiamylal, and methohexital
Muscle relaxation	Depolarizing and nondepolarizing neuromuscular blocking agents	Succinylcholine, pancuronium
Analgesia	Short-acting, intravenous opiates	Fentanyl
Amnesia	Short-acting benzodiazepines (doses given are higher than anxiolytic doses)	Diazepam, midazolam, and lorazepam
Autonomic stabilization	Anticholinergic drugs Antiadrenergic drugs	Atropine and glycopyrrolate Esmolol

Drugs used as anesthetics

PREOPERATIVE MEDICATIONS

Analgesics
Antacids
Antiemetics
Benzodiazepines*

ANALGESICS

Acetaminophen TYLENOL, OFIRMEV
Celecoxib CELEBREX
Gabapentin NEURONTIN
Ketamine KETALAR*
Opioids (see Chapter 14)

GENERAL ANESTHETICS: INHALED

Desflurane SUPRANE
Isoflurane FORANE
Nitrous oxide GENERIC ONLY
Sevoflurane ULTANE

GENERAL ANESTHETICS: INTRAVENOUS

Dexmedetomidine PRECEDEX
Etomidate AMIDATE
Methohexital BREVITAL
Propofol DIPRIVAN

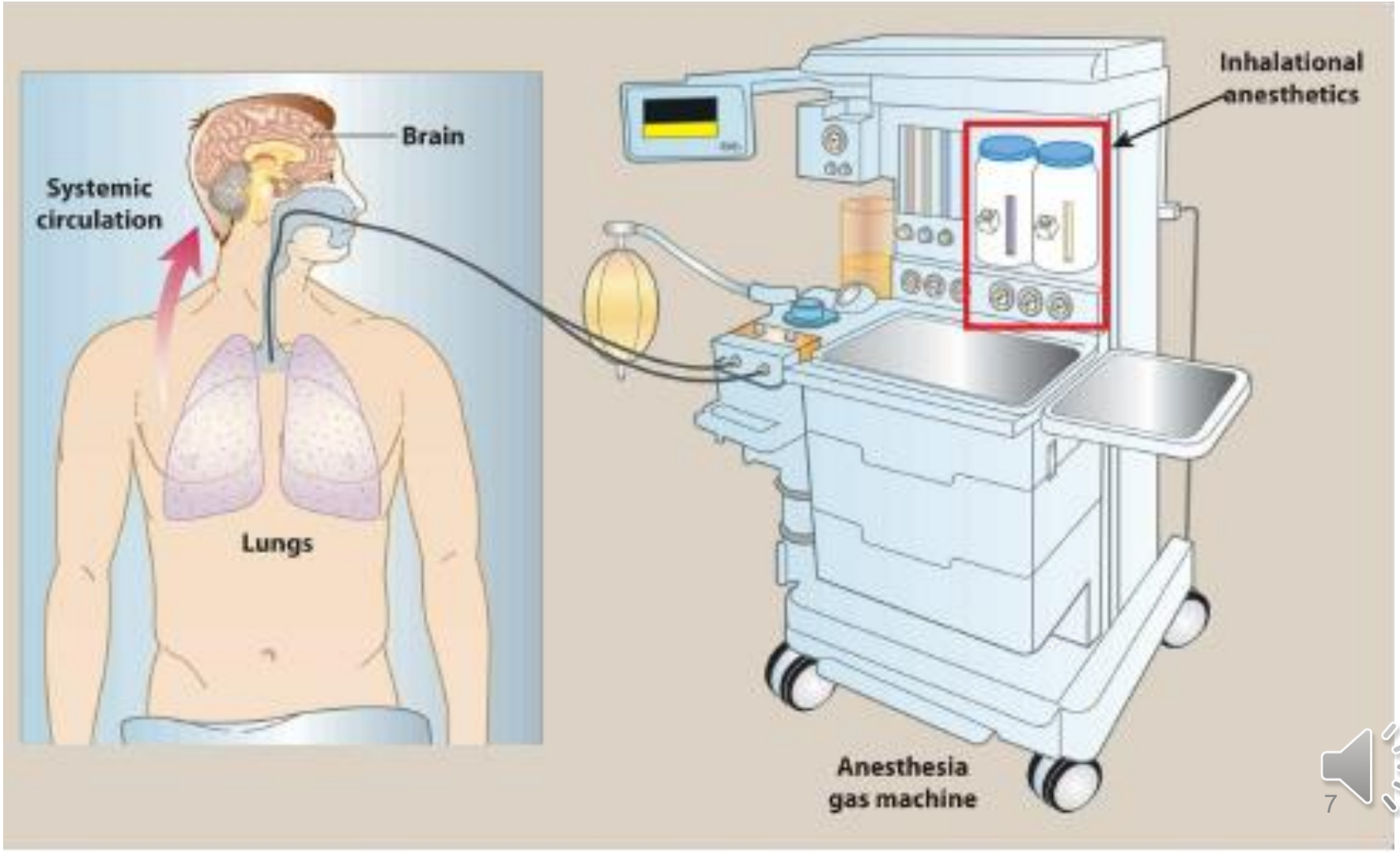
NEUROMUSCULAR BLOCKERS (see Chapter 5)

Cisatracurium, mivacurium, pancuronium, rocuronium, succinylcholine, vecuronium

Inhalation agents

- The major anesthetic gases include several halogenated hydrocarbons (halothane, isoflurane, enflurane, desflurane, and sevoflurane) and nitrous oxide.
- These agents act in the brain to produce surgical anesthesia, but the precise mechanism of action for these agents and specific receptors with which these agents interact are not known.
- The pharmacokinetics of these agents is unique because they are administered as gases and exert their pharmacologic effects when in gaseous form. Thus, the important factor for determining the level of anesthetic effect is the partial pressure or tension of the anesthetic gas.
- The standard for anesthetic dosing is the minimal alveolar concentration (MAC), which is the alveolar concentration, expressed as a percentage of inspired gas, at which 50% of the patients fail to respond to a noxious stimulus.

Volatile anesthetics delivered to the patient are absorbed via the lungs into the systemic circulation causing dose-dependent CNS depression



Mechanism of action

- No specific receptor has been identified as the locus to create a state of general anesthesia. The fact that chemically unrelated compounds produce unconsciousness argues against the existence of a single receptor, and it appears that a variety of molecular mechanisms may contribute to the activity of anesthetics.
- At clinically effective concentrations, general anesthetics increase the sensitivity of the γ-aminobutyric acid (GABAA) receptors to the inhibitory neurotransmitter GABA. This increases chloride ion influx and hyperpolarization of neurons. Postsynaptic neuronal excitability and, thus, CNS activity are diminished
- Unlike other anesthetics, *nitrous oxide* and *ketamine* do not have actions on GABAA receptors. Their effects are mediated via inhibition of *N*-methyl-D-aspartate (NMDA) receptors. [Note: The NMDA receptor is a glutamate receptor, which is the body's main excitatory neurotransmitter.]
- Receptors other than GABA that are affected by volatile anesthetics include the inhibitory glycine receptors found in the spinal motor neurons. Additionally, inhalation anesthetics block excitatory postsynaptic currents found on nicotinic receptors. However, the mechanisms by which anesthetics perform these modulatory roles are not fully understood.

Factors influencing the rate of induction of inhalation anesthesia

Factor	Explanation
Concentration of gas in inspired air	The higher the concentration of anesthetic in inspired air, the more rapid the increase in tension of anesthetic in the blood and therefore the brain.
Ventilation rate and depth	Increased ventilation rate and depth lead to an increased rate of induction of anesthesia.
Blood solubility	The solubility of an anesthetic agent in the blood is a very important factor in determining the rate of induction of inhalation anesthesia. The blood:gas partition coefficient is the ratio of the concentration of anesthetic in the blood to the concentration of anesthetic gas at equilibrium. Note that anesthetic molecules that are dissolved in the blood are not exerting a partial pressure and therefore not contributing to anesthesia. Thus, an agent that has high blood solubility will show a slower increase in anesthetic tension and therefore a slower induction rate. Agents that are not soluble in the blood will have a rapid rate of induction.
Blood flow	Uptake of anesthetic into tissues is dependent on blood flow to those tissues, so highly perfused organs will see a more rapid rise in anesthetic tension.
Tissue solubility	In general, anesthetic gases are soluble in fatty tissues; therefore, the rate of rise of anesthetic tension in adipose tissue is slower than in lean tissues, such as the brain.*

* The brain is a lean, well-perfused organ; therefore, the rate of rise of anesthetic tension in the brain is rapid.

Isoflurane

- *Isoflurane* [eye-so-FLOOR-ane], like other halogenated gases, produces dose-dependent hypotension predominantly from relaxation of systemic vasculature. Hypotension can be treated with a direct-acting vasoconstrictor, such as *phenylephrine*. Because it undergoes little metabolism
- *isoflurane* is considered nontoxic to the liver and kidney. Its pungent odor stimulates respiratory reflexes (breath holding, salivation, coughing, laryngospasm), so
- it is not used for inhalation induction. With a higher blood solubility than *desflurane* and *sevoflurane*, *isoflurane* takes longer to reach equilibrium, making it less ideal for short procedures; however, its low cost makes it a good option for longer surgeries.

Desflurane

- *Desflurane* [DES-floor-ane] provides very rapid onset and recovery due to low blood solubility.
- This makes it a popular anesthetic for short procedures. It has a low volatility, which requires administration via a special heated vaporizer.
- Like *isoflurane*, it decreases vascular resistance and perfuses all major tissues very well. *Desflurane* has significant respiratory irritation like *isoflurane* so it should not be used for inhalation induction.
- Its degradation is minimal and tissue toxicity is rare. Higher cost occasionally prohibits its use.

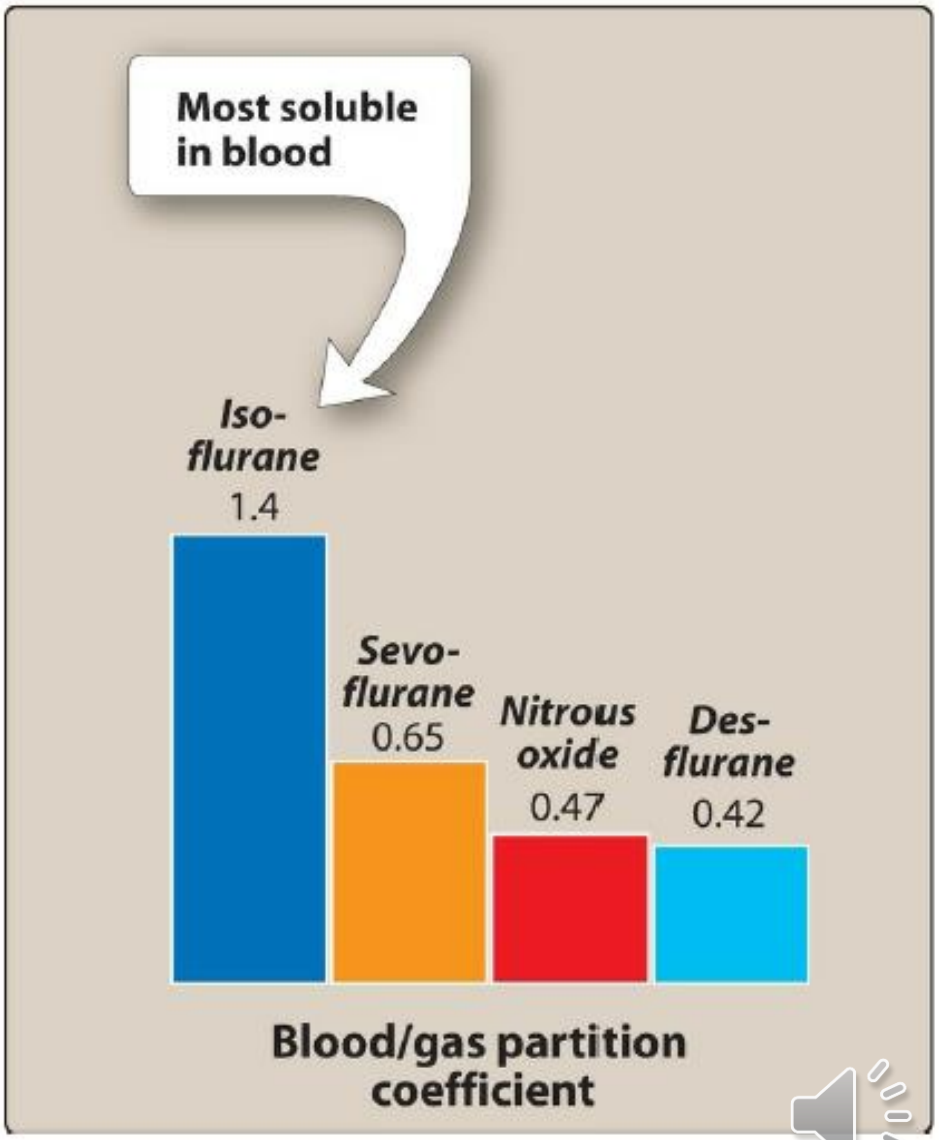
Sevoflurane

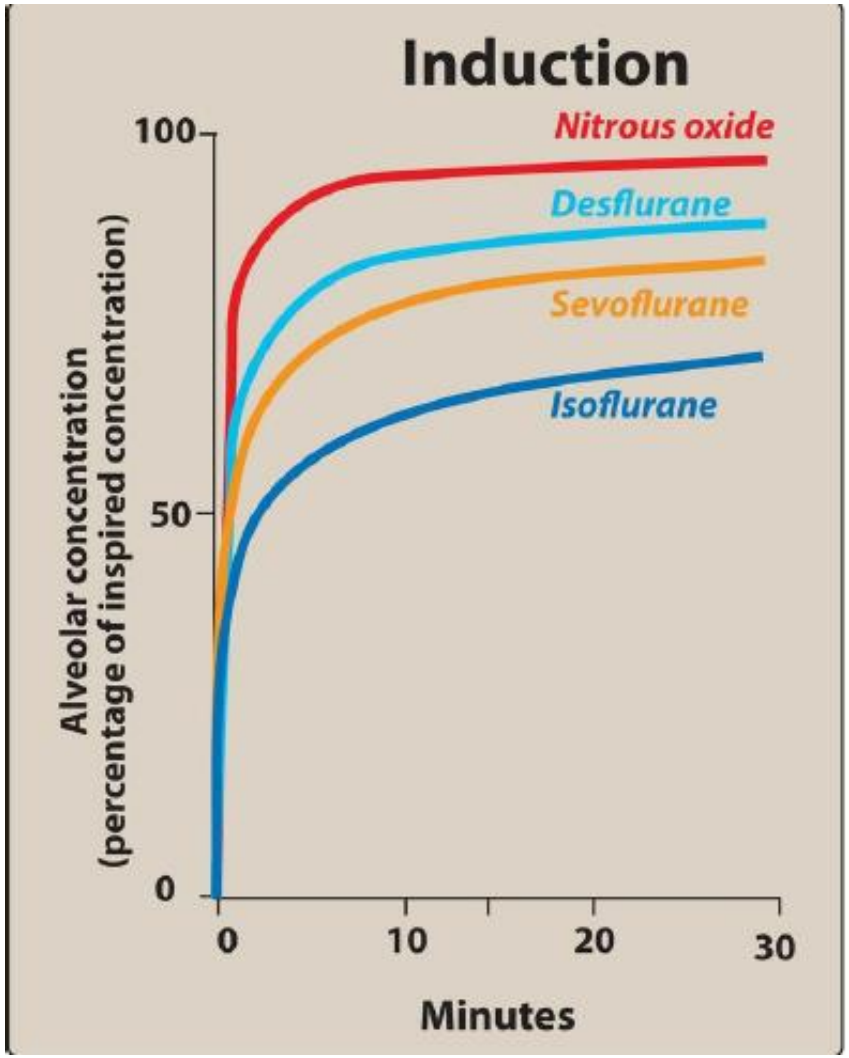
- *Sevoflurane* [see-voe-FLOOR-ane] has low pungency or respiratory irritation. This makes it useful for inhalation induction, especially with pediatric patients who do not tolerate IV placement. It has a rapid onset and recovery due to low blood solubility.
- *Sevoflurane* has low hepatotoxic potential, but compounds formed from reactions in the anesthesia circuit (soda lime) may be nephrotoxic with very low fresh gas flow that allows longer chemical reaction time.

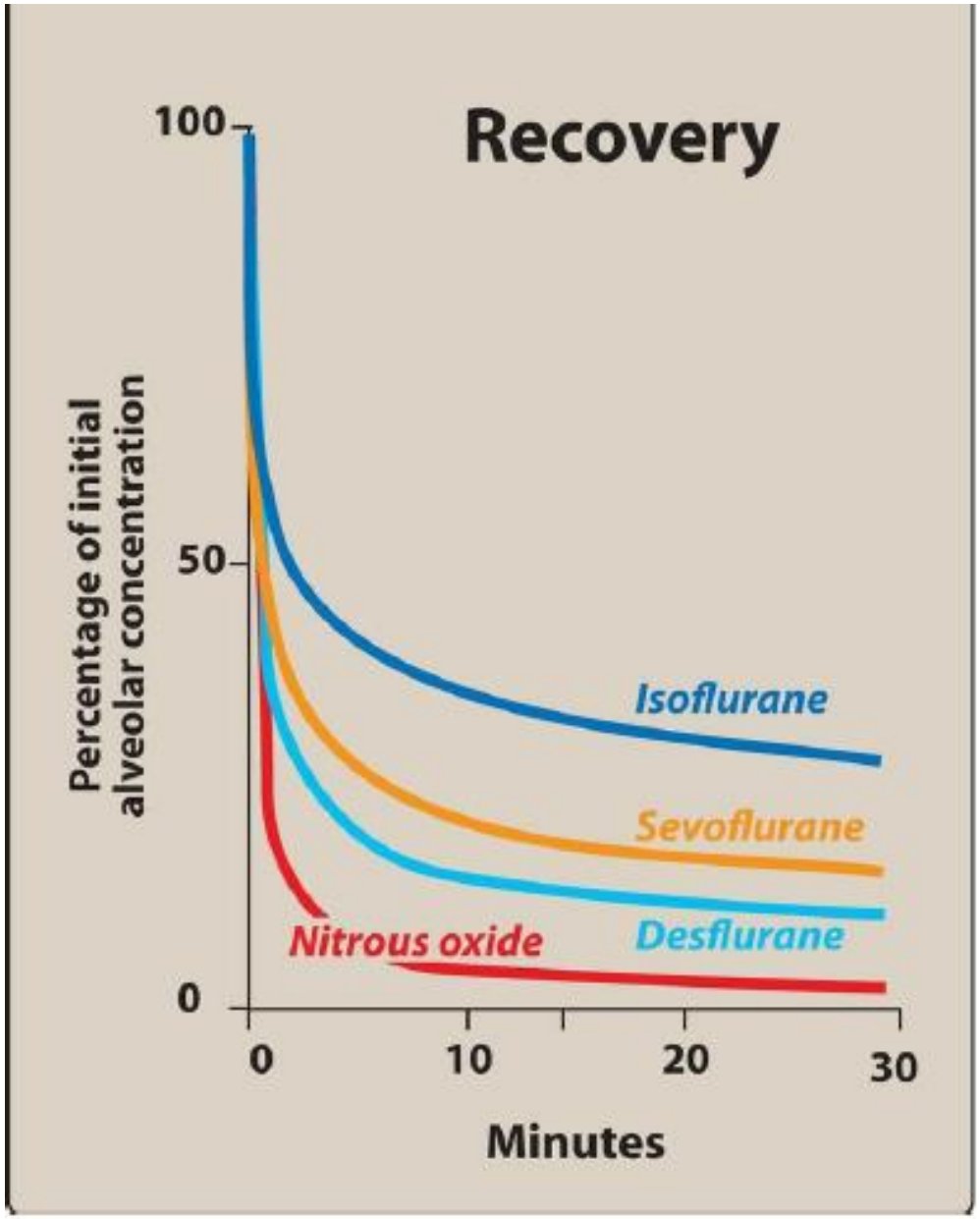
Nitrous Oxide

- **Uses**
- Nitrous oxide is a good analgesic (produces superior analgesia than halogenated agents
- without decreases in blood pressure or depressed respiration).
- It does not produce surgical levels of anesthesia except with very high doses when oxygenation
- is inadequate. It is therefore not used alone as an anesthetic agent but can be used as the sole agent for analgesia. It is frequently combined with one of the other anesthetic agents.
- **Side effects**
- It is always administered with 30 to 35% oxygen, as it can cause diffusion hypoxia.
- Long-term exposure to trace concentrations may cause pernicious anemia and an increased incidence of spontaneous abortions.

Blood/gas partition coefficients for some inhalation anesthetics.




Induction
Nitrous oxide
Desflurane
Sevoflurane
Isoflurane
100
50
0
Alveolar concentration
(percentage of inspired concentration)
0
10
20
30
Minutes


Recovery
100
50
0
Percentage of initial alveolar concentration
Isoflurane
Sevoflurane
Desflurane
Nitrous oxide
0
10
20
30
Minutes

Intravenous Anesthetic Agents

- **Propofol**
- **Mechanism of action.**
- The mechanism of action of propofol is not completely understood,
- but it enhances gamma-aminobutyric acid (GABA)–mediated neuronal inhibition (via GABAA receptors), and it also blocks Na+ channels **Pharmacokinetics**
- — Given intravenously (IV)
- — Metabolized rapidly by the liver
- — Rapid induction of anesthesia and recovery
- **Uses**
- — General anesthesia
- *Note*: Propofol is a poor analgesic, so it must be supplemented with an opiate.
- **Side effects**
- — Hypotension (due to decreased vascular resistance)

Ketamine

- This is a “dissociative anesthetic” similar to the street drug phencyclidine (angel dust).
- Dissociative anesthetics make the patient feel dissociated from the environment.
- **Uses**
- — Induction and maintenance of general anesthesia; it is not widely used due to side effects
- **Effects.**
- At anesthetic doses, it produces catatonia, analgesia, and amnesia.
- **Side effects**
- — Disorientation and hallucinations

Barbiturates

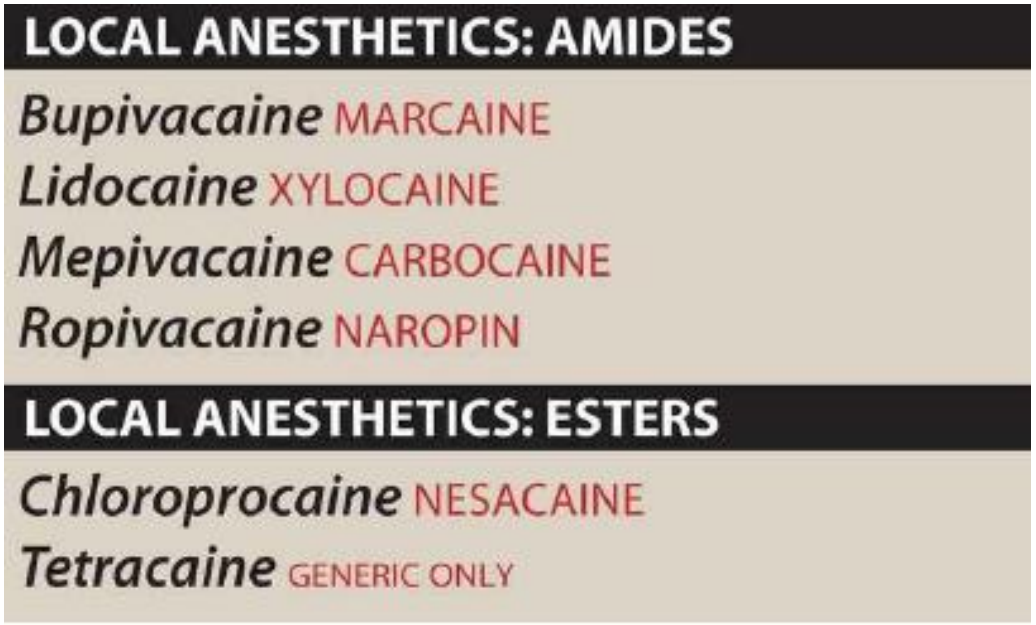
- Thiopental, Thiamylal, and Methohexital
- **Pharmacokinetics**
- Unconsciousness occurs within the circulation time from arm to brain and is then maintained with an inhalation agent.
- Termination of CNS action of the barbiturate is by redistribution of drug from the brain to other tissues
- **Uses**
- Induction of anesthesia
- **Side effects**
- Respiratory and cardiovascular depression

Benzodiazepines

- These drugs are discussed later on
- **Diazepam, Midazolam, and Lorazepam**
- Pharmacokinetics
- Given IV.
- Uses.
- These agents are used as anesthetic premedications to produce sedation and amnesia.

Local Anesthetics

- Local anesthetics act directly on nerve axons to reversibly block nerve conduction. They produce a lack of sensation in the area innervated by those nerve fibers.



The methods by which local anesthetics can be administered

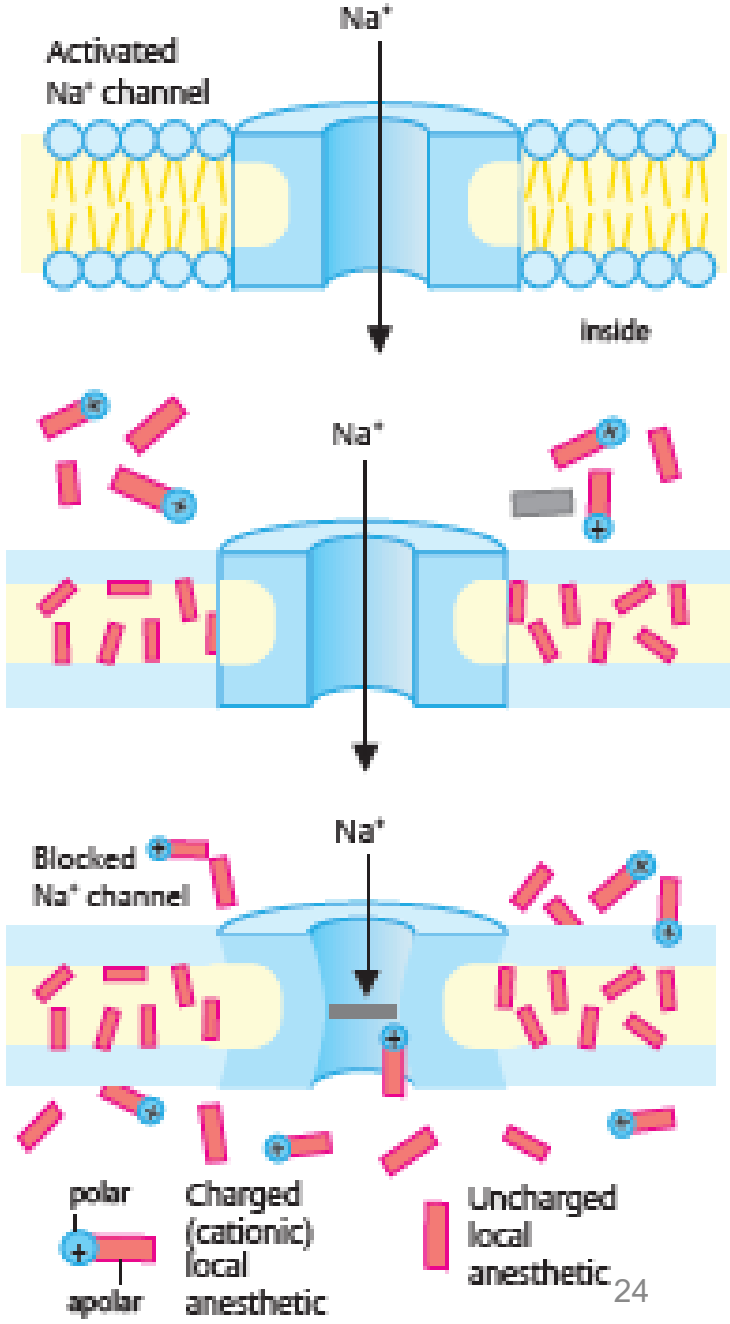
Methods of Local Anesthetic Administration	Technique	Clinical Situation
Topical	Applied to skin or mucous membranes	Typically used prior to injection of anesthetics to make the procedure less painful Also used prior to eye surgery and endoscopy
Infiltration	Inject dilute solution and let diffuse (e.g., subcutaneous or submucosal)	Very common in dentistry to anesthetize most teeth
Nerve block	Inject close to the nerve trunk, proximal to the intended area of anesthesia	Very common in dentistry to anesthetize mandibular teeth Can be useful in cases where pain sensation to a limb needs to be blocked (e.g., following femur fracture)
Spinal	Inject anesthetic in the subarachnoid space	Chronic pain or surgery
Epidural	Inject within the vertebral canal but outside the dura	Very commonly used in labor and delivery

Lidocaine, Articaine, and Bupivacaine (Amides); Benzocaine, Procaine,and Tetracaine (Esters)

- Mechanism of action.
- Local anesthetics exist in two forms in the body: as an uncharged base and as a charged acid. Only the uncharged base can cross nerve membranes. However, once inside the axon, the charged form is active.
- Local anesthetics interfere with the propagation of action potentials in nerve axons by blocking Na+ channels from the cytoplasmic side of the channel

▶ Effects of local anesthetics.

Local anesthetics block the inner gate of the Na+ channels in nerve cells, preventing Na+ influx and action potential initiation and propagation. Charged (cationic) local anesthetic is thought to block the sodium channel by becoming incorporated into the phospholipid membrane or channel protein. Uncharged local anesthetic may also become incorporated into the apolar region of the channel protein. (CNS, central nervous system.)



Pharmacokinetics

- — Local anesthetics differ mainly in their rate of onset and duration of action
- — Termination of action at the site of injection is by diffusion of the active drug into the systemic
- circulation followed by metabolism. Ester local anesthetics are inactivated primarily by hydrolysis via esterases in plasma and the liver. Amide local anesthetics are metabolized primarily by the live

Rate and Onset of action of Some Common Local Aesthetic Agents

Local Anesthetic Agent	Rate of Onset	Duration of Action*
Lidocaine	Rapid	Short
Articaine	Rapid	Intermediate
Bupivacaine	Slow	Long
Procaine	Rapid	Short
Tetracaine	Slow	Long

* The duration of action is prolonged when combined with epinephrine.

Side effects

- The toxic effects of local anesthetics are dependent on the amount of drug that gains entry into the systemic circulation.
- ***CNS effects****:* These include stimulation, restlessness, and tremor that may lead to clonic convulsions.
- This is followed by depression and death due to respiratory failure. Direct systemic
- injection may lead directly to death.
- ***Cardiac effects****:* Direct effects on the myocardium include decreased electrical excitability,
- decreased conduction rate, and a negative inotropic effect. Sudden cardiac death may occur.
- ***Hypersensitivity:*** This is rare, but it can cause dermatitis, asthma attacks, or fatal anaphylactic reactions. Allergy is more frequent with esters.