LOCAL ANESTHETICS

Local anesthetics (LAs)

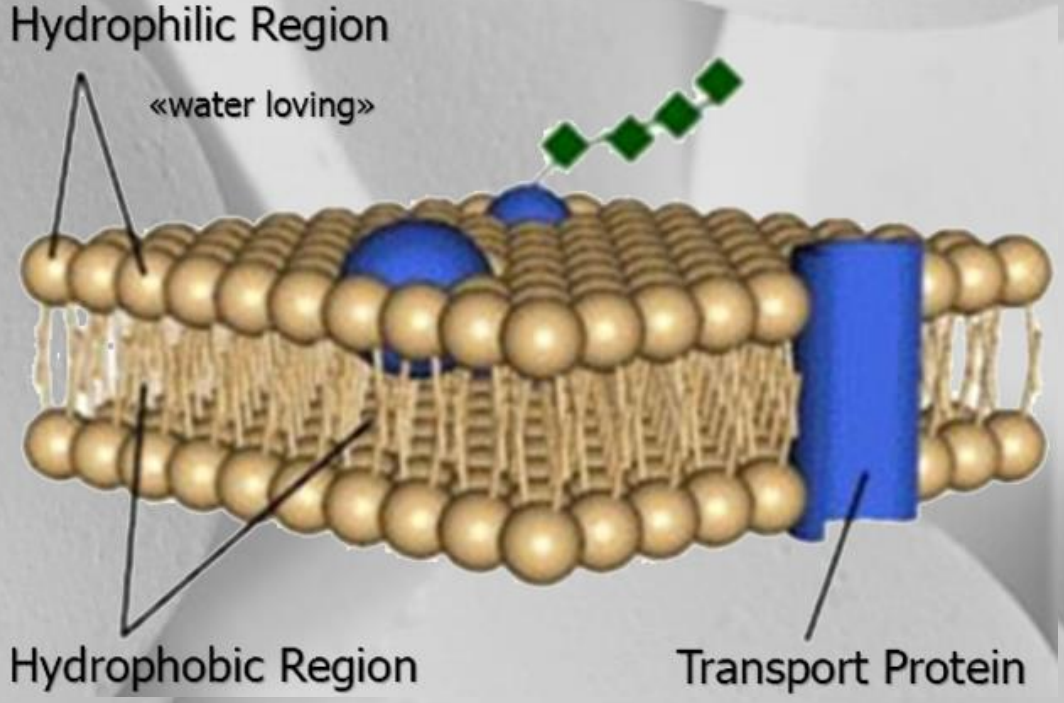
are drugs that cause reversible loss of sensory perception, specially of pain, in a restricted area of the body.

- They block generation and conduction of nerve impulse at all parts of the neuronal system where they come in contact, without causing any structural damage.
- Thus, not only sensory but also motor impulses are interrupted when LAs are applied to a mixed nerve, resulting in muscular paralysis and loss of autonomic control as well.

Mechanism of action

The LAs block nerve conduction by decreasing the entry of Na^+ ions during upstroke of action potential.

The LAs interact with a receptor situated within the voltage sensitive Na^+ channel and raise threshold of channel opening.



Ionization Factors

- Local anesthetics are weak bases occurring equilibrated between their 2 forms, the fat soluble, free base and water-soluble hydrochloride salt.
- The portion of drug in each form is determined by the pKa of the local anesthetic and the pH of the environment.
- Once injected into local tissue, the amount of local anesthetic in the free base form increases and allows for greater tissue penetration.
- If there is an infection or inflammation, the free base form decreases and less drug penetrates the tissue.
- Other factors that can affect tissue penetration include inflammation, vasodilation, and dilution by fluid.

Chemistry

Local anesthetics are divided into 2 chemical groups; esters and amides.

Classification by chemical structure:

Ester linked LAs: *Cocaine, Procaine, Tetracaine, Benzocaine.*

Amide linked LAs: *Lidocaine , Bupivacaine, Prilocaine, Articaine, Ropivacaine.*

- Amide linked LAs differ from the ester linked LAs in that they bind to α_1 glycoprotein in plasma, are not hydrolyse by plasma esterases, are generally longer acting and less frequently produce hypersensitivity reactions, no cross sensitivity with ester linked LAs.
- Metabolism of LAs:

Amides – in the liver

Esters – firstly by plasma cholinesterase

Classification

1)Injectable:

a) low potency, short duration: *Procaine;*

b) intermediate potency and duration: *Lidocaine;*

c) high potency, long duration: *Tetracaine, Bupivacaine.*

2) Surface anesthetics:

a) Soluble: *Cocaine, Lidocaine, Tetracaine*;

b)Insoluble: *Benzocaine*

Adverse effects:

1. Local reactions
2. Systemic reactions depending on concentration attained in the plasma and tissues.

CNS

All LAs are capable of producing a sequence of stimulation following by depression.

Only *Cocaine* is a powerful CNS stimulant. It causes in sequence euphoria and excitement, mental confusion and restlessness

Symptoms: sedation or excitement – visual or sensitive disturbances - tremors and twitching of muscles – convulsions – unconsciousness – respiratory depression – death, in dose dependent manner.

Heart and BP

Local anesthetics also have a direct effect on the cardiac muscle by blocking cardiac Na channels and depressing abnormal cardiac pacemaker activity, excitability, and conduction.

LAs tend to produce fall in BP. This is primarily due to sympathetic blockade, but high doses do cause direct relaxation of arteriolar smooth muscle. Toxic doses of LAs produce cardiovascular collapse.

Only *Cocaine* has sympathomimetic property: produces marked rise in BP and tachycardia.

- Combination of LAs with Vasoconstrictors can lead to the delay of local anesthetic absorption, reduction of systemic toxicity, and to the prolongation of the duration of action.

GENERAL ANESTHETICS

General anesthetics (GAs)

These are drugs that produce reversible loss of all sensation and consciousness.

The **cardinal features** of general anesthesia are:

1) Loss of all sensation
2) Sleep (unconsciousness)
3) Muscle relaxation
4) Abolition of reflexes

Stages of anesthesia

1) Stage of analgesia.

Starts from beginning of anesthetic inhalation and lasts up to the loss consciousness.

Pain is progressively abolished during this stage. Patient remains conscious, can hear and see, and feels a dream like state.

Reflexes and respiration remain normal.

2) Stage of Delirium.

From loss of consciousness to beginning of regular respiration. Apparent excitement is seen – patient may shout, struggle and hold his breath, muscle tone increases, jaws tightly closed , breathing is jerky, vomiting, involuntary micturition or defecation may occur.

Heart rate and BP may rise and pupils dilate due to sympathetic stimulation.

3) Surgical anesthesia.

As anesthesia passes to deeper planes, progressively – muscle tone decreases, BP falls, heart rate increases with weak pulse, respiration decreases.

More operative procedure can be carried out during this stage.

4) Medulla paralysis and death.

Fall in BP and cardiac depression are signs of deep anesthesia.

Properties of an ideal anaesthetic

a) For the patient.

It should be pleasant, nonirritating.

It should not cause nausea or vomiting.

Induction and recovery should be fast with no after effects.

b) ***For the surgeon.***

It should provide adequate analgesia, immobility and muscle relaxation.

It should be noninflammable and nonexplosive.

C) For the anesthetist.

It's administration should be easy, controllable and versatile.

This properties (of an ideal anesthetic) depends mostly on ***blood-gas solubility coefficient*** of general anesthetic. This physical constant of GAs determines the rate of induction and rate of recovery.

Classification

1) Inhalational:

Gases: *Nitrous oxide (N_2O);*

Liquids*: Enflurane, Isoflurane, Sevoflurane, Halothane.*

*2)***Intravenous***: Tiopentone sod., Ketamine, Propofol*

Although inhalation general anesthetics have low therapeutic index, their clinical safety is enhanced because of **rapid tissue redistribution**. **They are very controllable.** But the intravenous general anesthetics are not controllable.

Potency of inhalational GAs is defined quantitatively as the minimum alveolar concentration (MAC), the end-tidal concentration of inhaled anesthetic

needed to eliminate movement in 50% of patients stimulated by a standardized incision.

Individual compounds

1. Nitrous oxide (N_2O)

It is low potency anesthetic, but is a good analgesic.

As the sole agent N_2O has been used with O_2 for dental and obstetric analgesia.

It is nontoxic to liver, kidney and brain.

Metabolism of N_2O does not occur: it is quickly removed from body to lungs.

It is cheap and very commonly used.

2. *Halothane*

a) It is a potent anesthetic, but not a good analgesic.

b) It causes direct depression of cardiac contractility and fall in BP.

c) It tends to sensitize the heart to the arrhythmogenic action of *Adrenaline*.

d) It causes early abolition of pharyngeal and laryngeal reflexes, suppresses coughing and dilates bronchi – preferable for asthmatics.

e) It is currently one of the most popular anesthetic because of nonirritant, noninflammable, pleasant and rapid action.

3) Enflurane

It is less potent than *Halothane*, but it produces rapid induction and recovery.

About 2% of the agent is metabolized to fluoride ion, which is excreted by the kidney. Therefore, *Enflurane* is contraindicated in patients with kidney failure.

Enflurane anesthesia exhibits the following differences from *Halothane*: fewer arrhythmias, less sensitization of the heart to catecholamines, and greater potentiate of muscle relaxants, due to a more potent "curare-like" effect.

4) Isoflurane

This is a newer anesthetic that has low biotransformation and low organ toxicity. It does not induce cardiac arrhythmias and does not sensitize the heart to the action of catecholamines.

But:

It produces dose-dependent hypotension.

It has a pungent odor and stimulates respiratory reflexes (for example, breath holding, salivation, coughing, laryngospasm)

5) Sevoflurane

has low pungency, allowing rapid induction without irritating the airways

But:

May cause nephrotoxicity

6) Propofol

Induction is smooth and occurs 30 to 40 seconds after administration.

But:

- It is occasionally accompanied by excitatory phenomena (muscle twitching, spontaneous movement, yawning, and hiccups).
- Transient pain at the injection site is common.
- It does not provide analgesia

7) Thiopental

It is a potent anesthetic but a weak analgesic

But:

It can cause apnea, coughing, chest wall spasm, laryngospasm, and bronchospasm.

7) *Ketamine*

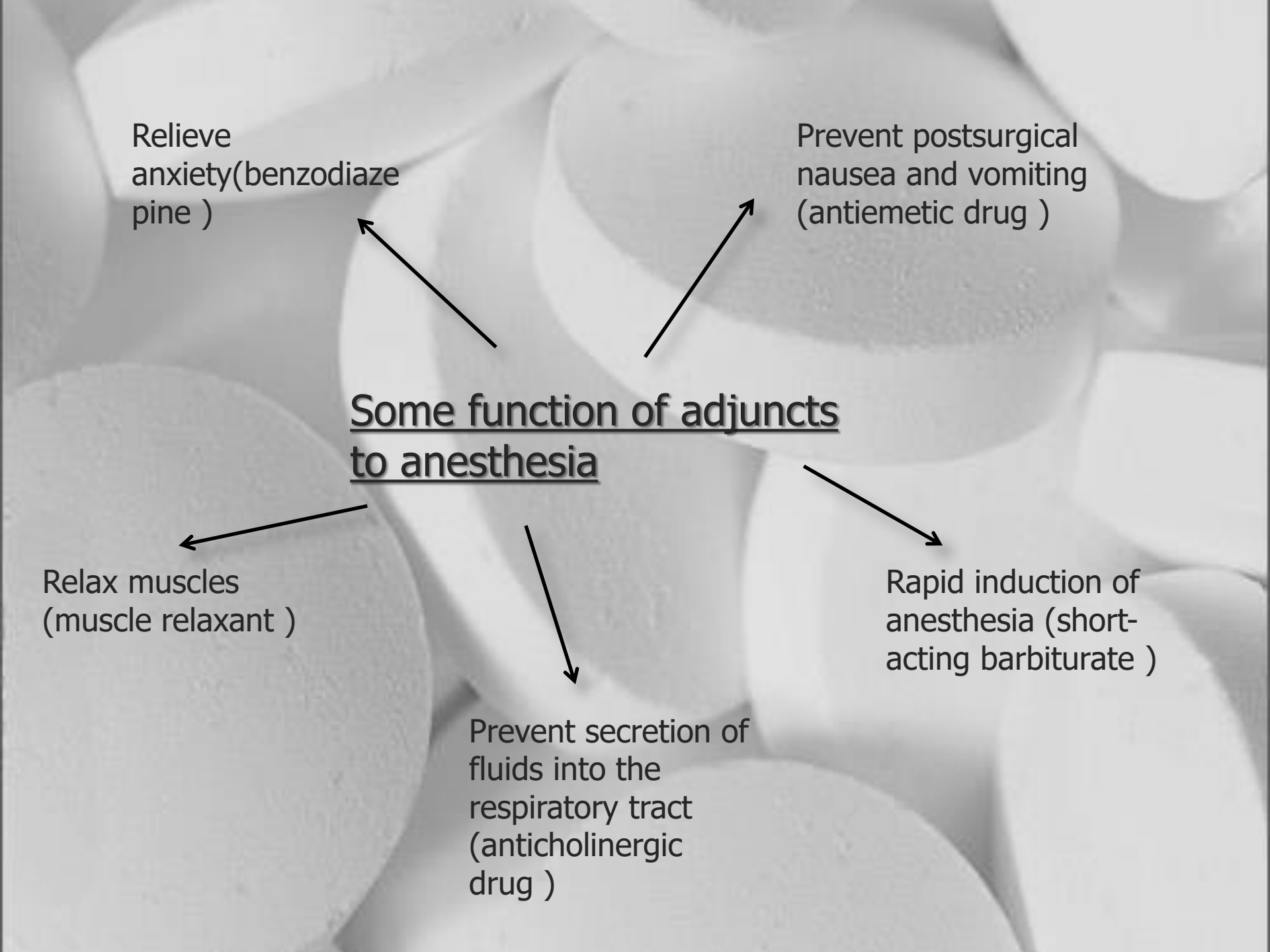
Is short-acting, induces a dissociated state in which the patient is unconscious (but may appear to be awake) and does not feel pain. This dissociative

anesthesia provides sedation, amnesia, and immobility.

But:

It stimulates central sympathetic outflow (causing increased blood pressure and CO).

It may induce hallucinations


Relieve anxiety(benzodiaze pine)
Prevent postsurgical nausea and vomiting (antiemetic drug)
Some function of adjuncts to anesthesia
Relax muscles (muscle relaxant)
Prevent secretion of fluids into the respiratory tract (anticholinergic drug)
Rapid induction of anesthesia (short-acting barbiturate)