Medicinal Chemistry

Chapter 13 & 14

ANESTHETICS

Contents

General Anesthesia

General anesthesia (GA) is the state produced when a patient receives medications for amnesia, analgesia, muscle relaxation, and sedation. An anesthetized patient can be thought of as being in a controlled, reversible state of unconsciousness. General anesthetics depress the central nervous system to a sufficient degree to permit the performance of surgery and other noxious or unpleasant procedures.

General anesthesia uses intravenous and inhaled agents to allow adequate surgical access to the operative site. A point worth noting is that general anesthesia may not always be the best choice; depending on a patient's clinical presentation, local or regional anesthesia may be more appropriate.

General anesthesia is a reversible state of CNS depression, causing loss of response to and perception of stimuli.

For patients undergoing surgical or medical procedures, anesthesia provides five important benefits:

- Sedation and reduced anxiety
- Lack of awareness and amnesia
- Skeletal muscle relaxation
- Suppression of undesirable reflexes
- Analgesia

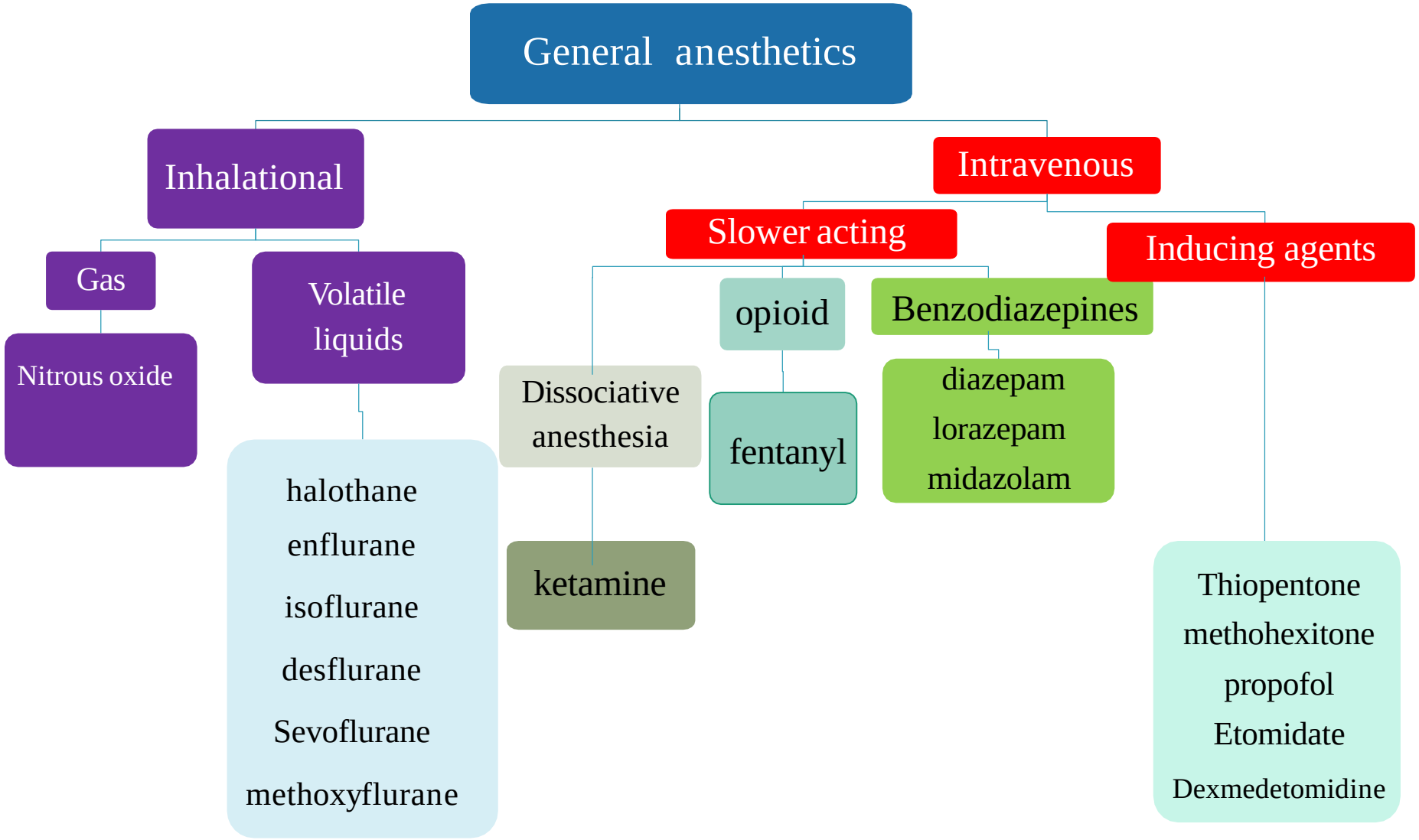
Because no single agent provides all desirable properties both rapidly and safely, several categories of drugs are combined (I.V and inhaled anesthesia and preanesthetic medications) to produce optimal anesthesia known as a **Balanced anesthesia.**

Patient factors in selection of anesthesia

Drugs are chosen to provide safe and efficient anesthesia based on:

1. The type of the surgical or diagnostic procedure
2. Patient characteristics such as organ function, medical conditions, and concurrent medications. e.g., HTN, bronchial asthma.

CLASSIFICATION



Status of organ systems

Respiratory system:

All inhaled anesthetics depress the respiratory system. They are bronchodilators.

Liver and kidney:

The release of fluoride, bromide, and other metabolic products of the halogenated hydrocarbons can affect these organs, especially with repeated anesthetic administration over a short period of time.

Pregnancy:

Effects on fetal organogenesis are a major concern in early pregnancy.

1.Nitrous oxide can cause aplastic anemia in the unborn child. Oral clefts have occurred in the fetuses of women who have received benzodiazepines.

2.Diazepam should not be used routinely during labor, because it results in temporary hypotonia and altered thermoregulation in the newborn.

Nervous system:

- The existence of neurologic disorders (e.g., epilepsy or myasthenia gravis) influences the selection of anesthetic.
- A patient history of a genetically determined sensitivity to halogenated hydrocarbon-induced **malignant hyperthermia** "an autosomal dominant genetic disorder of skeletal muscle" that occurs in susceptible individuals undergoing general anesthesia with volatile agents and muscle relaxants (eg, succinylcholine).
- The malignant hyperthermia syndrome consists of the rapid onset of tachycardia and hypertension, severe muscle rigidity, hyperthermia
- Rx Dantroline

Preanesthetic Medications

Preanesthetic medications serve to

- calm the patient, relieve pain,
- protect against undesirable effects of the subsequently administered anesthetics or the surgical procedure.
- facilitate smooth induction of anesthesia,
- lowered the required dose of anesthetic

Preanesthetic Medicine:

- Benzodiazepines; midazolam or diazepam: Anxiolysis & amnesia.
- Diphenhydramine: Prevention of allergic reactions: antihistamines

- H2 receptor blocker- famotidine, ranitidine: Reduce gastric acidity.
- Antiemetics ondansetron: Prevents aspiration of stomach contents and post surgical vomiting:
- Acetaminophen or opioids (fentanyl) for analgesia
- Anticholinergics: (glycopyrrolate, scopolamine):
- Reduce bronchial and salivary secretion: irritant inhaled anesthetic cause excessive salivation and secretion.

Stages and depth of anesthesia

General anesthesia has three stages: induction, maintenance, and recovery.

Use preanesthetic medication

↓

Induce by I.V thiopental or suitable alternative

↓

Use muscle relaxant → Intubate

↓

Use, usually a mixture of N_2O and a halogenated hydrocarbon→ maintain and monitor.

↓

Withdraw the drugs ⟶ recover

Induction: The period of time from the onset of administration of the anesthetic to the development of effective surgical anesthesia in the patient. It depends on how fast effective concentrations of the anesthetic drug reach the brain.

Thus GA is normally induced with an I.V thiopental, which produces unconsciousness within 25 seconds or propofol producing unconsciousness in 30 to 40 seconds after injection.

At that time, additional inhalation or IV drugs may be given to produce the desired depth of surgical stage III anesthesia. This often includes an IV neuromuscular blocker such as rocuronium, vecuronium, or succinylcholine to facilitate tracheal intubation and muscle relaxation.

Maintenance: After administering the anesthetic, vital signs and response to stimuli are monitored continuously to balance the amount of drug inhaled and/or infused with the depth of anesthesia.

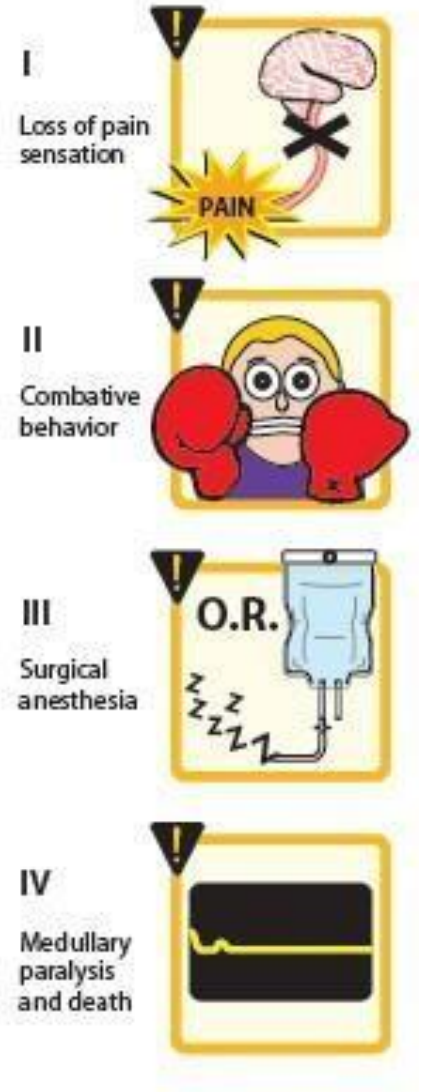
Maintenance is commonly provided with volatile anesthetics, which offer good control over the depth of anesthesia.

Recovery: The time from discontinuation of administration of the anesthesia until consciousness and protective physiologic reflexes are regained. It depends on how fast the anesthetic drug diffuses from the brain.

The patient is monitored to assure full recovery, with normal physiologic functions (spontaneous respiration, acceptable blood pressure and heart rate, intact reflexes, and no delayed reactions such as respiratory depression).

Depth of anesthesia

- Depth of anesthesia is the degree to which the CNS is depressed and is a useful parameter for individualizing anesthesia
  - Stage I Analgesia
  - Stage II Delirium
  - Stage III Surgical anesthesia
  - Stage IV Medullary paralysis



Stage I (Analgesia): The patient is conscious and experiences sensations of warmth, remoteness, drifting, falling, and giddiness. There is a marked reduction in the perception of painful stimuli. This stage is used often in obstetrics and minor surgery.

Stage II (Delirium): This stage begins with the loss of consciousness. Depression of higher centres produces a variety of effects including excitement, involuntary activity, and increased skeletal muscle tone and respiration.

Stage III (Surgical anaesthesia): This is the stage of unconsciousness and paralysis of reflexes. Respiration is regular and blood pressure is maintained. All surgical procedures are carried out in this stage.

Stage IV (Medullary paralysis): Respiratory and circulatory failures occur as depression of the vital centres of the medulla and brain stem occur.

Inhalation anesthetics

Inhaled gases are used primarily for maintenance of anesthesia.

Depth of anesthesia can be rapidly altered by changing the inhaled concentration.

Common features of inhaled anesthetics

- Modern inhalation anesthetics are nonflammable, nonexplosive agents.
- Decrease cerebrovascular resistance, resulting in increased perfusion of the brain
- Cause bronchodilation, and decrease both spontaneous ventilation and hypoxic pulmonary vasoconstriction (increased pulmonary vascular resistance in poorly aerated regions of the lungs, redirecting blood flow to more oxygenated regions).
- Movement of these agents from the lungs to various body compartments depends upon their solubility in blood and tissues, as well as on blood flow. These factors play a role in induction and recovery.

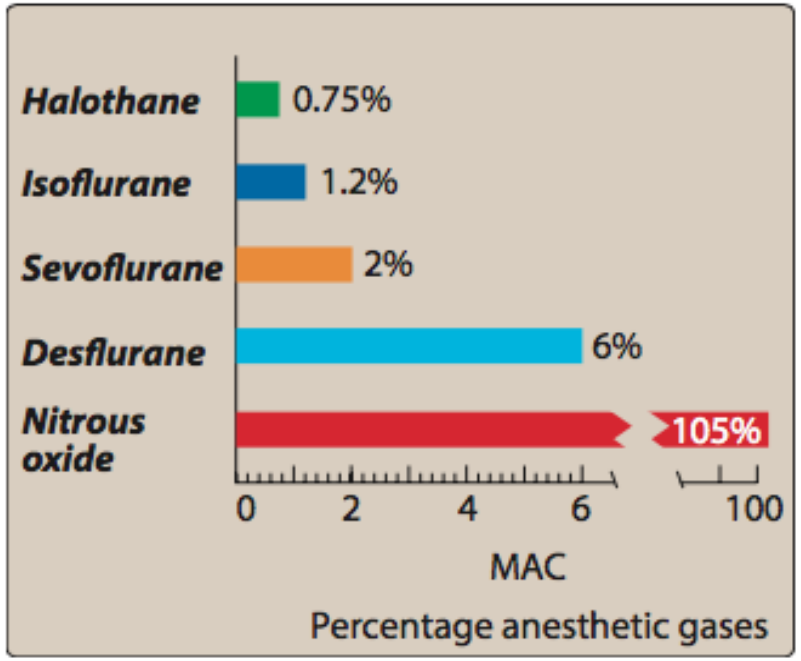
Minimum alveolar concentration

MAC (potency): is the concentration of a vapour in the alveoli of the lungs that is needed to prevent movement (motor response) in 50% of subjects in response to surgical (pain) stimulus.

- MAC is the ED_{50} of the anesthetic.

MAC expressed as the percentage of gas in a mixture required to achieve the effect.

Numerically, MAC is small for potent anesthetics such as sevoflurane and large for less potent agents such as nitrous oxide.



Uptake and distribution of inhalation anesthetics

- The principal objective of inhalation anesthesia is a constant and optimal brain partial pressure (P_{br}) of inhaled anesthetic (partial pressure equilibrium between alveoli [P_{alv}] and brain [P_{br}]).

- Thus, the alveoli are the "windows to the brain" for inhaled anesthetics.

- The partial pressure of an anesthetic gas at the origin of the respiratory pathway is the driving force moving the anesthetic into the alveolar space and, thence, into the blood (P_a), which delivers the drug to the brain and other body compartments.

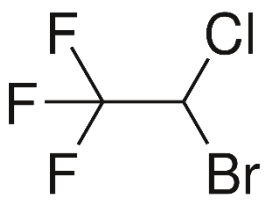
- Because gases move from one compartment to another within the body according to partial pressure gradients, a **steady state** (SS) is achieved when the partial pressure in each of these compartments is equivalent to that in the inspired mixture.

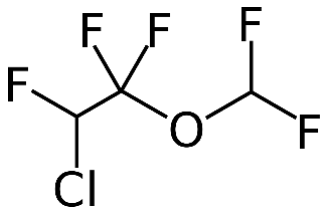
$$\mathbf{P_{alv} = P_a = P_b}$$

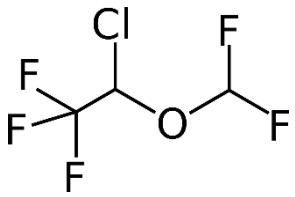
Factors Determine the time course for attaining Steady State:

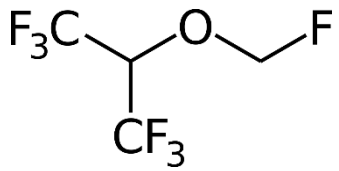
- Solubility in the blood: called the blood/gas partition coefficient.
- The solubility in blood is ranked in the following order:

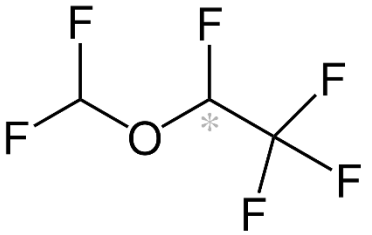
halothane>enflurane>isoflurane>sevoflurane>desflurane>N_2O.











- An inhalational anesthetic agent with low solubility in blood shows fast induction and also recovery time (e.g., N_2O), and an agent with relatively high solubility in blood shows slower induction and recovery time (e.g., halothane).

Effect of different tissue types on anesthetic uptake:

- It is also directly proportional to the capacity of that tissue to store anesthetic (a larger capacity results in a longer time required to achieve steady state).

- Capacity, in turn, is directly proportional to the tissue's volume and the tissue/ blood solubility coefficient of the anesthetic.

Four major tissue compartments determine the time course of anesthetic uptake:

a. **Brain, heart, liver, kidney, and endocrine glands:** these highly perfused tissues rapidly attain a SS

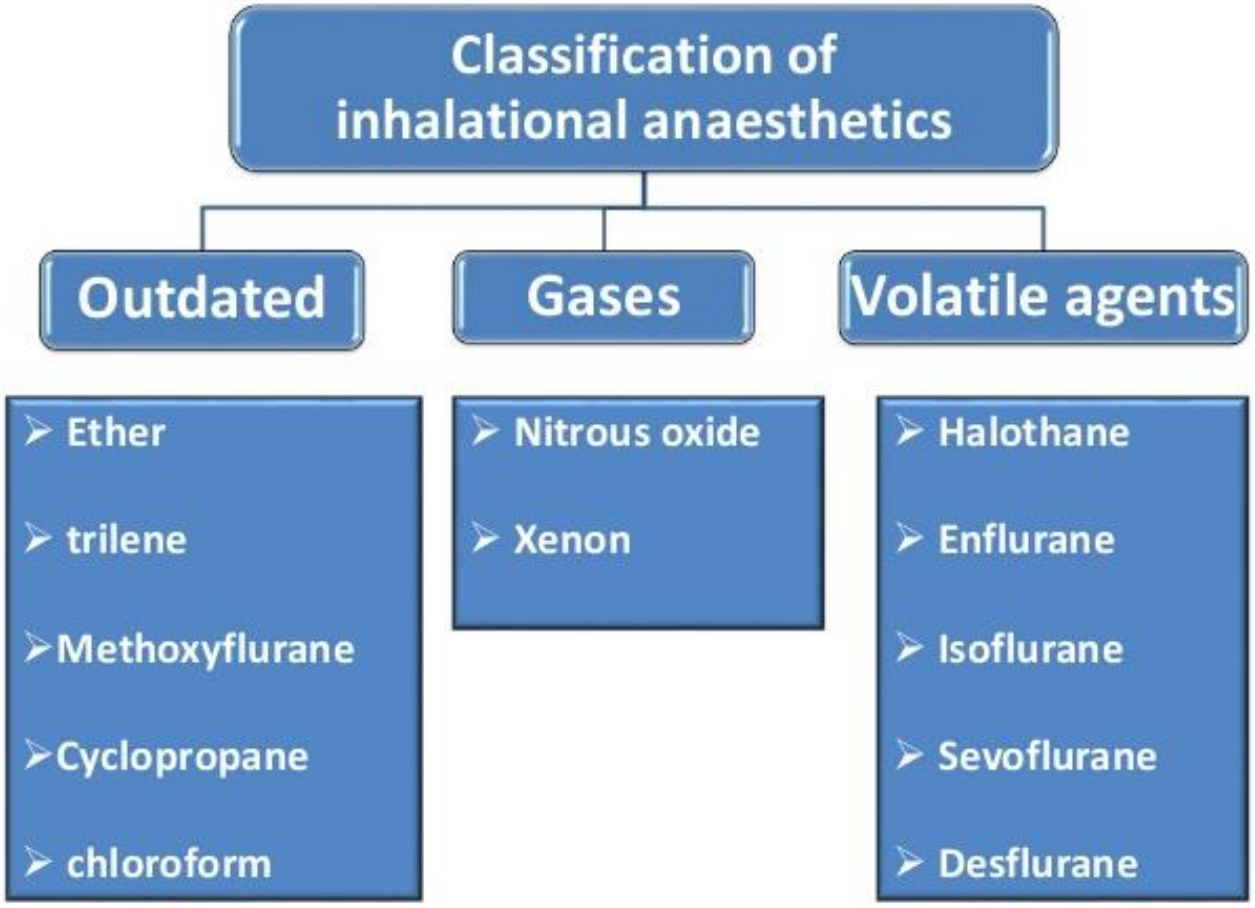
b. **Skeletal muscles:** poorly perfused, and have a large volume, prolong the time required to achieve SS

c. **Fat:** poorly perfused. However, potent GA are very lipid soluble. Therefore, fat has a large capacity to store anesthetic. So slow delivery to a high capacity and prolongs the time required to achieve SS

d. **Bone, ligaments, and cartilage:** these are poorly perfused and have a relatively low capacity to store anesthetic.

The ideal should:

1. high margin of safety,
2. have rapid and pleasant induction and recovery,
3. be easily controlled and regulated,
4. have no side-effects or toxicity,
5. should not depress the cardiovascular and respiratory systems,
6. be non-flammable and non-explosive,
7. provide good analgesia and muscle relaxation,
8. and have low cost.



Mechanisms of anesthesia

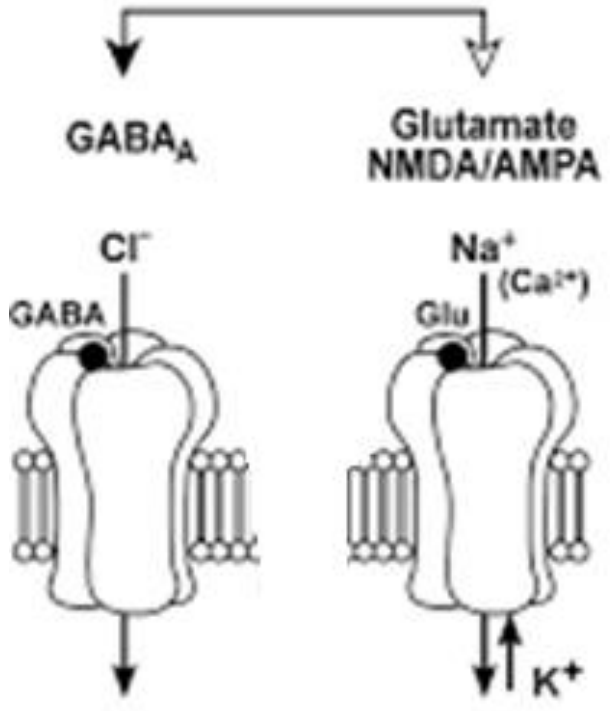
1-Blocking the NMDA and glutamate controlled channels.

Glutamate or NMDA (N-methyl-D-aspartate) receptors in the CNS are activated by the excitatory AA neurotransmitter glutamic acid. This activation opens the channel, allowing K^+ to flow to the extra cellular fluid and Na and Ca^{++} to flow into the nerve cell.

2- Activation of the inhibitory GABA receptor controlled channel.

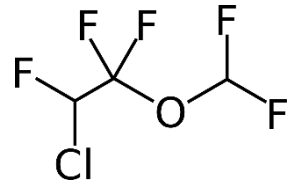
Binding of GABA (inhibitory transmitter) to their receptors will open the Cl^- channel, leading to the influx of Cl^- and hyper- polarization of the neuron.

Halothane and isoflurane inhibit the synaptic destruction of GABA, thereby increasing the GABA-ergic neurotransmission.

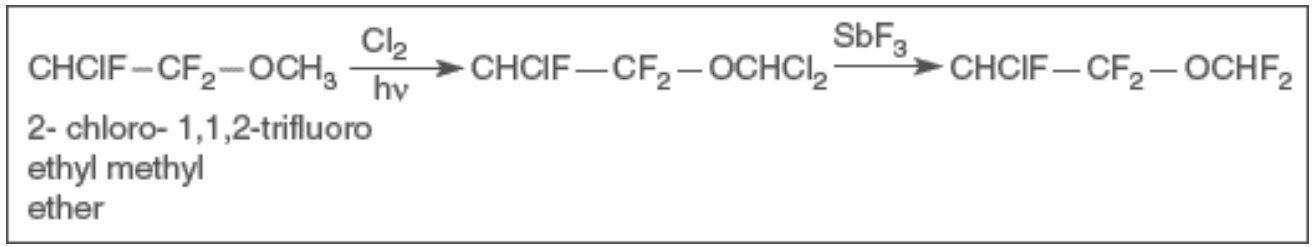


Enflurane

2-Chloro-1,1,2-trifluoroethyldifluoromethyl ether



***Synthesis*



Dose:

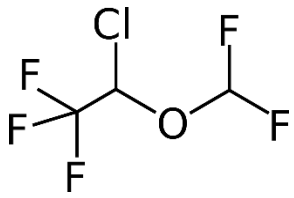
Induction: 2.0%–4.5% in oxygen or with oxygen-nitrous oxide mixtures. Induction usually requires 7–10 minutes. Maintenance usually is accomplished with 0.5%–3% concentrations.

Adv.
pleasant-smelling, non-flammable, halogenated ether anaesthetic that provides rapid induction with little or no excitement.

Dis. Adv.
high concentrations may cause CVS depression and CNS stimulation.

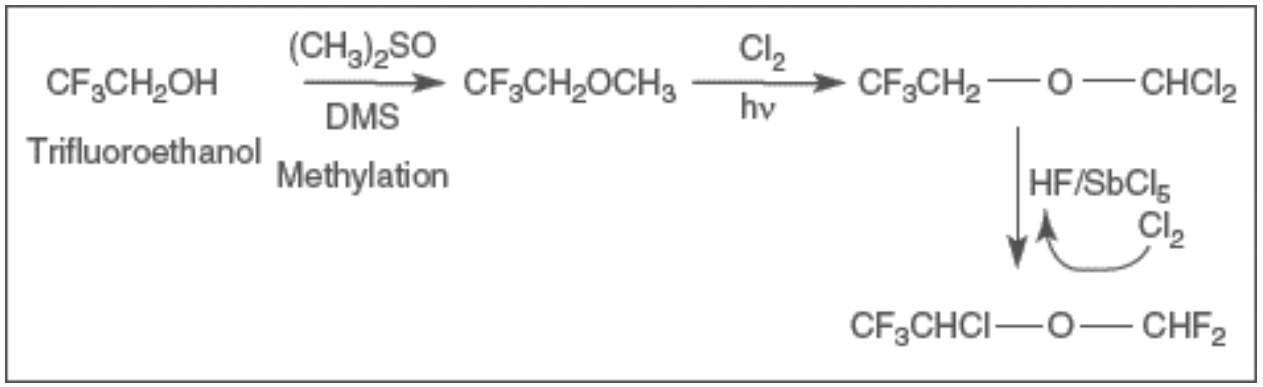
Isoflurane

1-Chloro-2,2,2-trifluoroethyl difluoromethyl ether



***Synthesis*

Methylating the 2,2,2-trifluoro/ethanol by with dimethylsulphate



Uses:

Adv.
is a non-flammable inhalation anaesthetic for induction and maintenance of general anaesthesia. Induction of and recovery from isoflurane anaesthesia is rapid. Isoflurane is said to offer advantages over all available inhalation anaesthetics, especially in its lack of any important toxicity.

Dose:

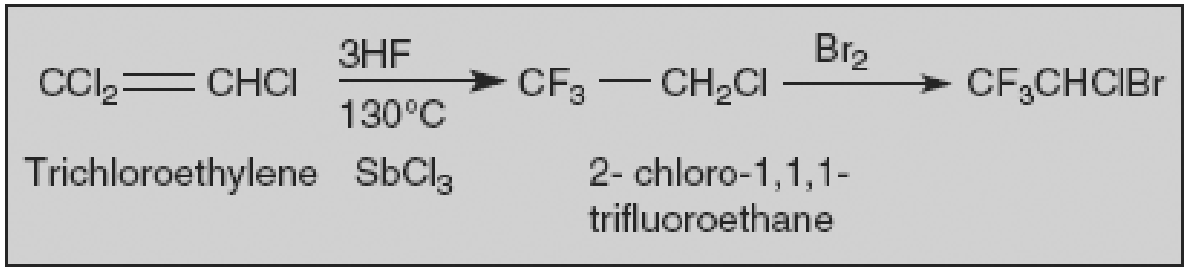
Induction: 1.5%–3.0% usually produce surgical anaesthesia in 7–10 minutes. Surgical levels of anaesthesia can be sustained with 1.0%–2.5% concentrations when nitrous oxide is used concomitantly.

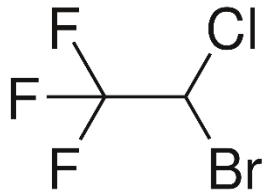
Halothane

2-Bromo-2-chloro-1,1,1- trifluoroethane

Synthesis

Addition of hydrogen fluoride to tricholoroethylene





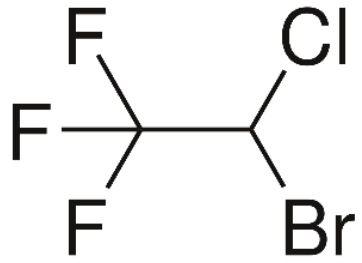
Uses:

Halothane is a potent, relatively safe, frequently employed general inhalation anaesthetic. Induction with halothane is smooth and rapid with little or no excitement. It is not a potent analgesic and skeletal muscle relaxant. Therefore, it is used frequently in conjunction with nitrous oxide and with succinylcholine, tubocurarine, or gallamine.

Dose:

For induction: 1.0%–4.0% vaporized by a flow of oxygen or nitrous oxide-oxygen mixture. For maintenance: 0.5%–1.5%.

Halothane



Advantages:

- Potent anesthetic, rapid induction &recovery
- Neither flammable nor explosive, sweet smell, non irritant
- Does not augment bronchial and salivary secretions.
- Low incidence of post operative nausea and vomiting.
- Relaxes both skeletal and uterine muscle, and can be used in obstetrics when uterine relaxation is indicated.
- Combined with its pleasant odor, this makes it suitable in children for inhalation induction.

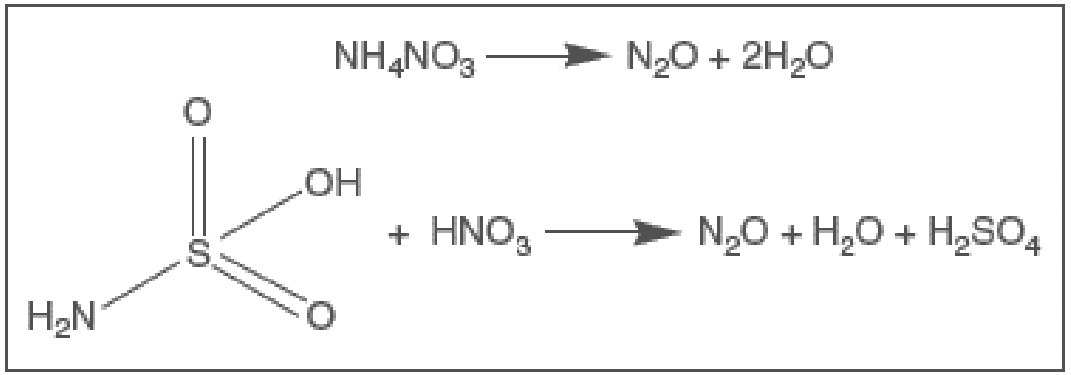
Disadvantages:

- Weak analgesic (thus is usually coadministerd with N_2O,opioids)
- Is a strong respiratory depressant
- Is a strong cardiovascular depressant; halothane is vagomimetic and cause atropine-sensitive bradycardia.
- Hepatotoxic: is oxidatively metabolized in the liver to tissuetoxic hydrocarbons (e.g., trifluroethanol and bromide ion).
- Malignant hyperthermia

Nitrous oxide

Synthesis

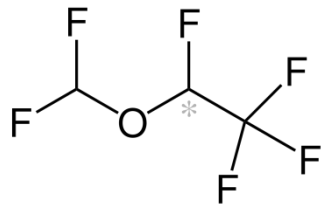
Thermal decomposition of ammonium nitrate



Dose: Analgesia: 25%–50%; maintenance: 30%–70%. Administered with at least 25%–30% oxygen

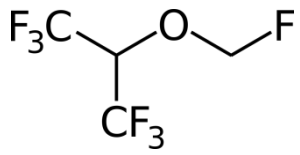
- ***It is a potent analgesic but a weak general anesthetic.***
- ***Rapid onset and recovery:***
- ***Does not depress respiration, and no muscle relaxation.***
- ***Clinical use: dental surgery, obstetrics, postoperative physiotherapy, refractory pain in terminal illness, and maintenance of anesthesia.***

Desflurane



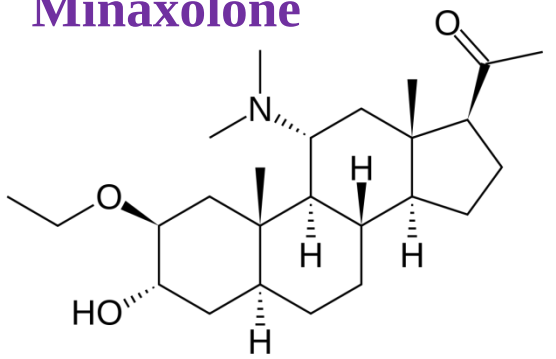
Used for maintenance of general ANA. Together with sevoflurane, it is gradually replacing isoflurane for human use. It has the most rapid onset and offset of the volatile ANA drugs used for general ANA due to its low solubility in blood.

Sevoflurane



It is a sweet-smelling, non-flammable, highly fluorinated methyl isopropyl ether used for induction and maintenance of general ANA. Together with desflurane, it is replacing isoflurane and halothane in modern anaesthesiology. It is often administered in a mixture of nitrous oxide and oxygen.

Minaxolone



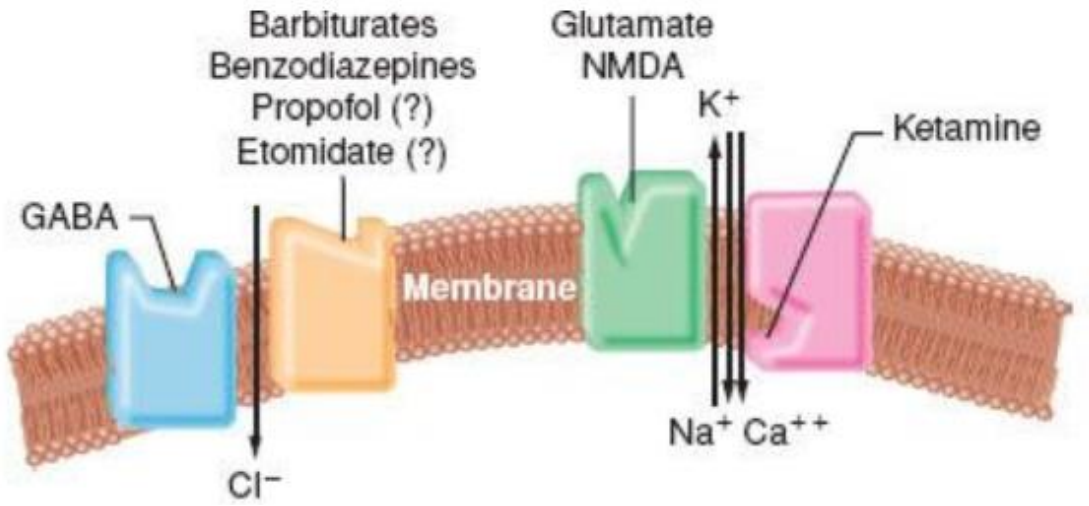
It is a new water-soluble steroid ANA, and it appears to be a safe and effective intravenous ANA with impressive recovery characteristics. Its only drawback would seem to be its high incidence of excitatory movements and hypertonus. It appears to be a promising intravenous anaesthetic agent worthy of further clinical investigation.

Intravenous Anesthetics

- Include:
  - Barbiturates
    - Thiopental & Methohexital
  - Opioids
    - Alfentanil, Meperidine, Fentanyl, Sufentanil (agonists)
    - Naloxone (antagonist)
  - Benzodiazepines
    - Diazepam, Midazolam
    - Flumazenil (antagonist)
  - Miscellaneous Agents
    - Etomidate – non-barbiturate hypnotic agent without analgesic properties
    - Droperidol - Neuroleptic (similar to Haloperidol) - combined with Fentanyl and is used for neuroleptanalgesia (state of analgesia and amnesia)
    - Ketamine - dissociative anesthetic
    - Propofol

General Uses of IV Anesthetics

- **Primary Use = induction of general anesthesia**
  - Supplement general anesthesia
  - maintain general anesthesia
  - provide sedation
  - control Blood Pressure

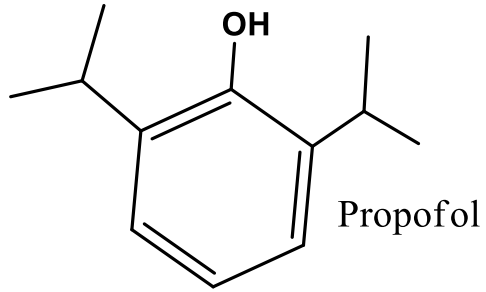


Mechanisms of Action

- Enhanced GABA effect on SABA Receptors: Etomidate, Barbiturates, Propofol, Benzodiazepines
- Activate K channels (hyperpolarize): ketamine, xenon
- Inhibit NMDA glutamate) receptors: ketamine, xenon, high dose barbiturates
- Inhibit synaptic proteins (reduce NT release) amnesia)
- Enhance glycine effect on glycine Rs (immobility)

Propofol (Deprivan)

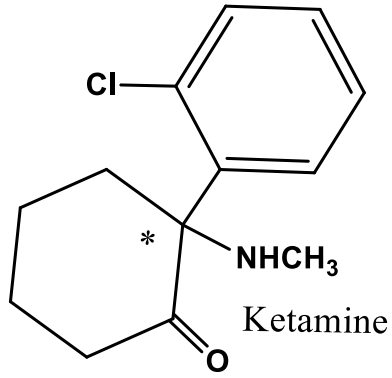
2,6-Di-isopropylphenol



- Propofol is a short acting anesthetic that act via enhancing the GABA-ergic neurotransmission in the CNS. It binds allosterically to GABA receptor at a site different from that of benzodiazepines. It achieves hypnosis in one minute & lasts for 5 minutes.
- Maintenance of anesthesia is achieved with volatile anesthetics or additional doses of it.
- It is formulated as 1 or 2% emulsion in soybean oil or glycerol.
- It is more, effective than thiopental. Rarely associated with vomiting.
- Metabolism proceeds rapidly via glucuronide and sulfate conjugation in liver.

Ketamine

2-(2-Chlorophenyl)-2-methylaminocyclohexanone



Ketamine

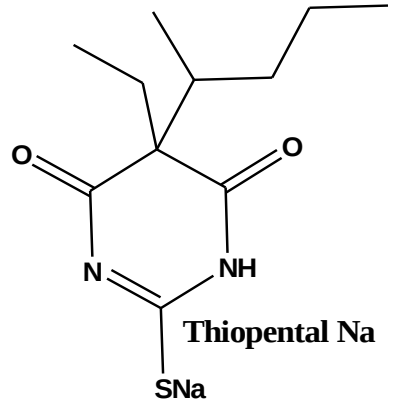
- Ketamine hydrochloride is a very potent, rapidly acting anesthetic agent.
- The S (+) ketamine is two to three times more potent than the R (-) ketamine as an analgesic.
- Its duration of action is relatively short (10-25 minutes).
- It produces anesthesia by blocking the NMDA controlled channels.

- ketamine is suitable for diagnostic purposes and for surgical procedures that do not require muscle relaxation.
- Patients older than 16 will often (27%) have wild dreams and hallucinations during emergence, that may last for 24 hours and so it is only indicated for children less than 16 years old.

Ultrashort-acting barbiturates:

A- Thiopental sodium

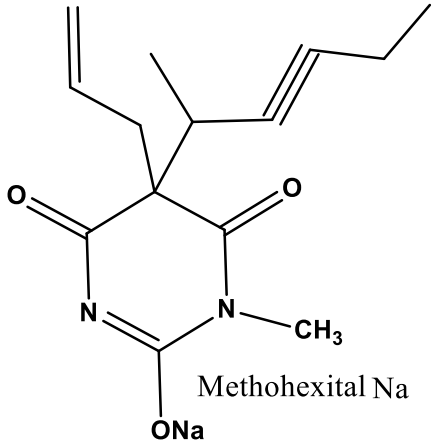
- Used to produce rapid unconsciousness for surgical and basal anesthesia (induce anesthesia).
The induction is very rapid. The long side chain substitution at position-5 is an essential feature for increasing lipid solubility and hence the rate of passing through the BBB.



Thiopental Na

- It is the most widely used ultrashort-acting barbiturate. The presence of sulfur in **thiopental** increases lipid solubility and facilitates its entry to the brain.
- Its short duration of action is due to partitioning from the brain into body fat. It is metabolized by oxidative desulphurization

B- Methohexital sodium

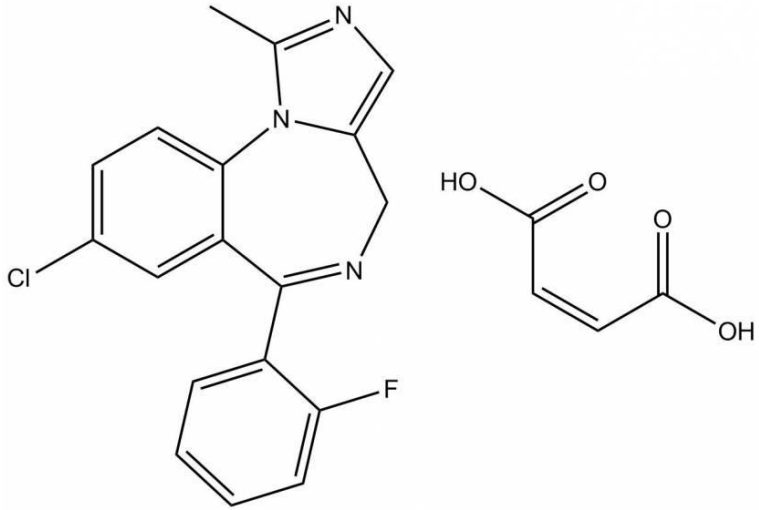


Methohexital Na

- It is N-methylated barbiturate that has pKa of 8.4, versus 7.6 for the non-methylated compound.
- This pKa value increases the concentration of the lipid-soluble free acid form at the physiological pH.
- N-methylation decreases duration of action.
- The compound also has extensive hydrophobic character because the long unsaturated side chains (9-Cs).
- Overall, it can rapidly penetrate the CNS after IV injection and then redistribute rapidly to other body sites and undergo rapid metabolic inactivation.
- Finally, it has an accessible site of metabolic inactivation, the CH_2 α to the triple bond.

Benzodiazepines

-Benzodiazepines alone can not produce surgical anesthesia. However, some benzodiazepines are used to induce anesthesia. e.g: Medazolam maleate



Adjuvant to general anesthesia

1.Narcotic analgesics: such as morphine and meperidine to reduce anxiety .

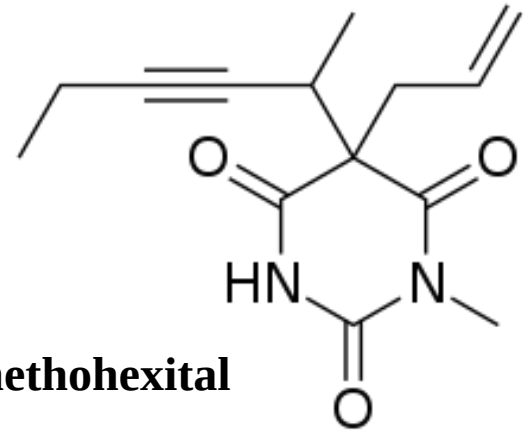
2.Sedatives: such as benzodiazepines, to produce sedation and reduce anxiety.

3.Anticholinergics: such as scopolamine, to inhibit excessive respiratory secretion.

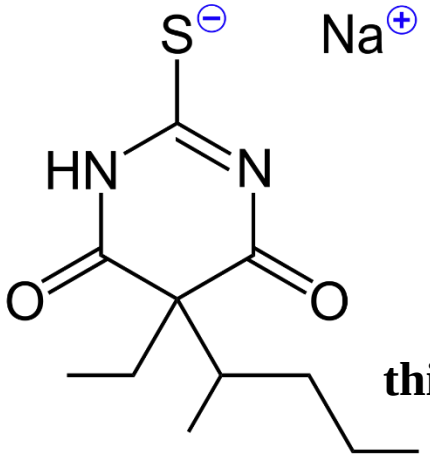
4.Skeletal muscle relaxants: such as succinylcholine and vencuronium to relax the muscles for optimum surgical working conditions.

Barbiturates (thiopental, methohexital)

- Potent anesthetic but a weak analgesic
- High lipid solubility; quickly enter the CNS and depress function, often in less than one minute, and redistribution occur very rapidly as well to other body tissues, including skeletal muscle and ultimately adipose tissue (serve as a reservoir).
- All barbiturates can cause apnea, coughing, chest wall spasm, laryngospasm, and bronchospasm



methohexital



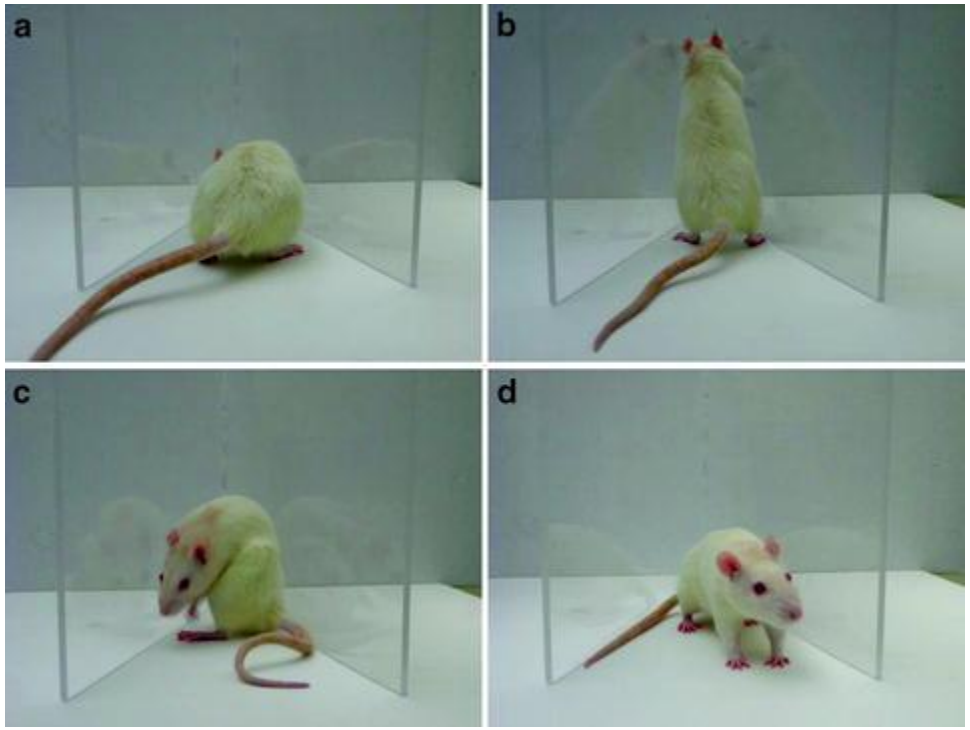
thiopental

Anesthetic Toxicity

The conventional view of general anesthesia is that anesthetics produce a reversible loss of consciousness and that CNS function returns to basal levels upon termination of anesthesia and recovery of consciousness.

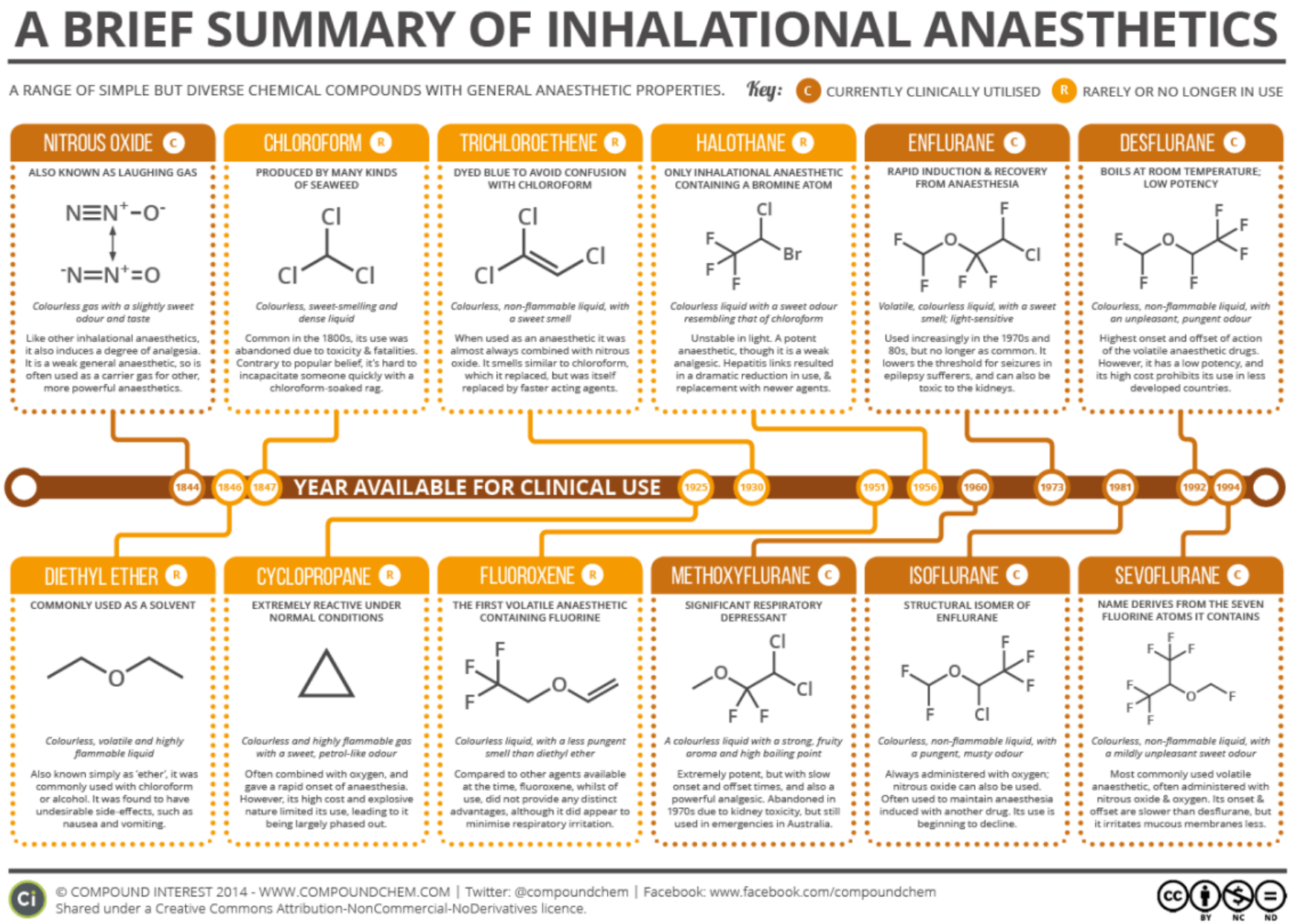
Recent data, however, have cast doubt upon this notion. Exposure of rodents to anesthetic agents during the period of birth results in widespread neurodegeneration in the developing brain. This neuronal injury, which is apoptotic in nature, results in disturbed electrophysiologic function and cognitive dysfunction in adolescent and adult rodents that were exposed to anesthetics during the neonatal period.

A variety of agents, including isoflurane, propofol, midazolam, nitrous oxide, and thiopental, manifest this toxicity.



Click to enlarge

https://i0.wp.com/www.compoundchem.com/wp-content/uploads/2014/11/Brief-Guide-to-Inhalational-Anaesthetics-2016.png?ssl=1



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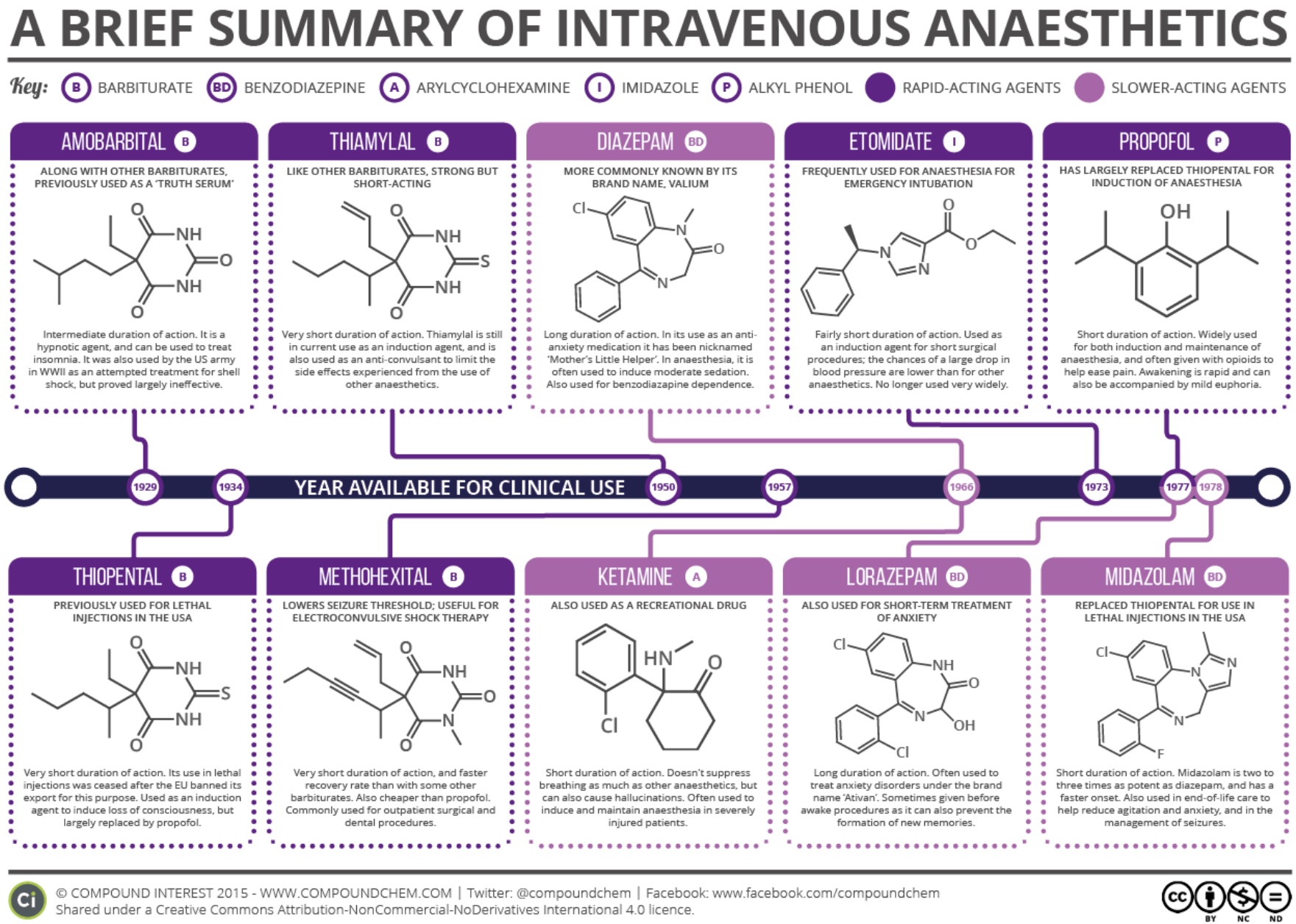


Local Anesthetic

- Local anesthetics are drugs used to reversibly depress CNS to prevent or relieve pain in specific regions of the body without loss of consciousness
- Unlike General Anesthetics, they generally don't block sense of touch, pressure or temperature or relax skeletal muscles
- Uses
  - Dentistry
  - Podiatry (treatment of disorders of the foot, ankle, and leg)
  - ENT operations
  - Surgery of skin
  - Labor pain
  - Postoperative pain
  - Skin Trauma

General Vs. Local Anesthetic

General Anesthetic	Local Anesthetic
Blocks pain in entire body	Blocks pain in specific region on body
Blocks sensation of temperature, touch and pressure	Selective to blocking pain only.
Muscle relaxation occurs	Muscle relaxation not caused
Drug intended to penetrate brain	Drug not intended to penetrate brain but act on local nerves branches
Receptor is ligand gated chlorine channel and binding site is outside of cell membrane	Receptor is voltage gated Sodium channel and binding site is inside of cell membrane

HISTORY

3000 B.C.: cocaine "Niemann"

1905: procaine "Einhorn"

1932: Tetracaine "Eisler"

1943: Lidocaine "Lofgren"

1957: Mepivacaine "Ekenstam"

1960: Prilocaine "Löfgren."

1963: Bupivacaine "Ekenstam"

1972: Etidocaine

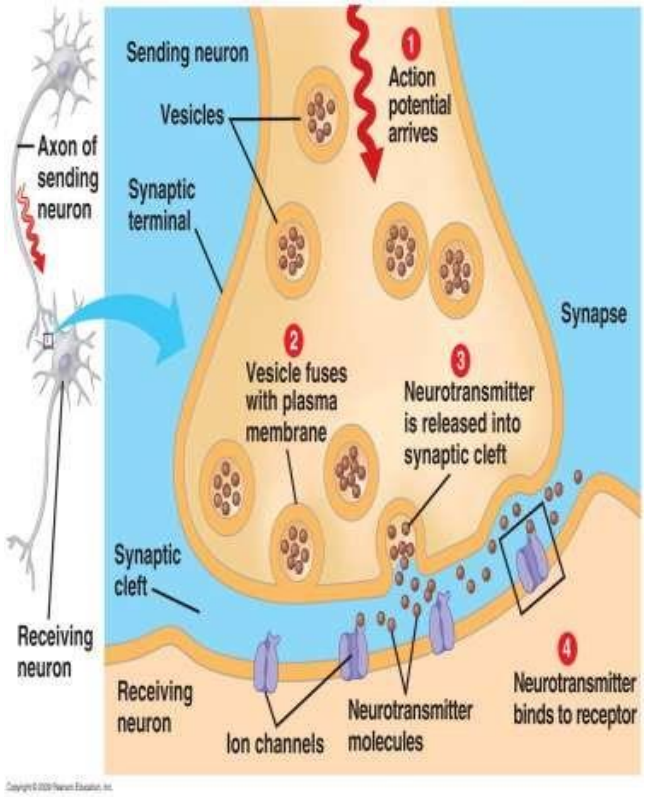
1996: Ropivacaine

1999: Levobupivacaine

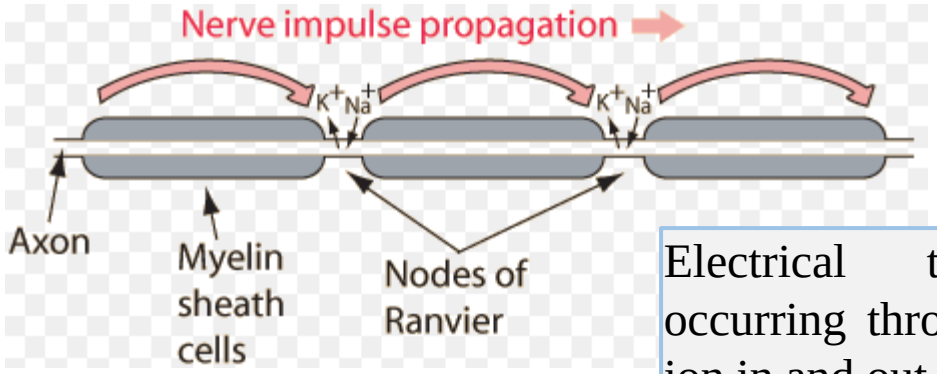
- The first local anesthetic introduced into medical practice Cocaine, was isolated from coca leaves by Albert Niemann in Germany in the 1860s.
- The very first clinical use of Cocaine was in 1884 by Sigmund Freud who used it to wean a patient from morphine addiction.
- Freud and his colleague Karl Kollar first noticed its anesthetic effect and introduced it to clinical ophthalmology as a topical ocular anesthetic.

How Nerve conduction occurs?

- Nerve conduction is a both electrical and chemical component
- The electrical component occurs within the axon. It involves membrane bound voltage gated ionic channels (responds to change in voltage across the membrane)
- The chemical component occurs at **synapse**. It involves *membrane bound* **ligand** gated *ionic channel (responds to binding of a NT)*

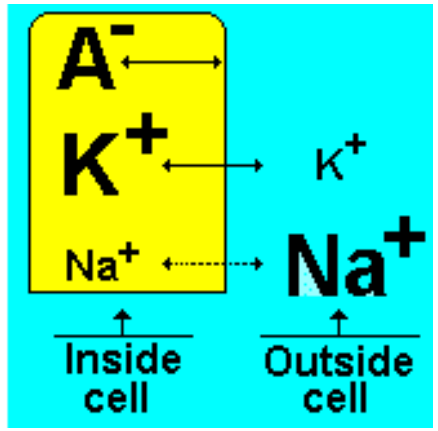


Chemical transmission of stimuli occurring at synapse through NT binding to their receptors

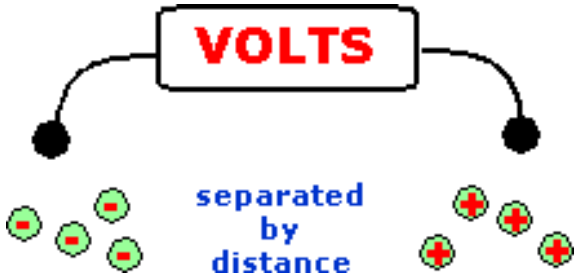


Electrical transmission of stimuli occurring through axon by movement of ion in and out

Concept of potential difference and its generation (-70mV) in resting cell

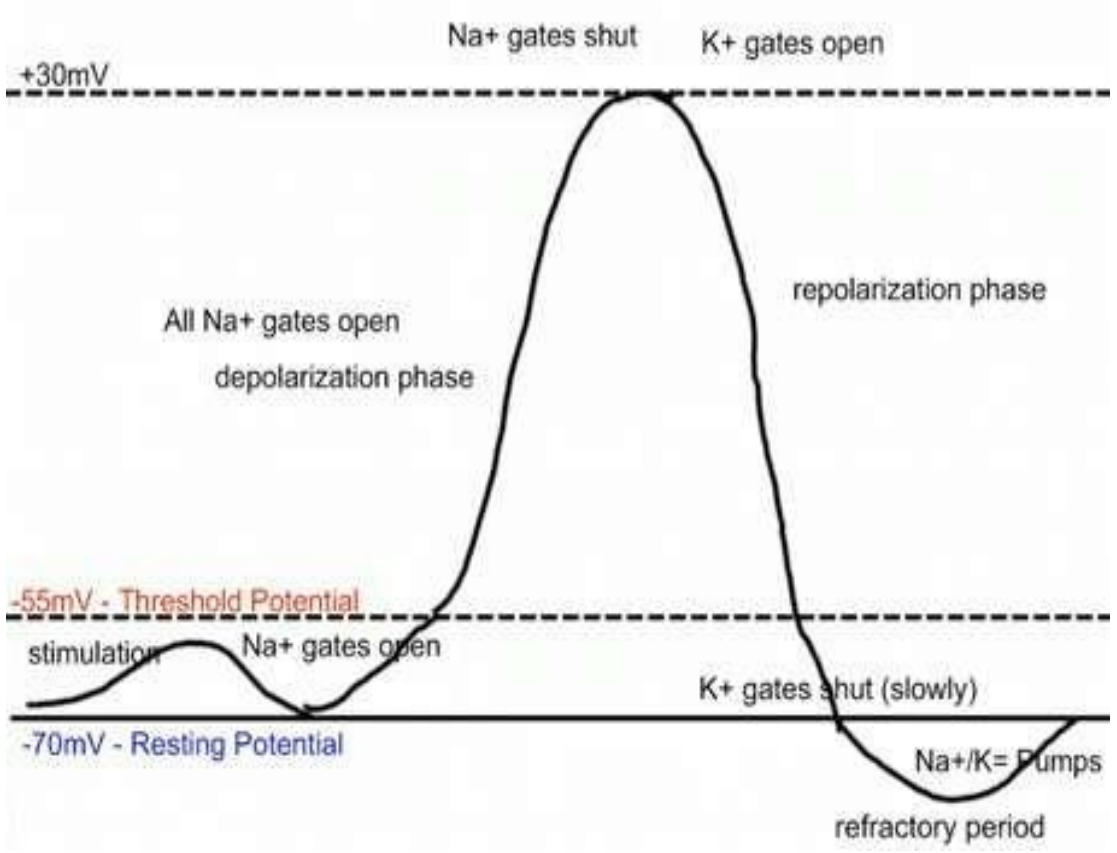


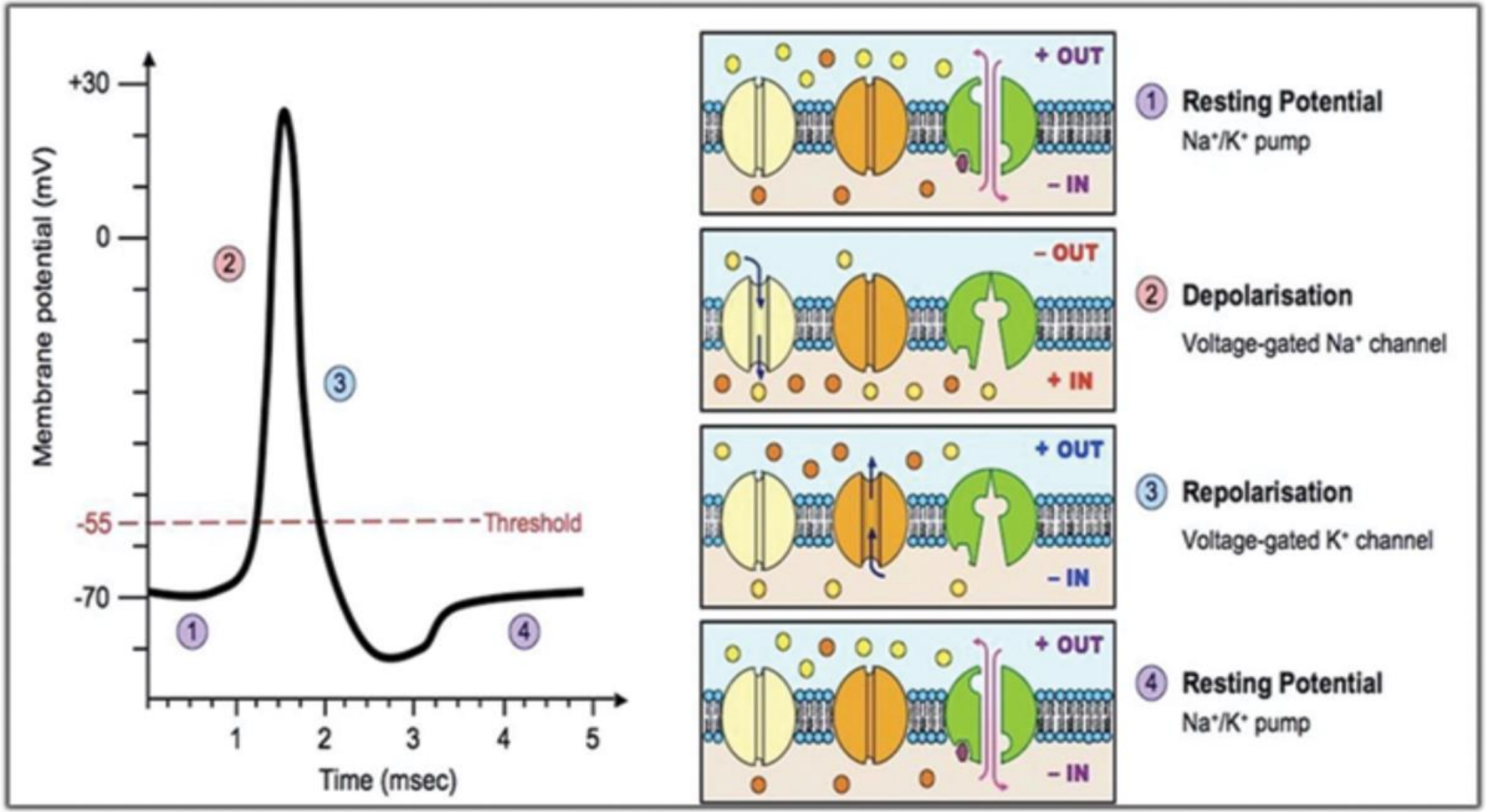
- When charges are separated by distance, potential **difference** is created
- The **inside** of cell has more potassium and less Sodium and large anionic Protein (A-) **that cannot cross the lipid membrane and is thus localized inside the cell**
- The **outside** of the cell has more Sodium and less potassium
- This difference is maintained by **Na/K** pumps that pump in 2K+ ion in cell and pump out **3Na+** ion out. Thus one extra positive charge out
- Overall, the **inside** of the cell has more **negative charge** and the **outside** has more **positive charge**
- This gives the cell a resting potential of -70mV



Steps in a action potential

1. A stimulus from a sensory cell or another neuron causes the target cell to depolarize toward the threshold potential.
2. If the threshold of excitation (-55mV) is reached, all Na+ channels open and the membrane **depolarizes**.
3. At the peak action potential (+30mV) K+ channels open and K+ begins to leave the cell. The membrane starts to **repolarized.** At the same time, all Na+ channels close.
4. The membrane becomes **hyperpolarized** (-90mV) as K+ ions continue to leave the cell. The hyperpolarized membrane is in a refractory period and cannot initiate another action potential
5. The K+ channels close and the Na+/K+ transporter restores the **resting potential** (-70mV).




+30
0
-55
-70
Membrane potential (mV)
Threshold
1
2
3
4
5
Time (msec)
1
2
3
4
+ OUT
– IN
– OUT
+ IN
+ OUT
– IN
+ OUT
– IN
1 Resting Potential
Na+/K+ pump
2 Depolarisation
Voltage-gated Na+ channel
3 Repolarisation
Voltage-gated K+ channel
4 Resting Potential
Na+/K+ pump

Changes in the resting membrane potential

Cell state	Active receptors	Potential
Resting potential	Na/K Atphase pump active	-70mV
Stimuli causes Depolarization beyond threshold potential (-55mV)	Voltage gated Na+ channel open Na comes inside cell	+30mV
Repolarized state	Voltage gated Na+ channel close Voltage gated K+ channel open K goes outside cell	+30 to -70mV
Hyperpolarized state	Voltage gated K+ channel close slowly	-90mV
Resting potential	Na/K Atphase pump active	-70mV

PROPERTIES OF AN IDEAL L.A

1. Its actions must be reversible.
2. It should be non irritating to the tissues.
3. It should have long shelf life.
4. It should be rapid in action
5. It should have a low degree of systemic toxicity.
6. It should have sufficient potency to provide complete local anesthesia.
7. It should be of sufficient duration to be advantageous.
8. It should have sufficient penetrating properties.
9. It should be either sterile or capable of being sterilized by heat without deterioration.
10. It should be stable in solution and undergo bio transformation readily within the body.
11. It should not produce any local reactions.
12. It should not produce any permanent damage.
13. It should not produce allergic reactions.
14. It should be stable in light.
15. It should be non addictive.
16. It should be combined with other agents.
17. It should have high therapeutic ratio.

CLASSIFICATION

- Method of administration.
- Classification on the basis of mode of application
- Based on duration of action
- Based on origin
- Based on chemical structure

➢ Method of administration.

Method of adm.	Definition	e.g. Clinical use
Surface anesthesia	application LA to the surface of the skin or mucosa	Eye surgery Dentistry, Surgery of skin
Infiltration anesthesia	injection of LA into the tissue	minor surgical and dental procedures
Nerve block	Injected of LA in the vicinity of major nerve or major branch nerve	surgical, dental, and diagnostic procedures and for pain management
epidural anesthesia	injected of LA into the epidural space where it acts primarily on the spinal nerve roots	Labor pain Postoperative pain
Spinal anesthesia	injected LA into the cerebrospinal fluid, usually at the lower back, where it acts on spinal nerve roots and part of the spinal cord.	operations below the umbilicus and Leg
Sympathetic block	injected LA around sympathetic nerves	Block some kind of pain (Cancer)

➢ Applications of LA

- ***A topical anesthetic*** is a local anesthetic that is used to numb the surface of a body part. They can be used to numb any area of the skin as well as the front of the eyeball, the inside of the nose, ear or throat, the anus and the genital area. Topical anesthetics are available in creams, ointments, aerosols, sprays, lotions, and jellies. Examples include benzocaine, lidocaine, oxybuprocaine,

- ***Infiltration*** It is the application of LA in intradermal or subcutaneous layers, were only the nerve fibers near the injected site is affected. The adequate dosage required depends on the extent of the area to be anesthetized and the expected duration of the surgical procedure.
    - Patients frequently experience pain immediately after infiltration injection of local anesthetic solutions. This response is due in part to the acidic nature of these solutions.
    - Used for postoperative pain control at incision site and suturing

❑ *Epidural block*

- Application of LA in the epidural space, ie just outside of the sac of cerebrospinal fluid, and thus blocking the transmission of pain signals from peripheral sensory neuron

Uses

- More effective and safe than N_2O during labor pain
- Management of back pain for hospitalized patient
- As a supplement to general anesthesia so that use of opiod analgesics can be avoided
- gynaecological surgery, orthopaedic (muscle n bone) surgery, vascular (artery n veins) surgery

❑ *Spinal block*

- Application of LA in the region containing cerebrospinal fluid ,which holds the spinal cord, thus blocking the transmission of pain signals from peripheral sensory neuron

Uses

- Total Hip Replacement, Total Knee Replacement, Caesarean sections, Lower limb Vascular surgery
- *limited to procedures involving regions below the upper abdomen.*
- Use in higher levels may affect the **ability to breathe** by paralyzing the intercostal respiratory muscles and the **disturb heart rate** by paralyzing cardiac nerve fibres

➢ Based on duration of action

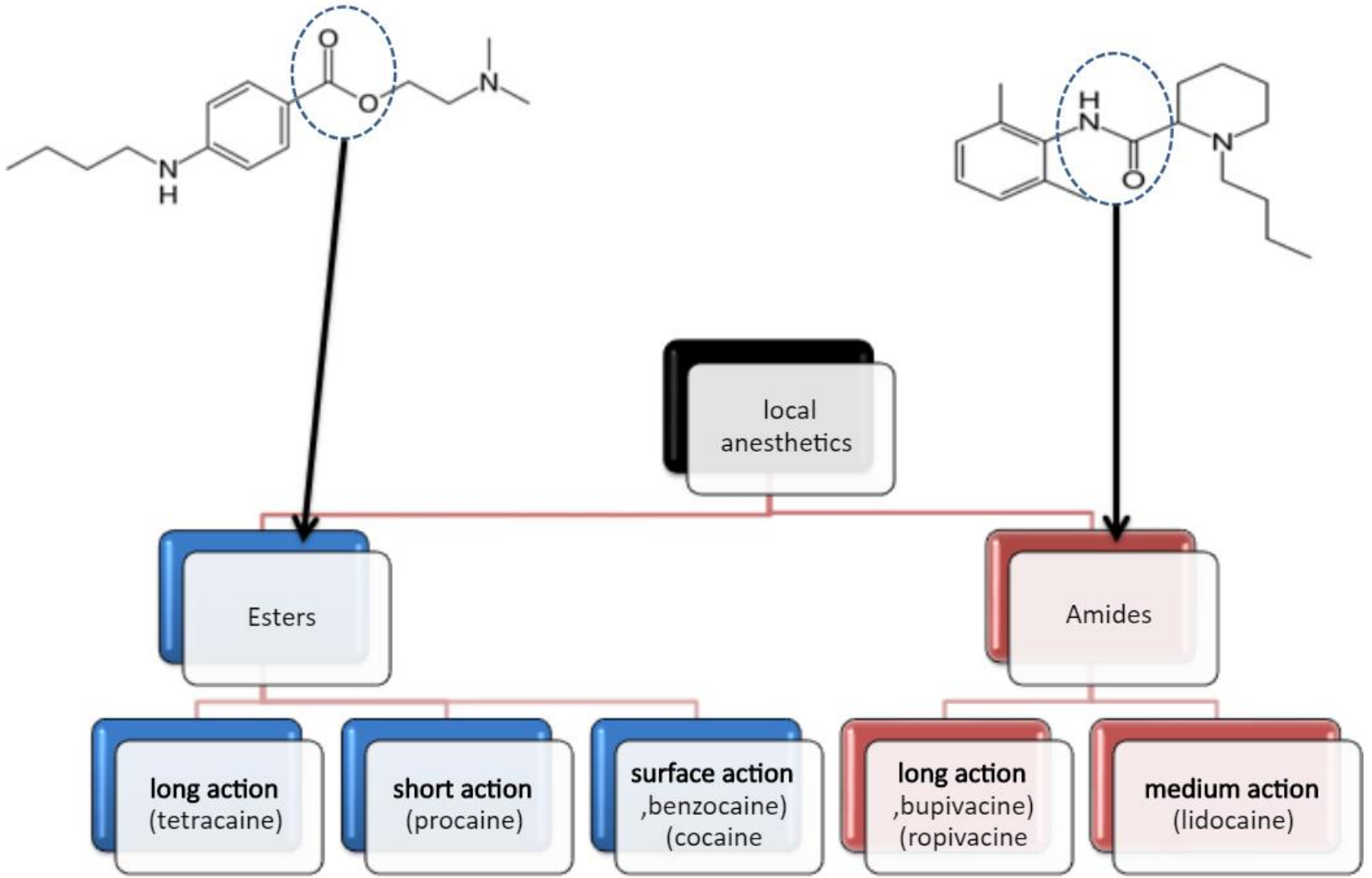
Ultra short duration	• 2% lignocane without vasoconstrictor
Short duration	• Procaine, 2% lignocane with 0.0001% Epinephrine
Intermediate duration	• Articaine, mepivacaine, prilocaine, 2% lignocane with 0.0002% Epinephrine
Long duration	• Bupivacaine (400-500 min), Etidocaine, 5% with lignocane with 0.0002% Epinephrine

➢ Based on origin

NATURAL	• cocaine
SYNTHETIC NITROGENOUS COMPOUND	• Amino esters of PABA- procaine • Alkyl esters of PABA- benzocaine • Amino esters of MABA- unacaine • Amino amides- xylocaine , bupivacaine
SYNTHETIC NON NITROGENOUS COMPOUND	• benzyl alcohol

MISCLLANEOUS DRUGS ------- Clove Oil, Phenol

- On the basis of chemical structure, local anaesthetics are classified as follows:



1st chemical structure classification

❖ Amino Ester

- Cocaine
- Procaine
- Tetracaine

❖ Amino Amides

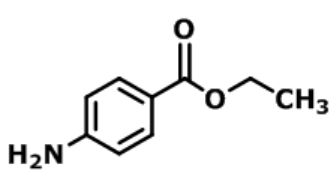
- Lidocaine
- Bupivicaine
- Etidocaine

❖ Amino Ether

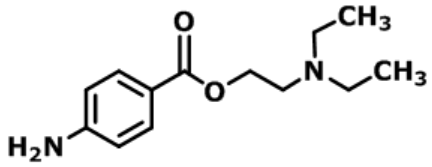
- Pramoxine
- Pramocaine

❖ Amino Ketones

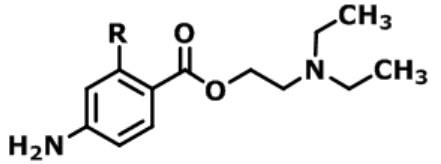
- Dyclonine



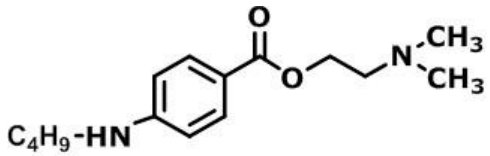
Benzocaine



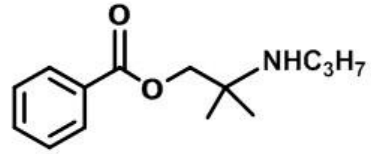
Procaine



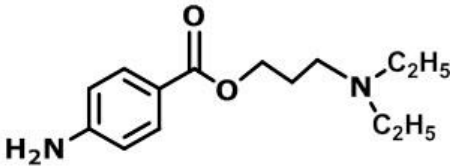
R=Cl Chloroprocaine
R=OH Hydroxyprocaine



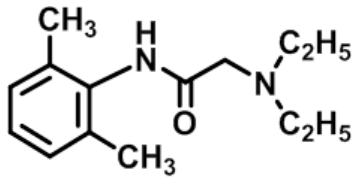
Tetracaine



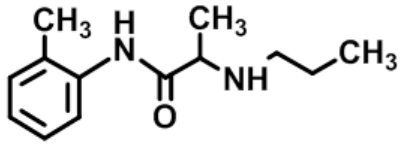
Meprylcaine



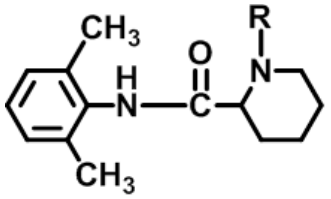
Butacaine



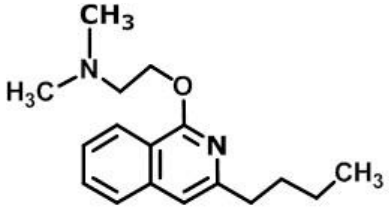
Lidocaine



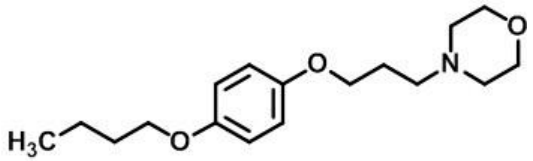
Prilocaine



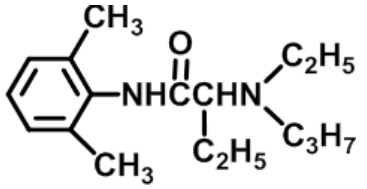
R=CH3, Mepivacaine,
R=C4H9, Bupivacaine,



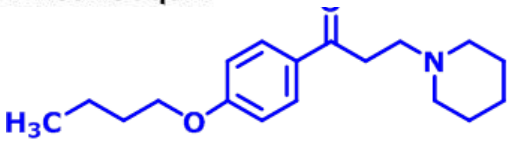
Dimethisoquin



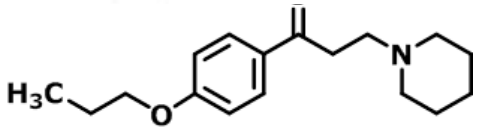
Pramocaine



Etidocaine,



Dyclonine



Falicaine

The difference between an ester and amide local anesthetic

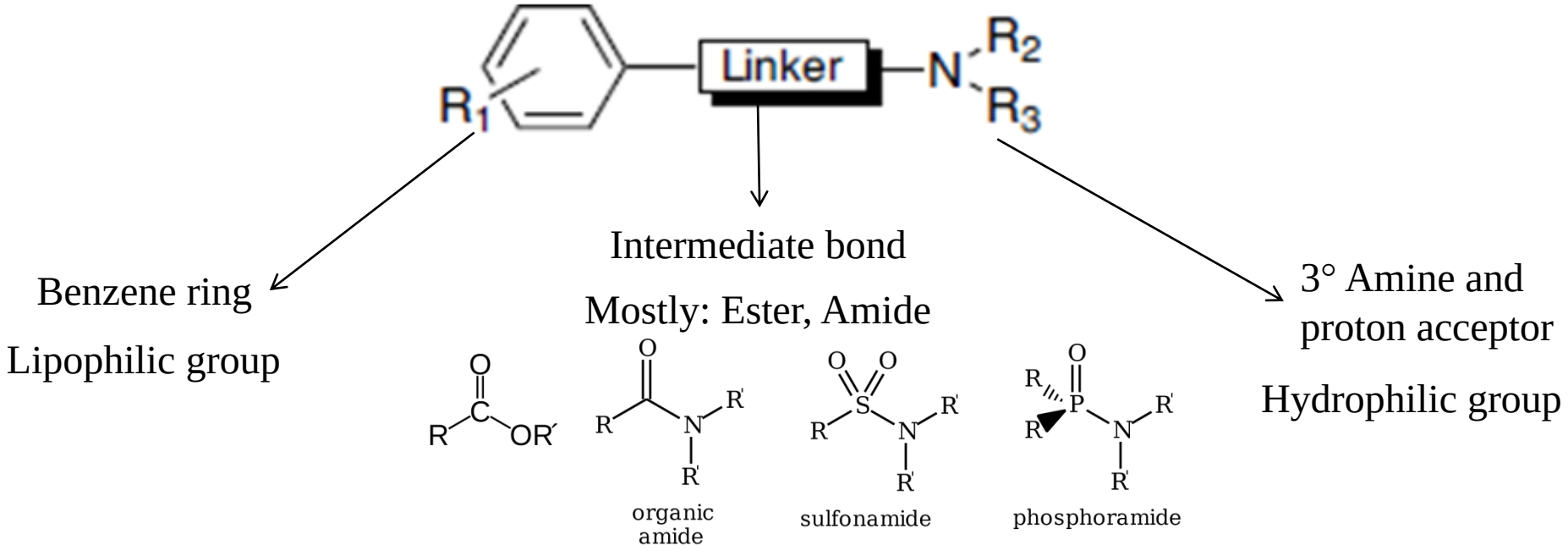
AMIDES	***ESTERS***
• longer lasting analgesia. • Produce more intense analgesia. • Rarely cause hypersensitivity reactions- no cross reactivity with ESTER L A s. • Bind to alpha1 acid glycoprotein in plasma • Not hydrolyzed by Plasma Cholinesterase, more slowly destroyed by liver microsomal P450 enzymes.	• Short duration of action • Less intense analgesia • Higher risk of hypersensitivity ESTER linked LA s are rarely used. • Hydrolyzed by Plasma Cholinesterase in blood. • Rarely used for Infiltration anesthesia • But useful for topical ana on mucous membranes.

Classes: The rule of "i"

- **Amides** will contain an "i" in the generic name prior to "-caine". (i.e. lidocaine, mepivacaine, prilocaine, bupivacaine, ropivacaine, and levo-bupivacaine).
- **Ester's** do not contain an "i" in the generic name prior to "-caine". (i.e. procaine, chloroprocaine, cocaine, benzocaine, and tetracaine).

STRUCTURE ACTIVITY RELATIONSHIP

- All local anesthetics have an amine on one end to an aromatic ring on the other
- The **amine** end is **hydrophilic**, and the **aromatic** end is **lipophilic**
- The two groups are connected by mostly an **ester** or an **amide** group and less commonly by ether or ketones



Lipophilic group

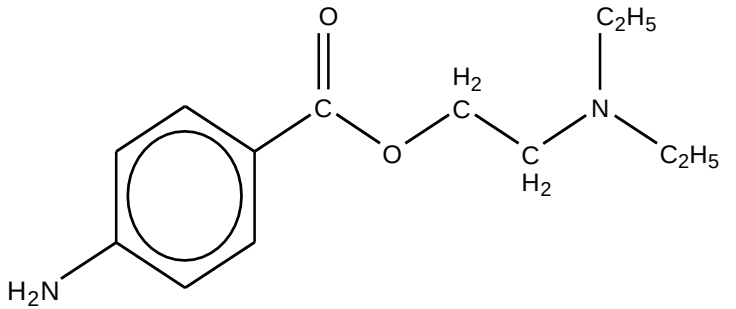
- **Lipophilicity is important to penetrate the lipid layer and reach the binding site on the side of the cell.**

RULE 1:

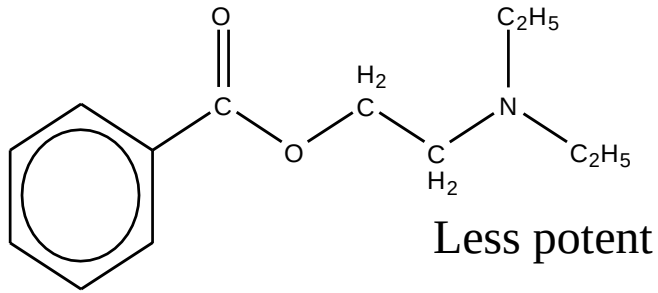
The presence of electron withdrawing group in ***ortho*** or ***para*** position will decreases the lipophilicity of the drug but still **important in increases the activity for the ester group.**

Procaine is more potent if it has a e-donating amine group in the aromatic ring.

Other e-donating groups: -OH, OCH_3, CH_3



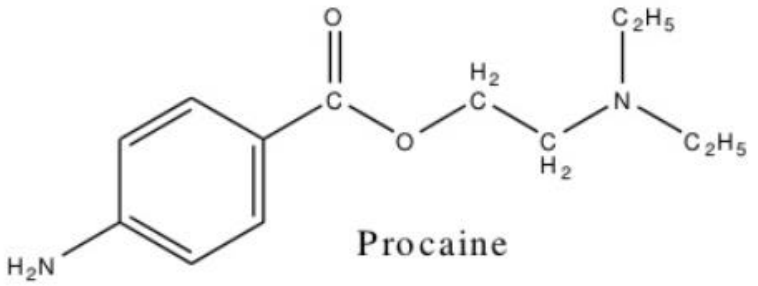
Procaine



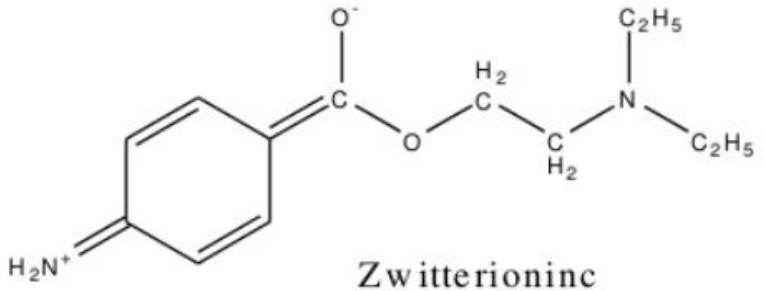
Less potent than procaine

RULE 2:

Zwitterion: this increasing the activity (for ester only) which enhance activity due to formation of quaternary amine witch important for binding



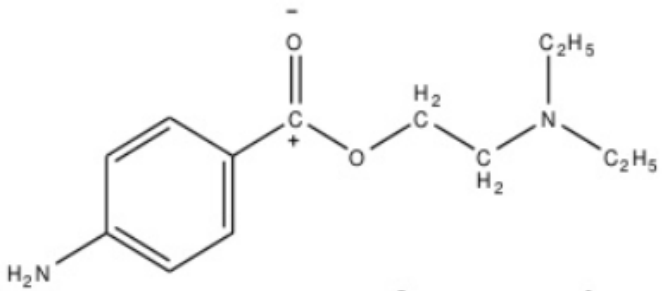
Procaine



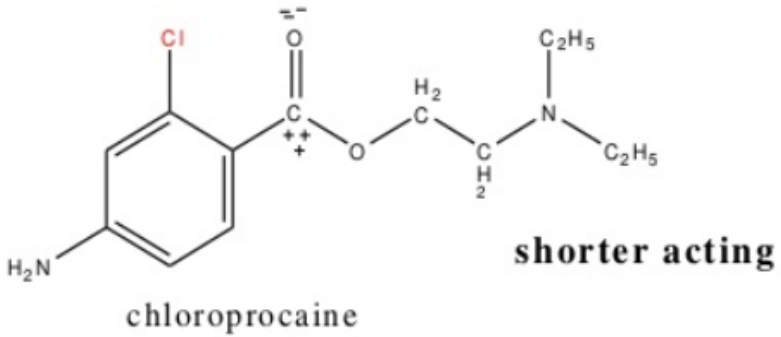
Zwitterioninc form

RULE 3:

Halogens: the presence of electron withdrawing halogens in ortho position only can decrease duration of by making the ester more Likely for a nucleophilic attack



Procaine **longer acting**



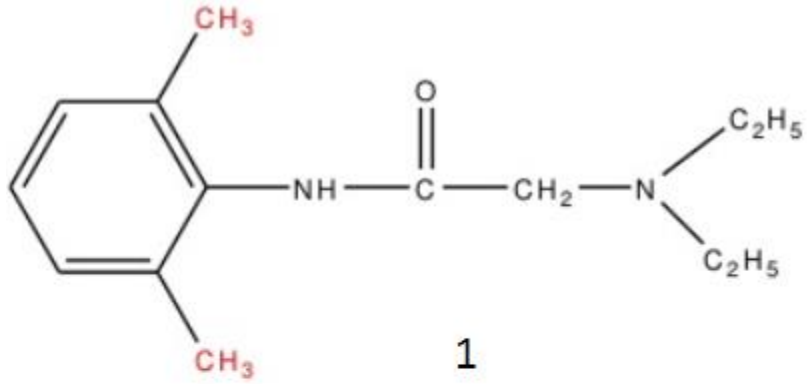
chloroprocaine **shorter acting**

Chlorine in ortho group makes the carbonyl carbon more positive and more likely to be attacked by nucleophiles that causes breakdown of compound.

Nucleophile contain a lone pair of electron. they attack atoms with positive charges. The more positive atom, the better for attack

RULE 4:

For amide only, presence of di-ortho substituted group prevent breakdown of amide and thus increase it's stability in both liquid formulation and the body enzymes

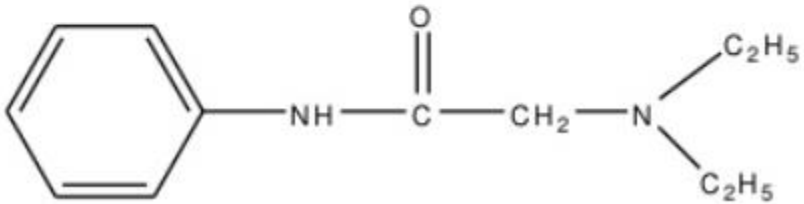


1

Structure 1:

CH_3 group:

- Make it difficult to hydrolyze
- Stable in water and blood
- More duration of action



2

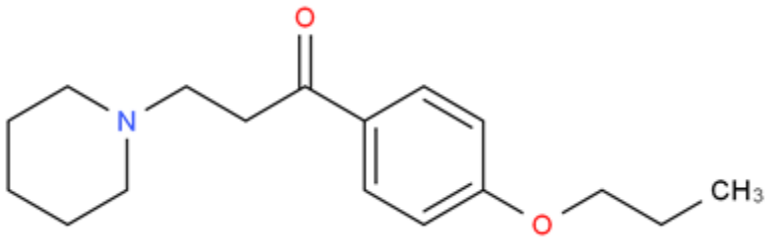
Structure 2:

- No protection against hydrolysis
- Unstable in water and blood
- Not enough duration of action

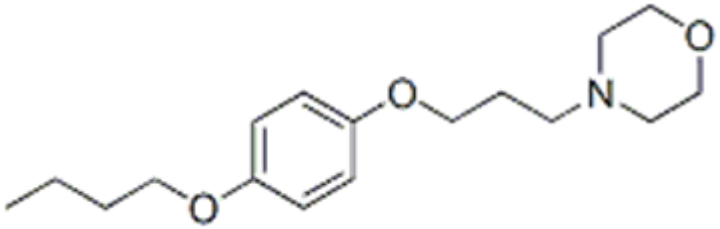
Note: instead of CH3, other groups such as OCH3 can also be used

Linker

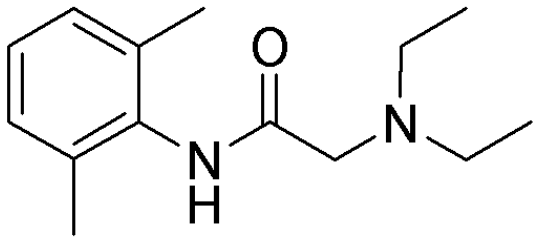
- **Linker group has short alkynene (–CH_2–) chain containing few carbon atom and various functional groups as Amids, ester, ether, or ketone.**



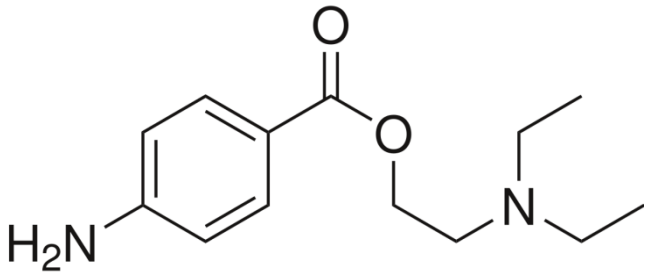
Ketone: Falicaine



Ether: Pramocoine



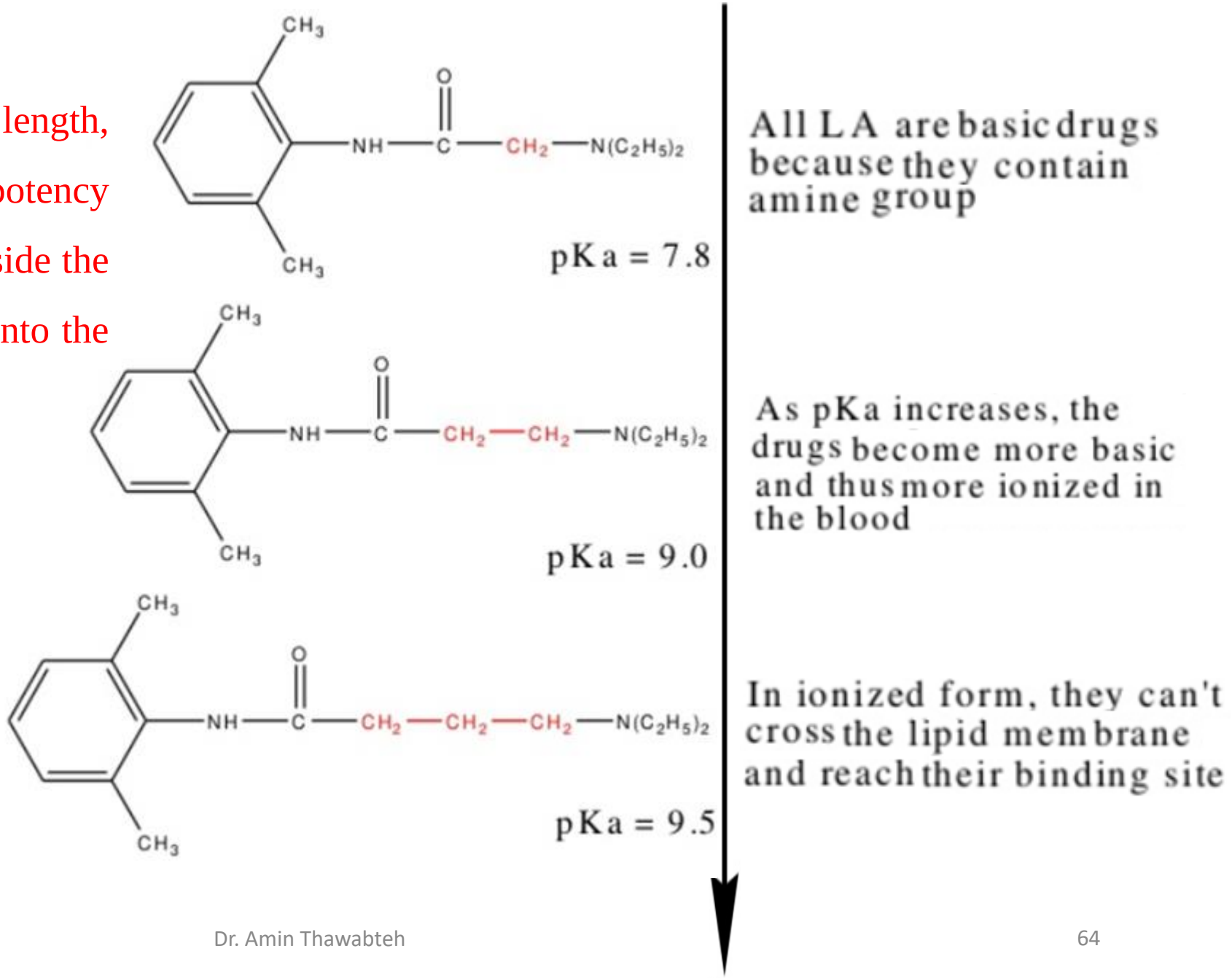
Amide: Lidocaine



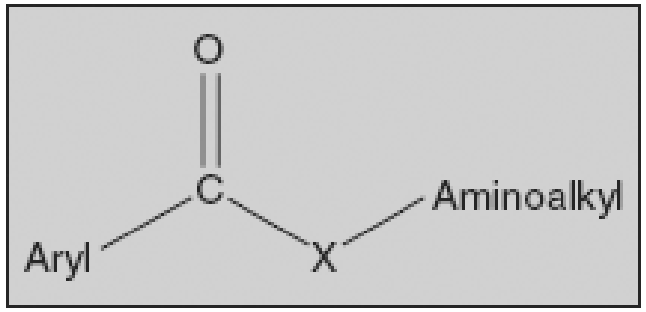
Ester: Procaine

The increasing of the alkylene chain length, increase the pKa which reduces potency because more drug get ionizied out-side the membrane and thus can't penetrate into the binding site.

Increasing CH_2 group = increased pka (increased basicity) = increased ionized form = decreased potency



Bridge X:



X: carbon, oxygen, nitrogen, or sulfur

The anesthetic potency decreased in the following order:

Sulphur, Oxygen, Carbon, Nitrogen.

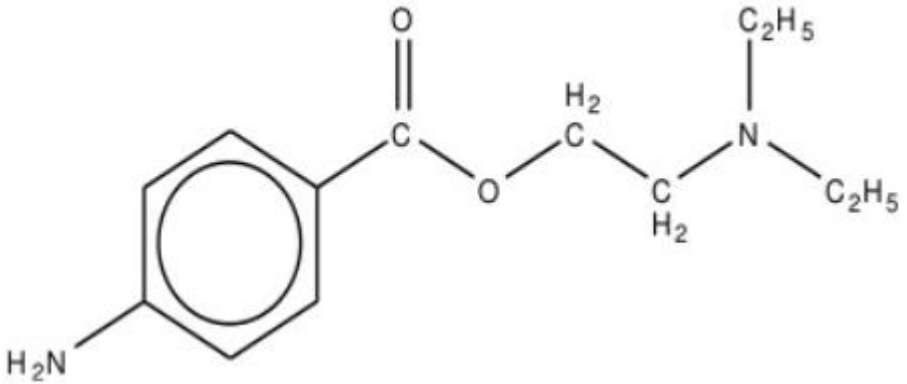
These modification also affect duration of action and toxicity.

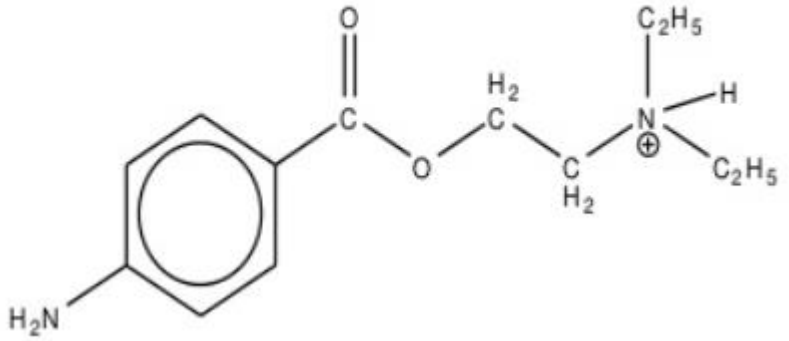
In general, amides (X=N) are more resistant to metabolic hydrolysis than esters (X=O). Thioesters (X=S) may cause dermatitis.

Hydrophilic group

- Usually be a secondary or tertiary amine group.
- It's important because it's believed that when they enter the cell they will accept a proton and form positively charged quaternary form (water soluble salt) that is needed for binding to voltage gated ion channel.

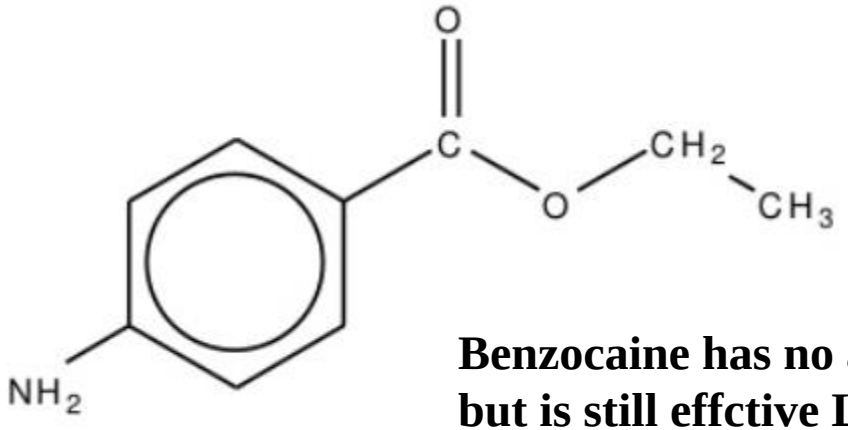
Procaine believed to bind to it's receptor when the amine group is positively charge quanternary form





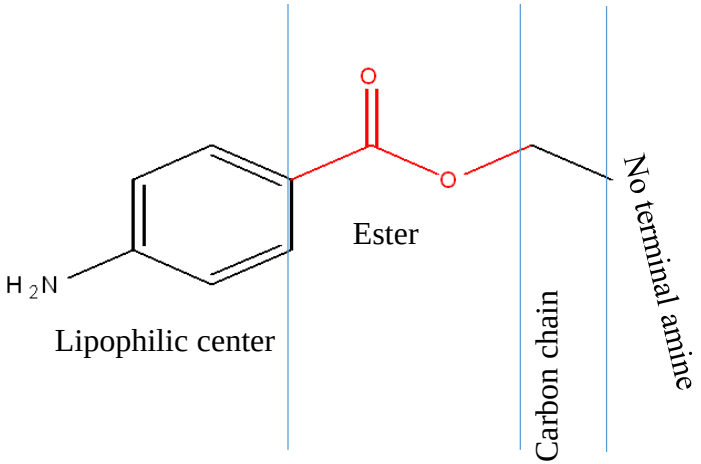
Charged Quanternary form is believed to bind to receptor

- However, ***Benzocaine*** has no anime portion but is still an effective topical LA
- Thus the use of Amine part could only be for proper water solubility and not directly related to proper binding

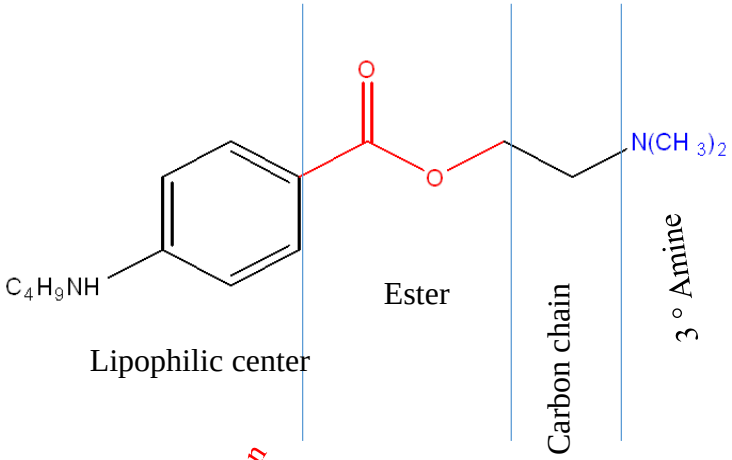


Benzocaine has no amine but is still effctive LA

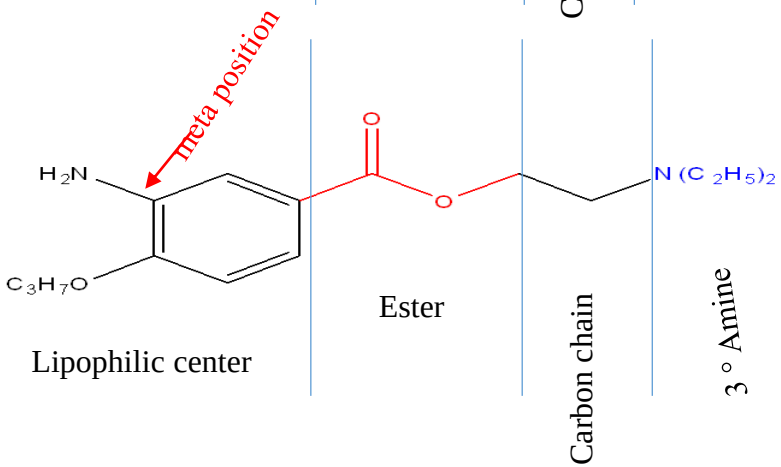
Amino Esters



Benzocaine: In *para* position of the lipophilic center there is an amino group Lacks the basic aliphatic amine function yet has potent local anesthetic activity Used topically

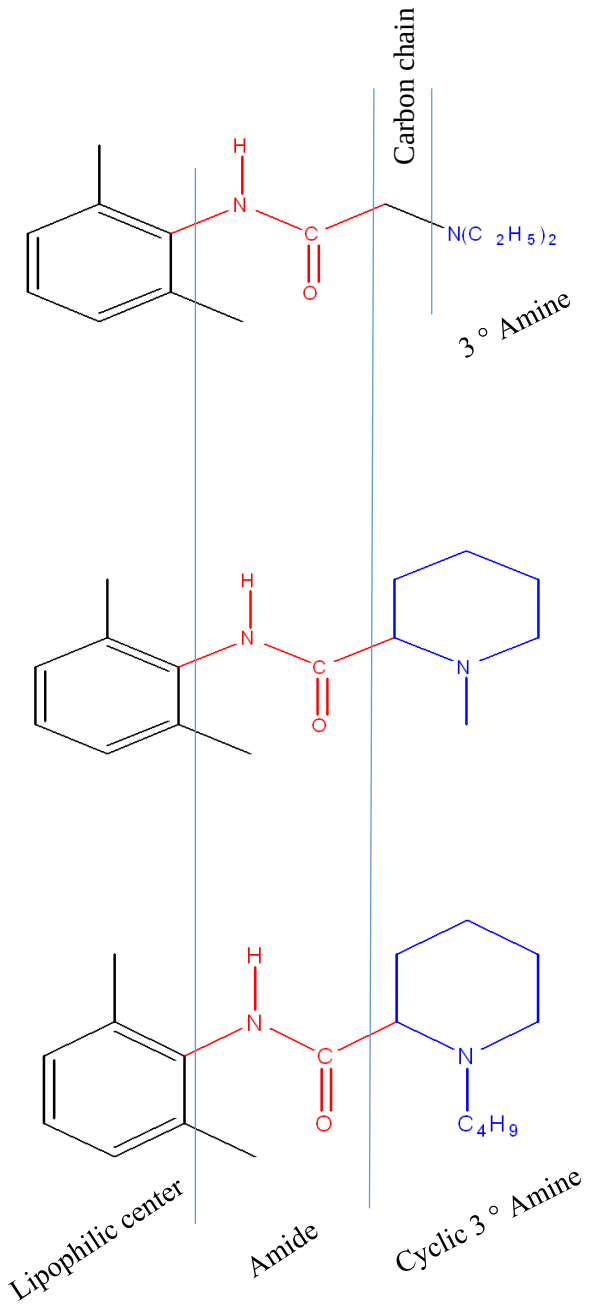


Tetracaine: In *para* position of the lipophilic center there is an alkylamino group



Proparacaine: There is an amino group in the meta position This group will decrease lipophilicity of the molecule

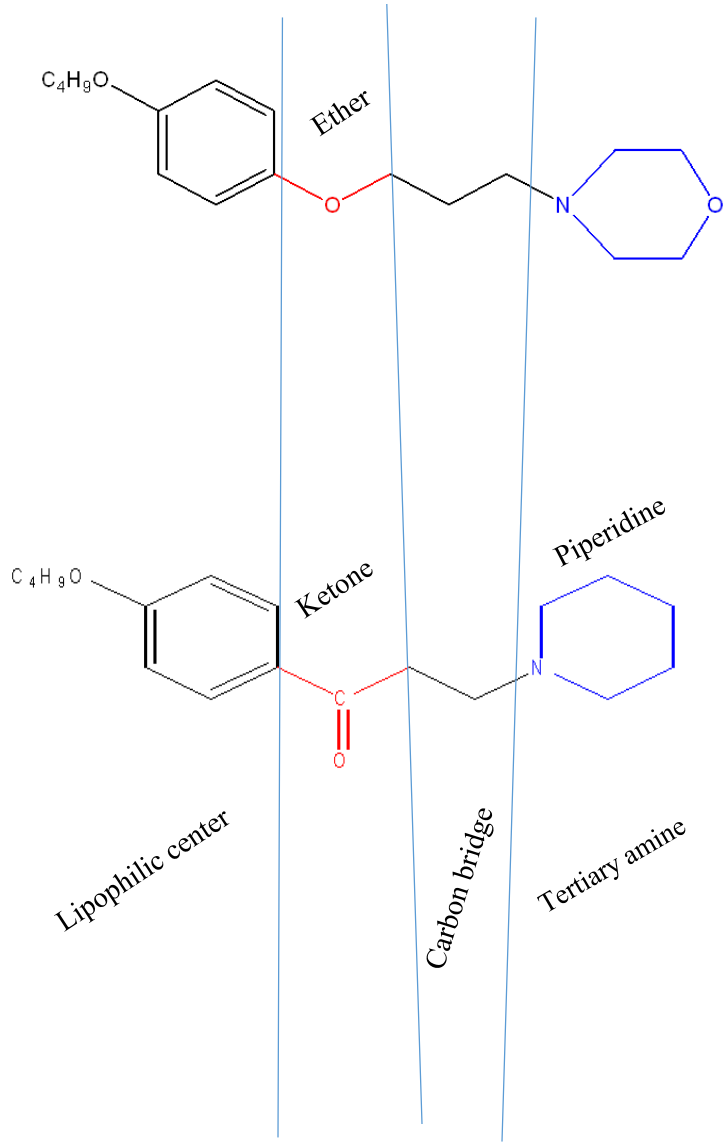
Amino Amides



Lidocaine: The o,o-dimethyl groups are required to provide suitable protection from amide hydrolysis to ensure a desirable duration of action

Mepivacaine: The o,o-dimethyl groups are required to provide suitable protection from amide hydrolysis to ensure a desirable duration of action. No carbon bridge. Cyclic amine (piperidine).

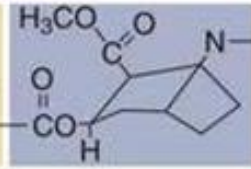
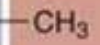
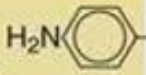
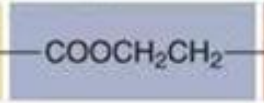
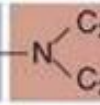
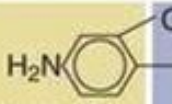
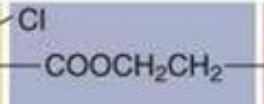
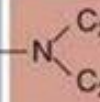
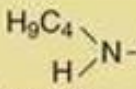
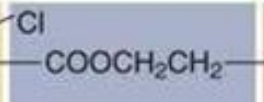
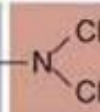
Bupivacaine: The o,o-dimethyl groups are required to provide suitable protection from amide hydrolysis to ensure a desirable duration of action No carbon bridge Cyclic amine (piperidine).



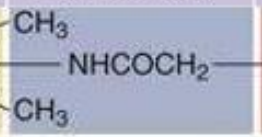
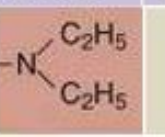
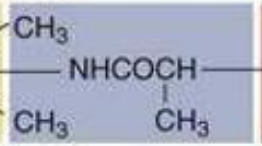
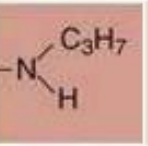
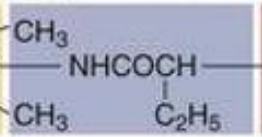
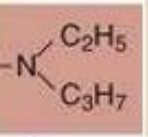
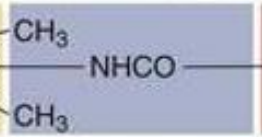
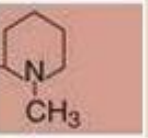
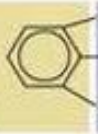
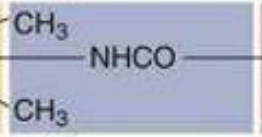
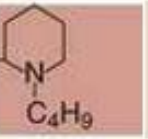
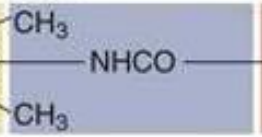
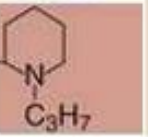
Amino Ether-Pramoxine: Lipophilic group has an alkoxy Substituent. Nitrogen is in a morpholino ring

Amino Ketone-Dyclonine: Lipophilic group has an alkoxy substituent Nitrogen is in a piperidine ring

Amino Esters

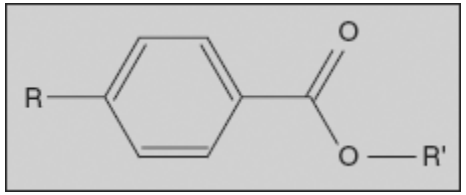
Lipophilic	Intermediate	Amine	Potency	Duration
Cocaine 			2	Medium
Procaine 			1	Short
2-Chloroprocaine 				
Tetracaine 			16	Long

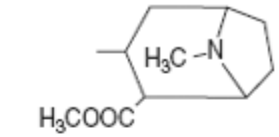
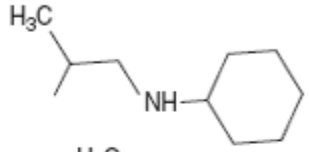
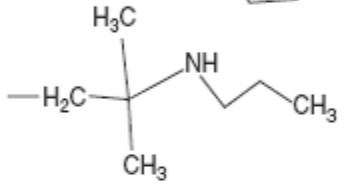
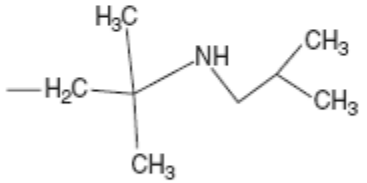
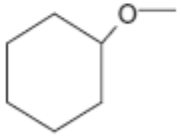
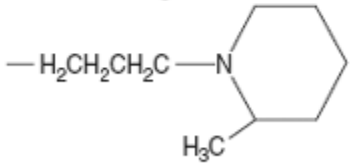
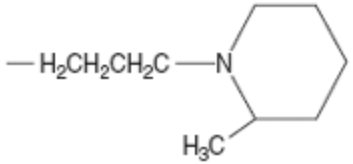
Amino Amides

Lipophilic	Intermediate	Amine	Potency	Duration
Lidocaine 			4	Medium
Prilocaine 			3	Medium
Etidocaine 			16	Long
Mepivacaine 			2	Medium
Bupivacaine 			16	Long
Ropivacaine 			16	Long

CLASSIFICATION AS:

1. Benzoic acid derivatives



	R	R′
Cocaine	H	
Hexylcaine	H	
Meprylcaine	H	
Isobucaine	H	
Cyclomethycaine		
Piperocaine	H	

2nd chemical structure classification

a. Benzoic acid derivatives

a.1 Derivatives of benzoic acid

a.2.Derivatives of para-amino benzoic acid

i. Freely soluble: Procaine, Amethocaine.

ii. Poorly soluble: Benzocaine, Orthocaine

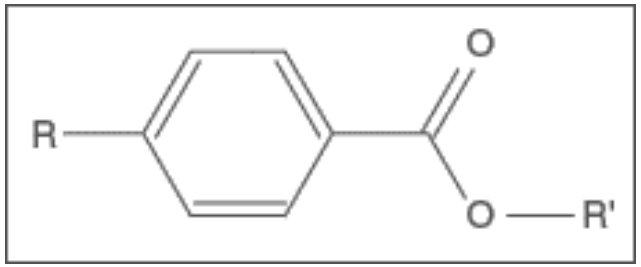
b. Derivatives of acetanilide: Lignocaine, Mepivacaine, Bupivacaine, Prilocaine, Etidocaine.

c. Miscellaneous: Dimethisoquin, Dibucaine, and Dyclonine.

d. Newer drugs: Ropivacaine, Levobupivacaine

a. Benzoic acid derivatives

a.1. Benzoic acid derivatives



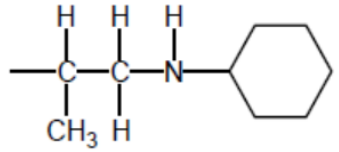
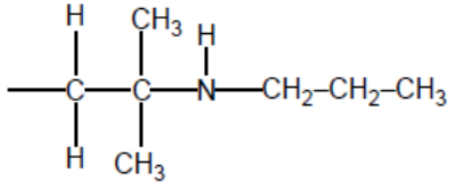
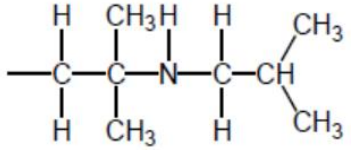
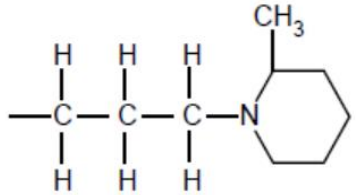
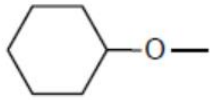
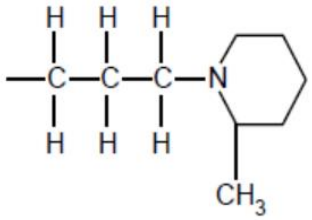
Hexylcaine

Meprylcaine

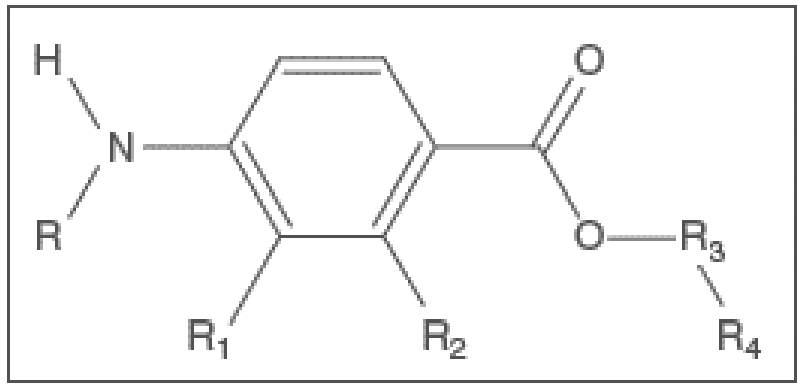
Isobucaine

Piperocaine

Cyclomethycaine

Name	R_1	R_2
Hexylcaine	–H	
Meprylcaine	–H	
Isobucaine	H	
Piperocaine	–H	
Cyclomethycaine		

a.2. p-Amino benzoic acid derivatives



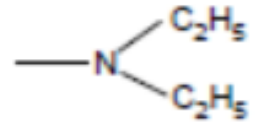
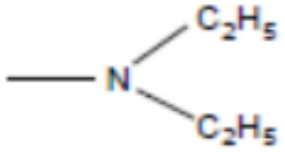
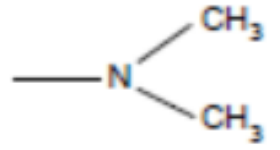
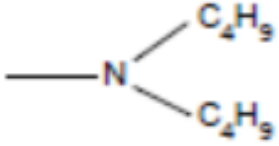
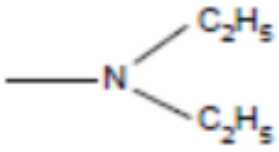
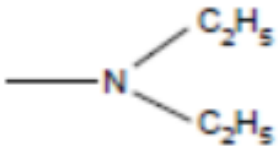
Benzocaine

Tetracaine

Butacaine

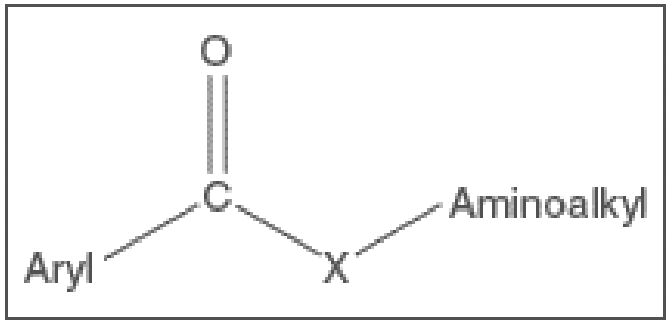
Procaine

Chlorprocaine

Name	R_1	R_2	R_3	R_4	R_5
Benzocaine	–H	–H	–H	$-CH_2-CH_3$	–
Butamben	–H	–H	–H	$-(CH_2)_3\ CH_3$	–
Procaine	–H	–H	–H	$-CH_2-CH_2-$	
Chlorprocaine	–H	–H	–Cl	$-CH_2-CH_2-$	
Tetracaine	–ⁿButyl	-H	–H	$-CH_2-CH_2-$	
Butacaine	–H	–H	–H	$-CH_2-CH_2-CH_2$	
Binoxinate	–H	ⁿButoxy	–H	$-CH_2-CH_2-$	
Propoxycaine	–H	–H	ⁿPropoxy	$-CH_2-CH_2-$	

SAR of benzoic acid derivatives

Aryl group

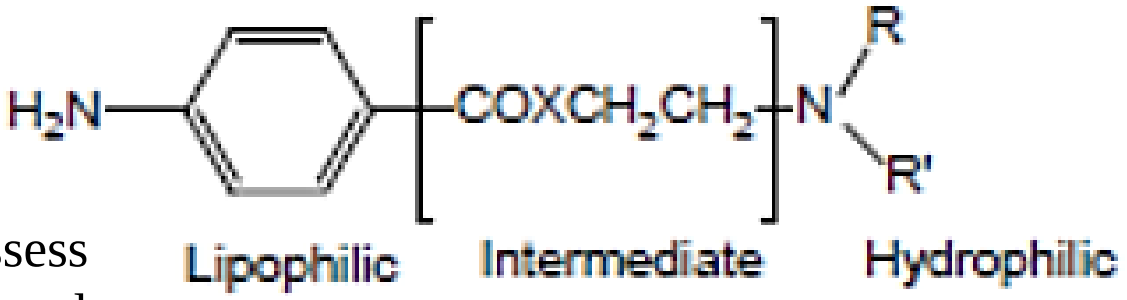


- The clinically useful local anaesthetics of this series possess an aryl radical attached directly to the carbonyl group.
- Substitution of aryl group with substituents that increase the electron density of the carbonyl oxygen enhances activity.
- Favorable substituents in aryl ring include (electron-donating groups) alkoxy (propoxycaine), amino (procaine), and alkylamino (tetracaine) groups in the *para* or *ortho* positions. This homologous series increases partition coefficients with increasing number of methylene group (-CH_2-). Local anaesthetics activity peaked with the C4-, C5-, or C6-homologous: e.g., tetracaine, cyclomethycaine.
- Aryl aliphatic radicals that contain a methylene group between the aryl radical and the carbonyl group result in compounds that have not found clinical use.

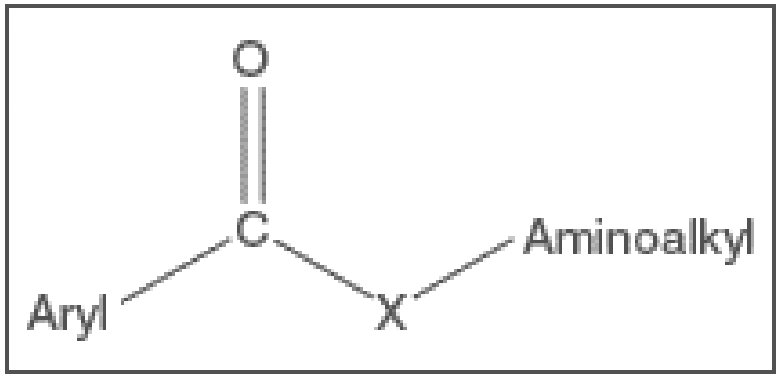
SAR of benzoic acid derivatives

- Most of these local anaesthetics are tertiary amines available as HCl salts with pKa in the range of 7.5–9.0.
- Any structural modifi cation of the local anaesthetic that causes change in pKa will have pronounced effect to reach hypothetical receptor or the binding sites.

Lipophilic " Aryl group "



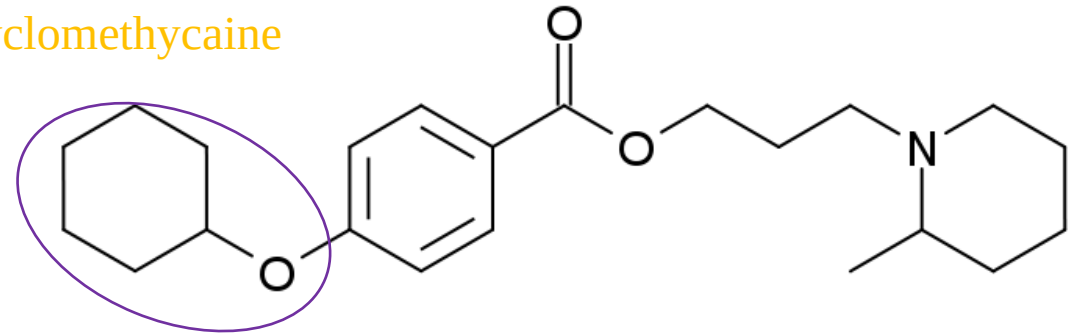
1. The clinically useful local anaesthetics of this class possess an aryl radical that is attached directly to the carbonyl group and are highly liphophilic. They appear to play an important role in the binding of local anaesthetics to the channel receptor protein.



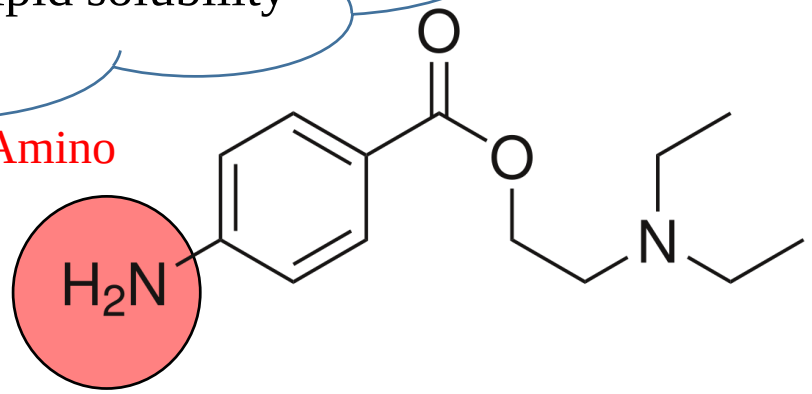
2. Amino (procaine, butacaine) alkyl amino (tetracaine) alkoxyl (cyclomethycaine) group can contribute to electron density in the aromatic ring by both resonance and inductive effects. Hence the increase in local anaesthetic property.

Tetracaine is more potent than procaine (40–50 times). Although the butyl group present in it increases lipid solubility

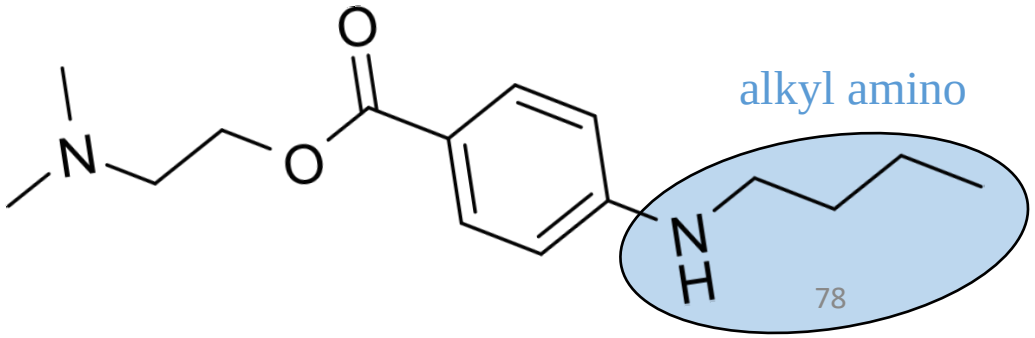
cyclomethycaine



Amino

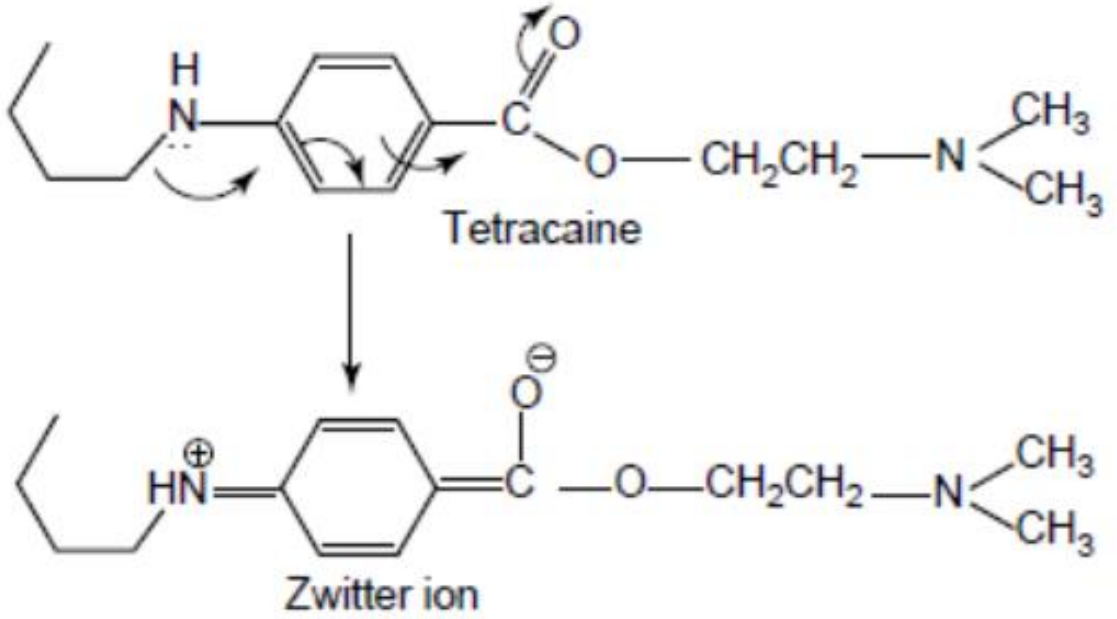


alkyl amino

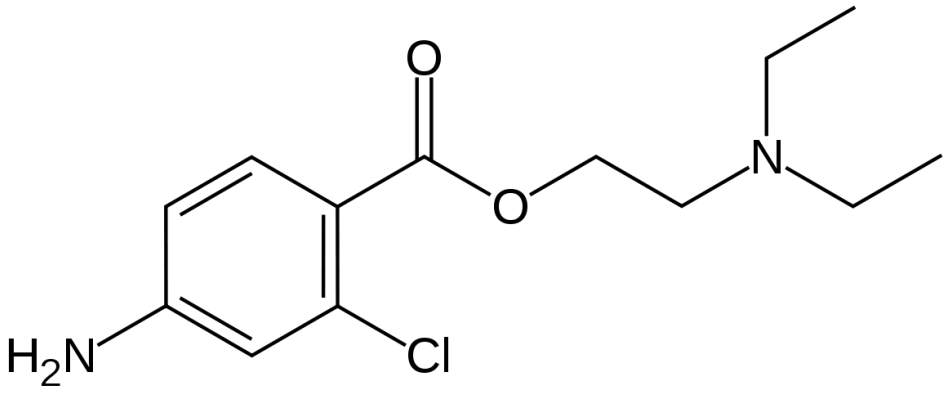


3. Any substitution that enhances zwitterion formation will be more potent. Hence *m*-position substitution decreases the activity.

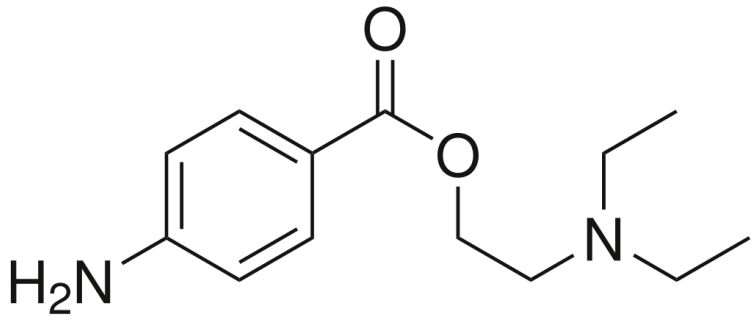
Tetracaine is more potent than procaine (40–50 times). Although the potentiation is partly due to electron releasing property of the *n*-butyl group via inductive effect, which intend to increase the formation of the Zwitterion.



4. Structural modification leads to change in physical and chemical properties. Electron withdrawing substituents in *ortho* or *para* or at both the positions leads to an increase of its local anaesthetic property.



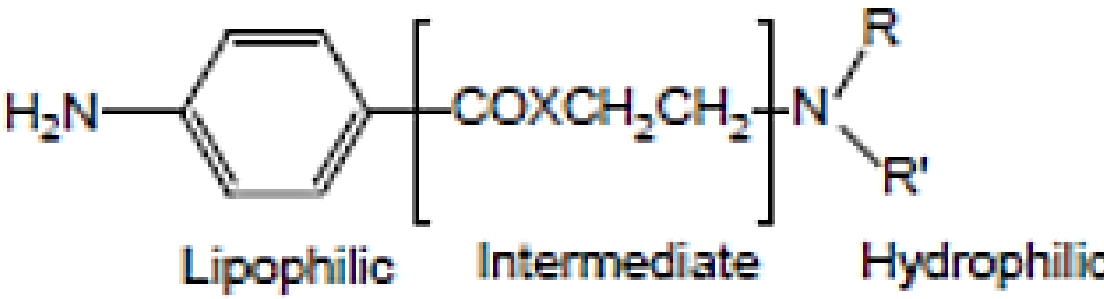
Chloroprocaine

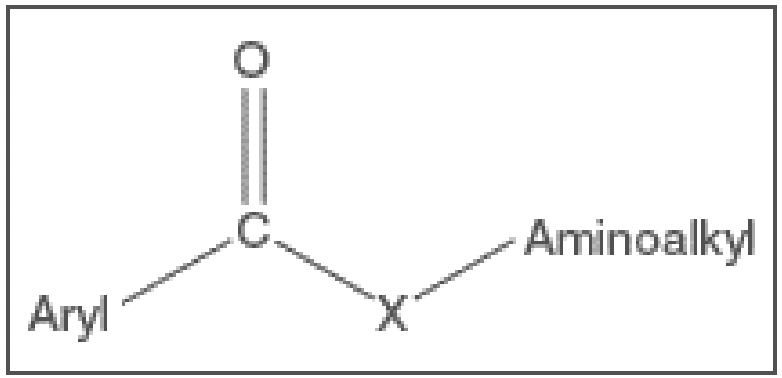


Procaine

Intermediate “Bridge X”

- The bridge X may be carbon, oxygen, nitrogen, or sulphur.
- In an procaine series, anaesthetic potency decreased in the following order: sulphur, oxygen, carbon, nitrogen.
- These modifications also affect duration of action and toxicity. In general, amides (X=N) are more resistant to metabolic hydrolysis than esters (X=O). Thioesters (X=S) may cause dermatitis.
- In procaine-like analogues, branching (especially at the alpha carbon) will increase duration of action. This effect is not seen in the lidocaine series.
- Increasing the chain length will increase potency but will also increase toxicity.





Hydrophilic portion “Aminoalkyl”

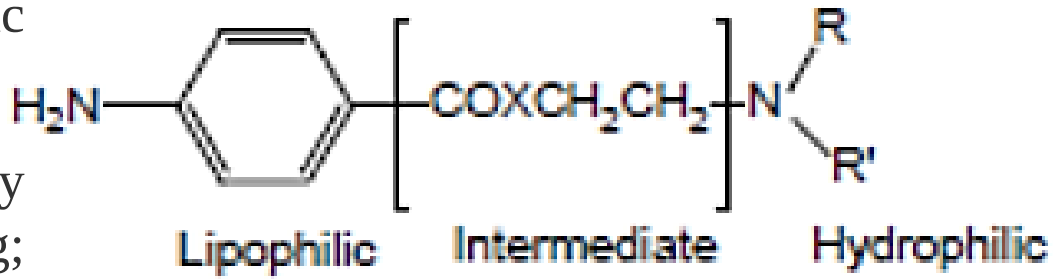
•The aminoalkyl group is not necessary for local anaesthetic activity, but it is used to form water-soluble salts (HCl salts).

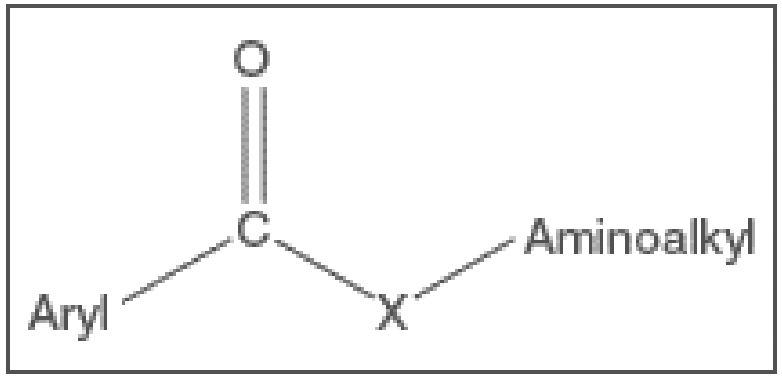
•Tertiary amines result in more useful agents. The secondary amines appear to be of longer activity, but they are more irritating; primary amines are not very active and cause irritation.

•The tertiary amino group may be diethylamino, piperidine, or pyrrolidino, leading to the products that exhibit essentially the same degree of activity.

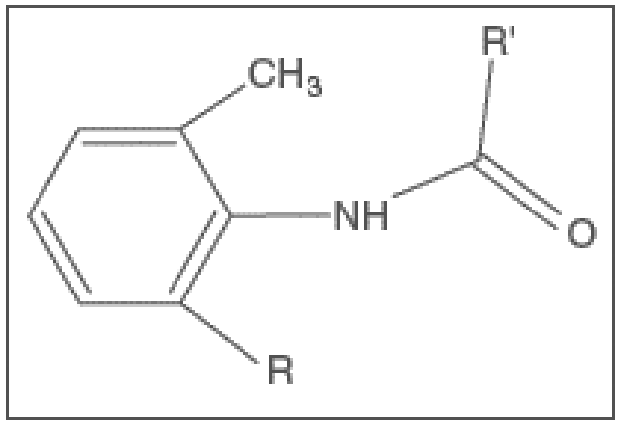
•The more hydrophilic morpholino group usually leads to diminished potency.

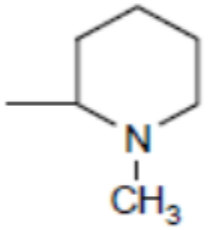
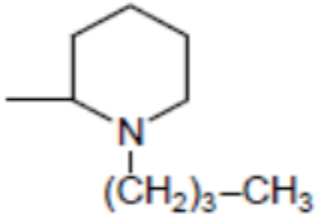
•Some analogues have no amino group at all, such as benzocaine. They are active but have poor water solubility.





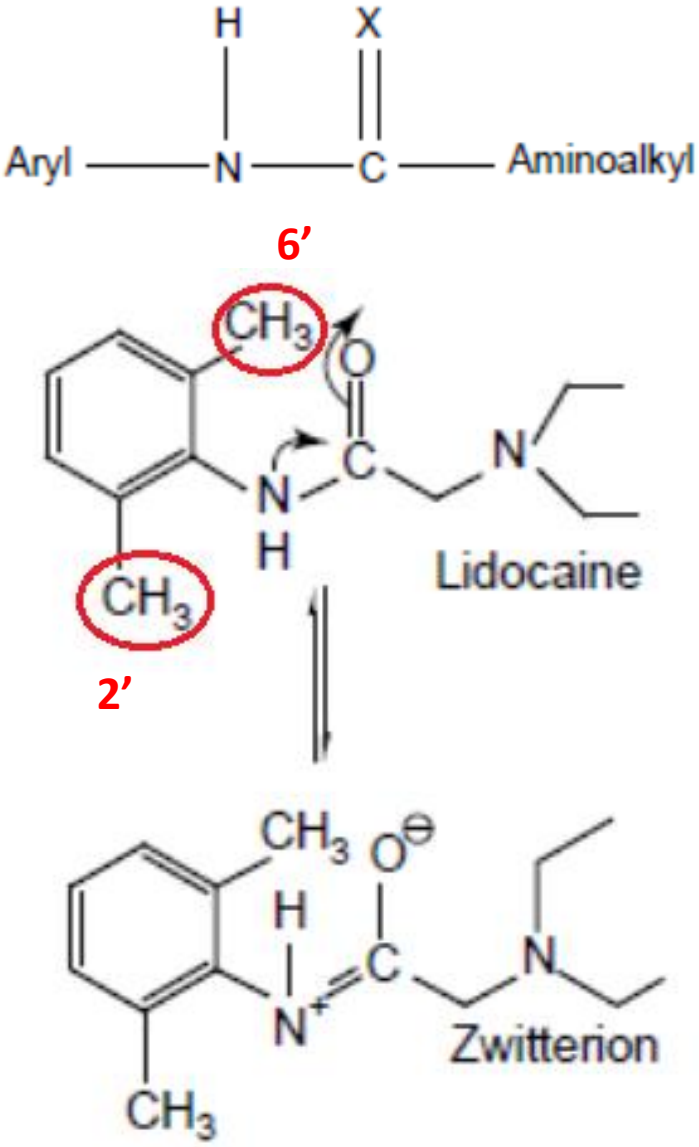
b. Anilide derivatives



Name	R_1	R_2
Lidocaine/Lignocane	$-CH_3$	$-CH_2-N(C_2H_5)_2$
Mepivacaine	$-CH_3$	
Prilocaine	$-H$	$-CH(CH_3)-NH-(CH_2)_2-CH_3$
Bupivacaine	$-CH_3$	
Etidocaine	$-CH_3$	$-CH(C_2H_5)-N(C_2H_5)-CH_2CH_2CH_3$

SAR of Anilides

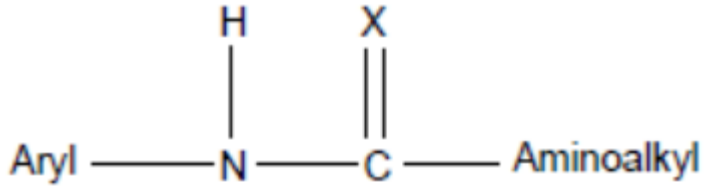
Aryl group



- The clinically useful local anaesthetics of this type possess a **phenyl group** attached to the sp^2 carbon atom through a nitrogen bridge.

- Placement of substituents on the phenyl ring with a methyl group in the 2 (or) 2 and 6-position enhances the activity. In addition, the methyl substituent " as lidocaine " provides steric hindrance to hydrolysis of the amide bond and enhances the coefficient of distribution.

- Any substitution on the aryl ring that enhances zwitterion formation will be more potent.



Substituent X

•X may be carbon, oxygen, or nitrogen. Among them Lidocaine series (X=O) has provided more useful products.

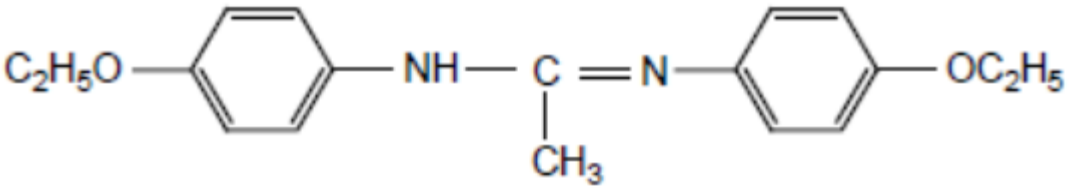
Aminoalkyl group

•The amino function has the capacity for salt formation and is considered the hydrophilic portion of the molecules.

•Tertiary amines (diethylamine, piperidines) are more useful because the primary and secondary amines are more irritating to tissue.

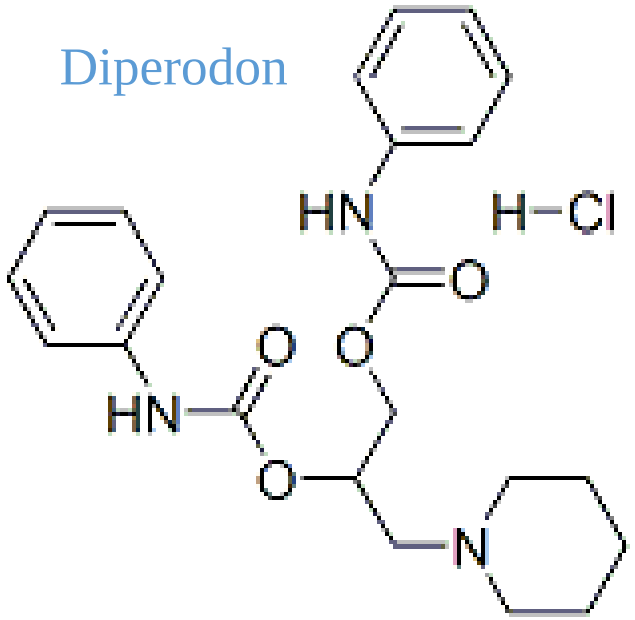
c. Miscellaneous

Phenacaine



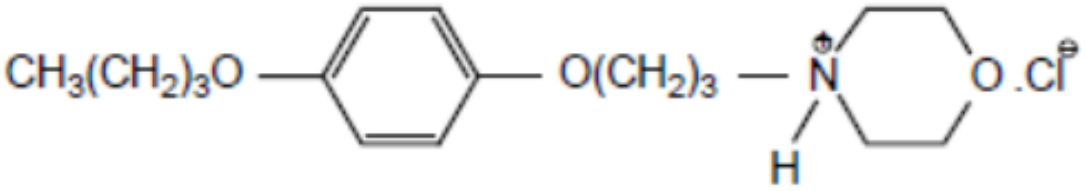
Structurally, it is related to anilides in that the aromatic ring is attached to a sp2 carbon through a nitrogen bridge. It is one of the oldest synthetic local anaesthetic. It is used mainly for producing local anaesthesia of the eye.

Diperodon



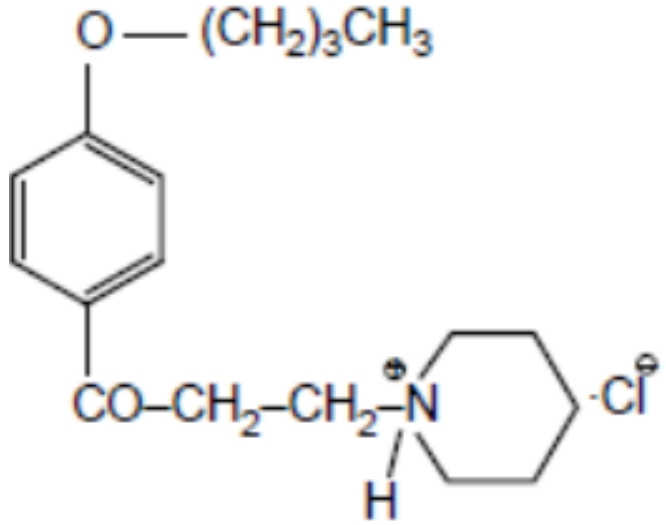
Soluble in water, and potent surface anaesthetic; used primarily for anus. Very toxic in nature.

Pramoxine HCl (Traonaolene)



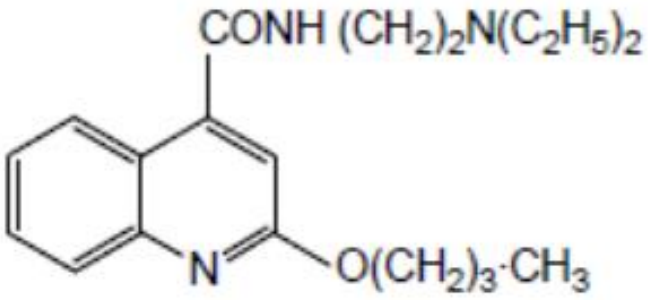
It is a surface anaesthetic, which possesses very low degree of toxicity and sensitization. It is applied locally as 1% solution in rectal surgery, itching, and minor burns.

Dyclonine (Dyclone)



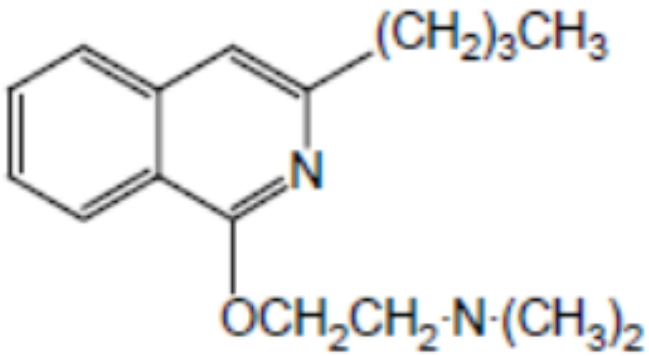
Containing lozenges are used to relieve minor sore throat and mouth discomfort. It is used to anesthetize mucous membranes of mouth, trachea, and urethra prior to various endoscopic procedures.

Dibucaine (Nupercaine)



It is several times more potent than procaine when injected subcutaneously and five times more toxic than cocaine, when injected intravenously. It is the most potent toxic and long-acting local anaesthetics used as infiltration, surface and spinal anaesthesia.

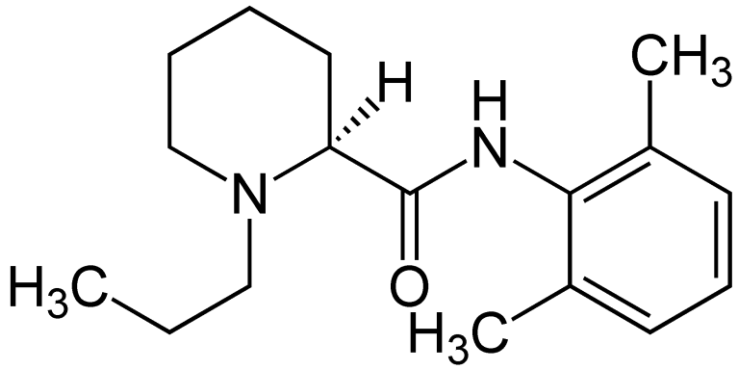
Dimethisoquin (Synonym: Quinisocaine, Quotane)



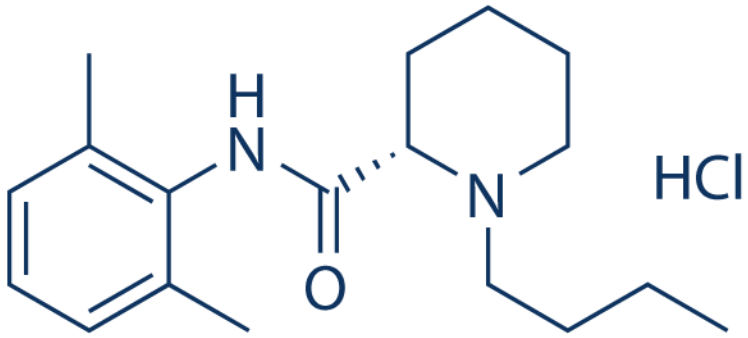
It is a surface anaesthetic used as an ointment or lotion for relief from irritation, itching, pain, or
burning.

d. Newer drugs: Ropivacaine, Levobupivacaine

Newer local anaesthetics were introduced with the goal of reducing local tissue irritation, minimizing systemic cardiac and central nervous system (CNS) toxicity, and achieving a faster onset and longer duration of action.

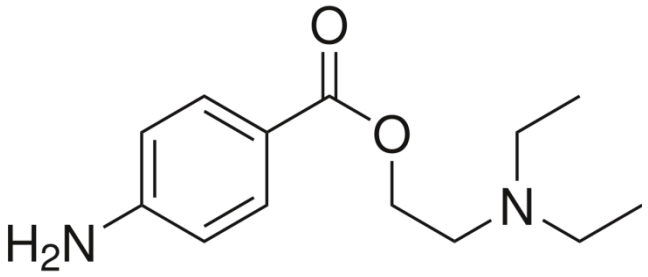


Ropivacaine



Levobupivacaine

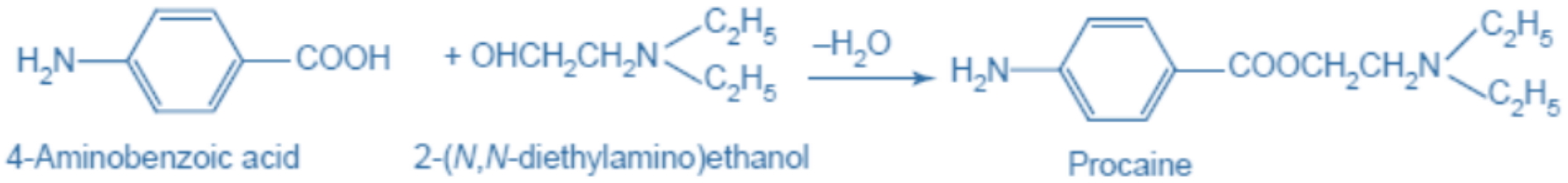
PROCAINE



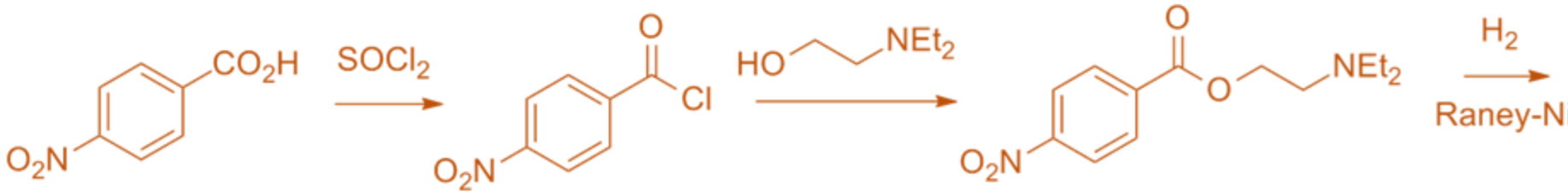
- Procaine is a local anesthetic drug of the ester group
- effective parental but are relatively weak when applied topically
- slow onset (4-5 min), short duration, pKa=8.8
- It has the advantage of lacking of local irritation, minimal systemic toxicity, longer duration of action, and low cost.
- It can be effectively used for causing anaesthesia by infiltration, nerve block, epidural block, or spinal anaesthesia.
- is metabolized by the plasma enzymes to form para-amino benzoic acid (PABA) which is causes allergic effect
- MOA – blocks pain by depressing CNS by antagonizing votage gated Na+ channel thus inhibiting generation of action potential

Synthesis

Route I. From: *p*-Amino benzoic acid: direct reaction of the 4-aminobenzoic acid with 2-diethylamino-ethanol in the presence of sodium ethoxide.

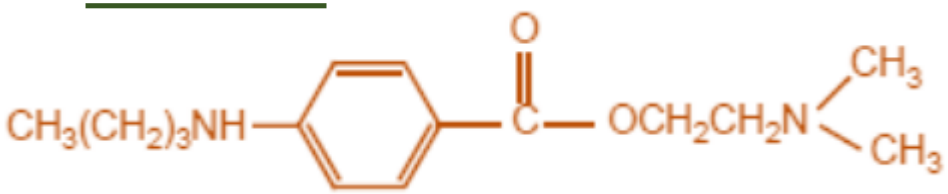


Route II. From: oxidizing 4-nitrotoluene to 4-nitrobenzoic acid, which is further reacted with thionyl chloride



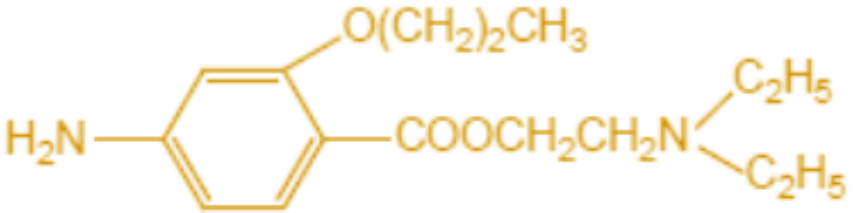
Procaine

Tetracaine



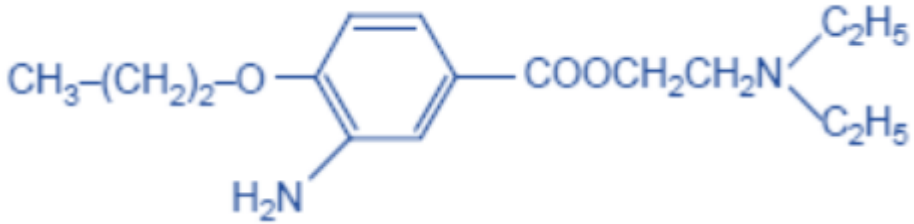
It is an all-purpose local anaesthetic drug used frequently in surface, infiltration block, caudal, and spinal anaesthesia. It is reported to be 10 times more toxic and potent than procaine. Its duration of action is twice than that of procaine.

Propoxycaine (Blockhain)



Its local anaesthetic potency is reported to be 7 or 8 times more than that of procaine. It is a structural isomer of proparacaine, and is less toxic with slightly lower potency than proparacaine. It is mainly used for infiltration and nerve block anaesthesia.

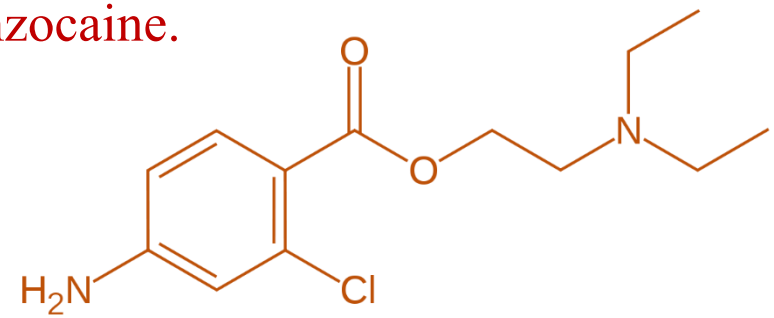
Proparacaine



An effective ester-type surface anaesthetic with potency about equal to that of tetracaine. It is a useful anaesthetic in ophthalmology and induces little or no initial irritation. It is useful for most occular procedures that require topical anaesthesia

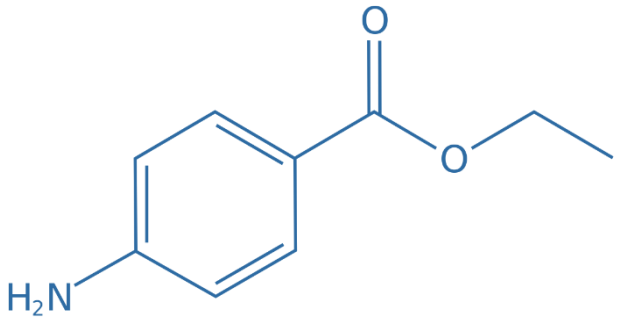
Chloroprocaine

Is a very short-acting, amino ester–type local anesthetic used to provide regional anesthesia by infiltration as well as by peripheral and central nerve block, including lumbar and caudal epidural blocks. The presence of a chlorine atom *ortho* to the carbonyl of the ester function increases its lipophilicity and its rate of hydrolysis by plasma cholinesterase at least threefold compared to procaine and benzocaine.



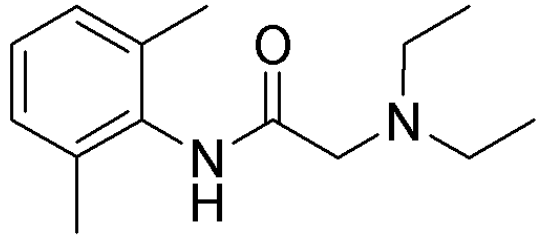
Benzocaine

Like most amino ester–type local anesthetics, it is easily hydrolyzed by plasma cholinesterase. However, because of its low p*K*a, it is un-ionized under most physiologic conditions and, therefore, can only bind to the lipid site in the sodium channel

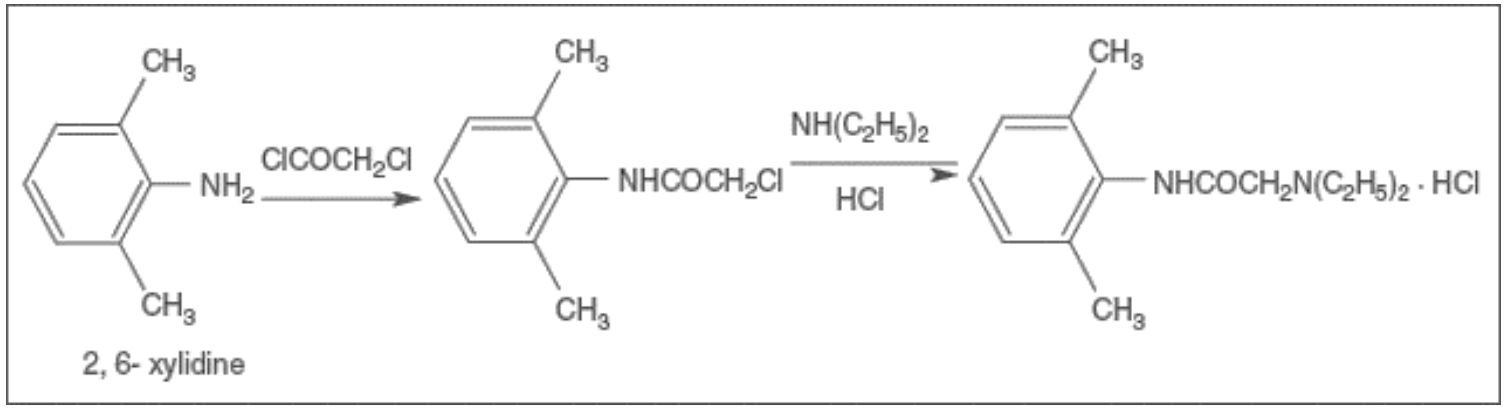


LIDOCAINE

- Most commonly used potent amide type local anesthetic for both parenteral and topical use
- has a rapid onset of action (Intravenous - 45 to 90 seconds).
- It is a potent local anaesthetic. It is reported to be twice as active as procaine hydrochloride in the same concentrations
- Di-ortho methyl groups make the amide group resistant to hydrolysis thus it has moderate duration of action (1-2 hrs)
- Produces eutectic mixture with prilocaine
- MOA – blocks pain by depressing CNS by antagonizing voltage gated Na+ channel thus inhibiting generation of action potential



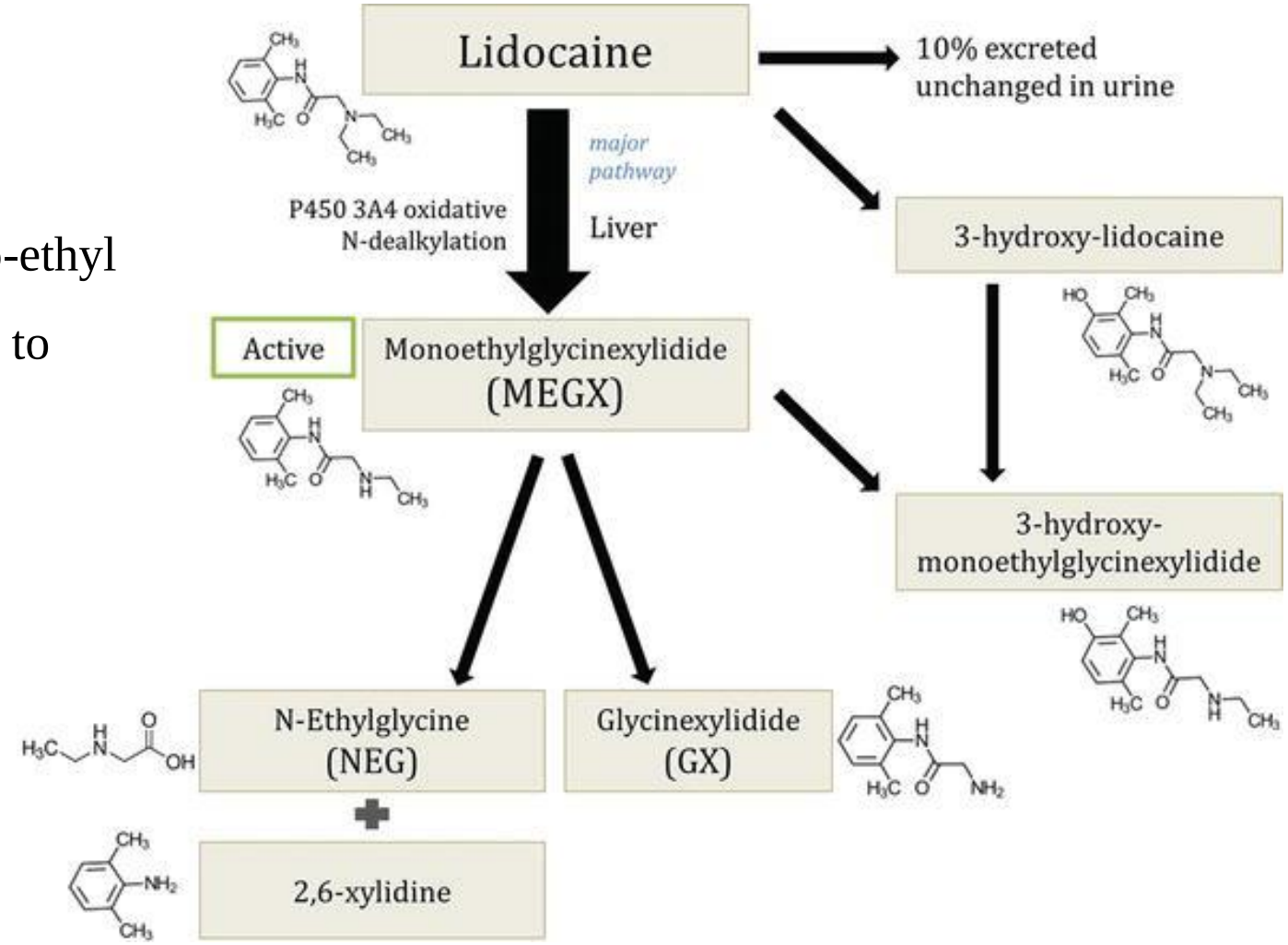
Lidocaine synthesis



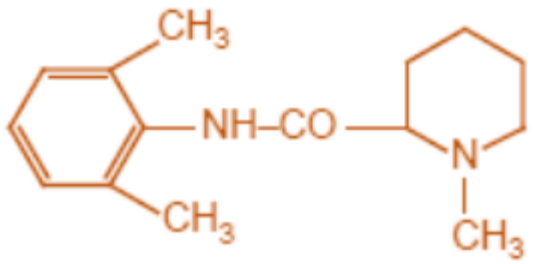
Lidocaine is synthesised from 2,6-dimethylaniline upon reaction with chloroacetyl chloride, which gives α-chloro-2,6-dimethylacetanilide, and its subsequent reaction with diethylamine affords lidocaine.

Metabolism of Lidocaine

Undergoes *N*-de-ethylation to yield mono-ethyl glycinexylide followed by amidase action to *N*-ethyl glycine and 2, 6-dimethylaniline.

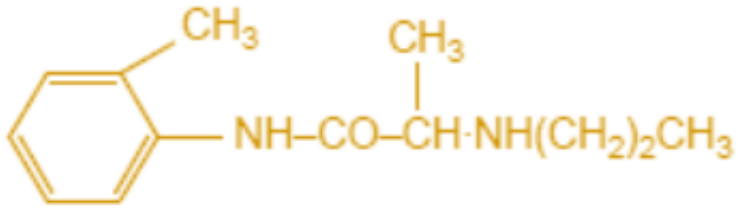


Mepivacaine (Polocaine)



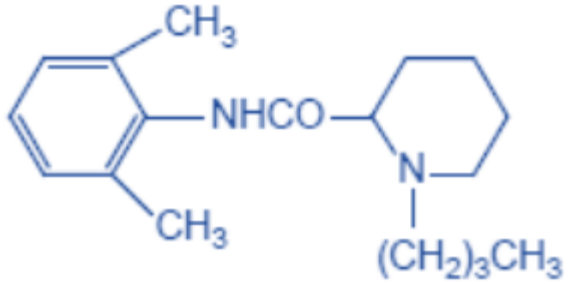
The duration of action is significantly longer than that of lidocaine, even without adrenaline. It is of particular importance in subjects showing contraindication to adrenaline. It is a local anaesthetic used for infiltration, peridural, nerve block, and caudal anaesthesia.

Prilocaine (Citanest hydrochloride)



Its duration of action is in between the shorter-acting lidocaine and longer-acting mepivacaine. The solution of prilocaine HCl is specifically used for such patients who cannot tolerate vasopressor agents, patients having cardiovascular disorders, diabetes, hypertension, and thyrotoxicosis.

Bupivacaine (Marcaine)



It is a long-acting local anaesthetic of the amide type, similar to mepivacaine and lidocaine, but about four times more potent. The effect of bupivacaine last longer than lidocaine hydrochloride. It is longacting local anaesthetic mainly employed for regional nerve block.

Ropivacaine

- *S*-Ropivacaine hydrochloride is the first optically active, amino amide type local anesthetic marketed in recent years. It combines the anesthetic potency and long duration of action of bupivacaine with a side effect profile intermediate between those of bupivacaine and lidocaine.

- Although ropivacaine has a p*K*a nearly identical to that of bupivacaine, it is two to threefold less lipid soluble and has a smaller volume of distribution, a greater clearance, and a shorter elimination half-life than bupivacaine in humans.

- The metabolism of ropivacaine in humans is mediated by hepatic CYP1A2 and, to a minor extent, by CYP3A4. The major metabolite is 3-hydroxyropivacaine, and the minor metabolite is *S*-2′,6′-pipecoloxylidide (an *N*-dealkylated product).