LOCAL ANESTHETICS

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- Definition of local anesthesia

1) It is a transient loss of all modalities of sensation such as pain, touch , temperature and pressure in a localized circumscribed anatomical area by blocking the nerve conduction without loss of consciousness.

2) Local anesthesia is defined as a loss of sensation in a circumscribed area of the body caused by a depression of excitation in nerve endings or an inhibition of the conduction process in peripheral nerve.
(Handbook of Local Anesthesia , Stanley.F.Malamed 6th ed)

Local Anesthetics
DEFINITION

- Drugs which
  - produce a *REVERSIBLE* loss of sensation …
  - in a localized part of the body…..
  - when applied directly onto nerve tissues or mucous membranes

- Local anesthetics are 'local' ONLY because of how they are administered! (*Selectivity*)

The first clinically used Local Anesthetic

Cocaine (ISA activity)

A natural alkaloid from Erythroxylon coca.

Prototype Drug — **Lignocaine (Synthetic)**

Composition of Local AnestheticSolution

Local Anesthetic agent- 2% Lidocaine

Vasoconstrictor- Epinephrine1:80,000 to1:200,000

Reducing Agent- Sodium Metabisulphite

Preservative- Methyl Paraben

Solvent- Distilled Water

IDEAL PROPERTIES OF LOCAL ANESTHESTIC

1) It should not be irritating to the tissue to which it is applied.

2) It should not cause any permanent alteration of nerve structure.

3) It's systemic toxicity should be low.

4) It must be effective regardless of whether it is injected into the tissue or is applied locally to mucous membranes.

5) The time of onset of anesthesia should be as short as possible.

6) The duration of action must be long enough to permit completion of the procedure yet not so long as to require an extended recovery.

- Other desirable qualities listed by Bennett :-

7) It should have have potency sufficient to give complete anesthesia without the use of harmful concentrated solutions.

8) It should be relatively free from producing allergic reactions.

9) It should be stable in solution and should readily undergo biotransformation in the body.

10) It should be sterile or capable of being sterilised by heat without deterioration.

CLASSIFICATION ACCORDING TO CHEMISTRY

- **ESTERS**
  - Cocaine
  - Procaine
  - Tetracaine
  - Benzocaine

(Contd)

- **AMIDES**
  - Lignocaine/Lidocaine
  - Bupivacaine
  - Levobupivacaine
  - Mepivacaine
  - Prilocaine
  - Etidocaine
  - Ropivacaine

2. According to Duration of action

Short Duration of Action

Procaine

Medium Duration of Action

Cocaine, Lidocaine, Mepivacaine, Prilocaine

Long Duration of Action

Tetracaine, Bupivacaine, Etidocaine, Ropivacaine

CLASSIFICATION ACCORDING TO CLINCIAL USES

- **SURFACE ANESTHESIA**
  - Tetracaine
  - Lignocaine
  - Cocaine
  - Benzocaine
- **INFILTRATION ANESTHESIA & FIELD BLOCK ANESTHESIA**
  - Lignocaine
  - Procaine
  - Bupivacaine

- **NERVE BLOCK ANESTHESIA**
  - Procaine
  - Lignocaine
  - Bupivacaine
  - Tetracaine
  - Ropivacaine

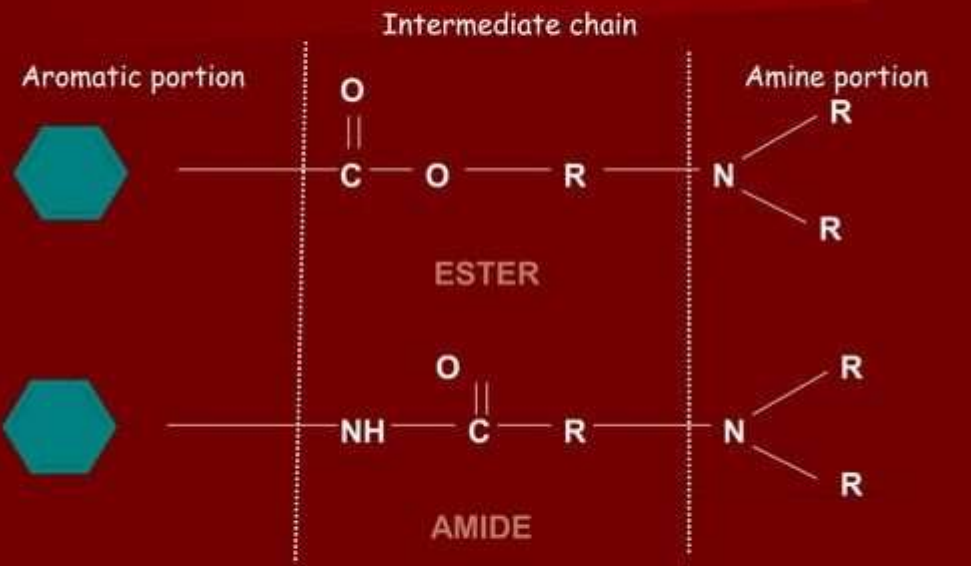
- **SPINAL ANESTHESIA**
  - Lignocaine
  - Tetracaine
  - Bupivacaine
- **EPIDURAL ANESTHESIA**
  - Lignocaine
  - Bupivacaine
- **ANESTHETIC USED IN OPHTHALMOLOGY**
  - Proparacaine

Chemistry

Most local anesthetics consist of 3 parts

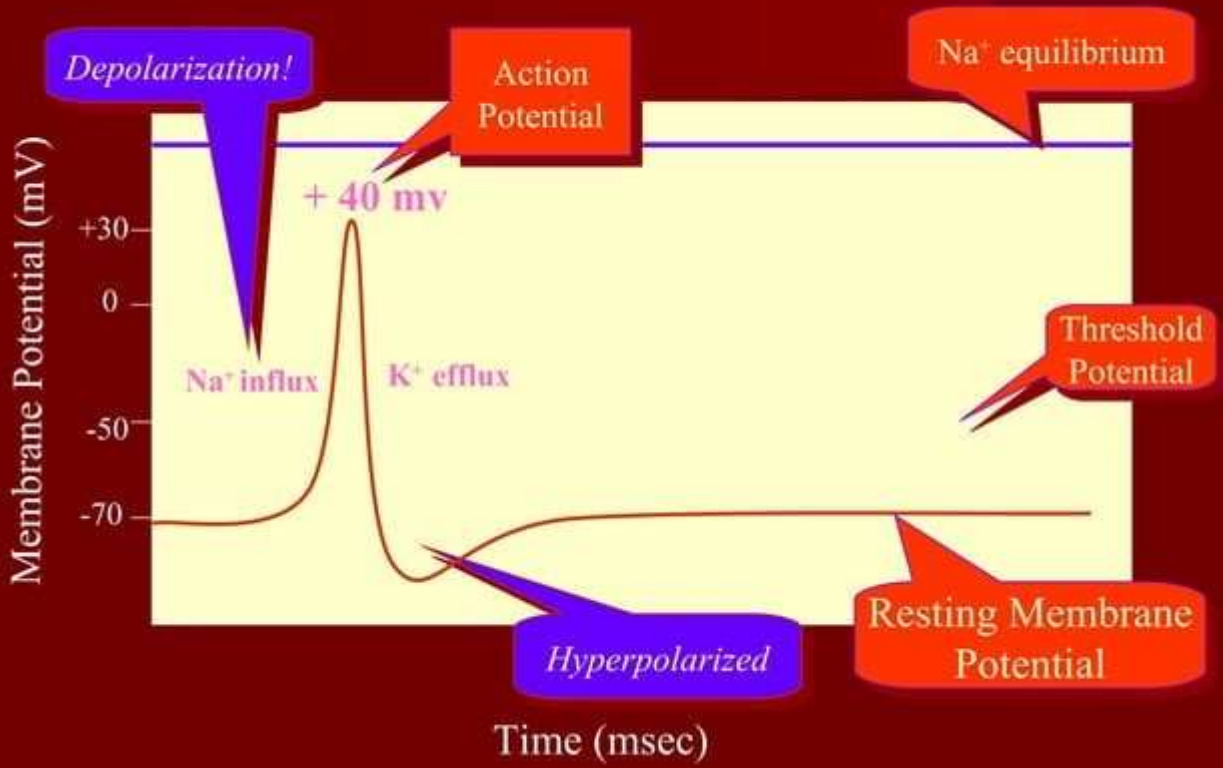
1. Lipophilic Aromatic group
2. Intermediate chain
3. Hydrophilic Amino group

LAs - Weak Bases (pKa:7.5-9)



MECHANISM OF ACTION

- Diffusion into the nerve fiber
- Blockade of sodium channels


Depolarization!
Action Potential
Na+ equilibrium
+ 40 mv
+30
0
-50
-70
Membrane Potential (mV)
Na+ influx
K+ efflux
Threshold Potential
Hyperpolarized
Resting Membrane Potential
Time (msec)

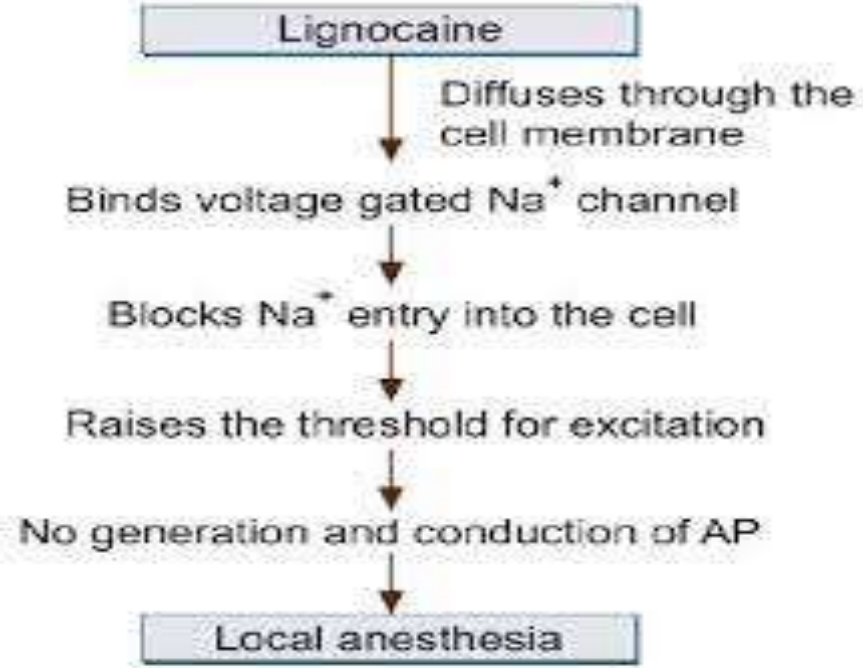
Progressively increasing conc. of a LA applied to a nerve fiber produce blockade of more & more Na+ channels :

- The threshold for excitation increases
- Impulse conduction slows
- The rate of rise of AP declines
- The AP amplitude decreases
- Finally the ability to generate an AP is abolished

- MECHANISM OF ACTION OF LOCAL ANESTHESIA
- 1. Displacement of calcium ions from the sodium channel receptor site, which permits……
- 2. Binding of the local anesthetic molecule to this receptor site , which thus produces….
- 3. Blockade of the sodium channel, and a …
- 4. Decrease in sodium conductance, which leads to….

5. Depression of rate of electrical depolarization…

- 6. And a failure to achieve threshold potential level….along with
- 7. A lack of development of propagated action potentials… which brings about..
- 8. CONDUCTION BLOCKADE


Lignocaine
Diffuses through the cell membrane
Binds voltage gated Na+ channel
Blocks Na+ entry into the cell
Raises the threshold for excitation
No generation and conduction of AP
Local anesthesia

SUSCEPTIBILITY OF NERVE FIBER TO LA

- Potency
- Size of nerve fiber (small fibers blocked 1st)
- Effect of fiber diameter
- Rate of firing (rapidly firing fibers blocked 1st)
- Effect of fiber position in the nerve bundle (outer fibers blocked 1st, then core fibers)

ORDER OF BLOCKADE

- AUTONOMIC
- PAIN
- TEMPERATURE
- TOUCH
- DEEP PRESSURE
- MOTOR

Recovery in reverse order

PHARMACOKINETICS

- Absorption

  Dosage

  Site of injection

(when used for major conduction blocks, the peak serum levels will vary as a function of the specific site of injection, with intercostal blocks among the highest, & sciatic & femoral among the lowest)

  Lipid solubility

(more lipid soluble – longer DOA)

PHARMACOKINETICS

Ph

Vascularity (highly vascular area – more rapid absorption – higher blood levels)

- Combination with vasoconstrictors (resultant reduction in blood flow reduces rate of systemic absorption & diminishes peak serum levels)
- Distribution
- Biotransformation & Excretion

Comparison of LA characteristics

	Relative lipid solubility	Relative potency	onset	pKa	Local duration	vasodilation	Plasma protein binding
procaine	1	1	slow	8.9	short	+++	5%
lidocaine	4	4	rapid	7.9	moderate	+++	55%
tetracaine	80	16	slow	8.5	long	+	75%
bupivacaine	130	16	slow	8.1	long	+	90%

Plasma protein binding may be used as an indirect measure of tissue binding tendencies

ADVERSE EFFECTS

- CNS (1st stimulation, then depression)
- Local Neurotoxicity
  (cauda equina syndrome associated with continuous spinal anesthesia – CSA)
- CVS (bupivacaine – most cardiotoxic)
- ANS
- Motor Paralysis
- Hematological Effects
- Hypersensitivity reactions

- **Cocaine**
  - Medical use limited to surface or topical anesthesia
  - Avoid epinephrine because cocaine already has vasoconstrictor properties. (EXCEPTION!!!)
  - A toxic action on heart may induce rapid and lethal cardiac failure.
  - A marked pyrexia is associated with cocaine overdose.

SELECTIVE PHARMACOLOGICAL

- **Benzocaine**
  - pKa ~ 3,
  - Available in many preps for relief of pain and irritation
  - for surface anesthesia (topical) only ... ointments, sprays, etc.
  - Used to produce anesthesia of mucous membranes
  - methemoglobinemia

SELECTIVE PHARMACOLOGICAL PROPERTIES OF SOME AMIDE - type LA

- **LIDOCAINE** (Xylocaine) Most widely used LA
  - Effective by **all routes**.
  - Faster onset, more intense, longer lasting, than procaine.
  - Good alternative for those allergic to ester type
  - More potent than procaine but about equal toxicity
  - ***More sedative*** than others

SELECTIVE PHARMACOLOGICAL PROPERTIES OF SOME AMIDE - type LA

- **Bupivacaine** (Marcaine)
  - No topical effectiveness
  - Slower onset and one of the longer duration agents
  - Unique property of *sensory and motor dissociation* can provide sensory analgesia with minimal motor block
    - has been popular drug for analgesia during labor
  - More cardiotoxic than other LA

SELECTIVE PHARMACOLOGICAL PROPERTIES OF SOME AMIDE - type LA

- **Ropivacaine**
  - Enantiomer of bupivacaine (S stereoisomer)
  - No topical effectiveness
  - Clinically ~ equivalent to bupivacaine
  - Similar sensory versus motor selectivity as bupivacaine with significantly less CV toxicity

CLINICAL APPLICATIONS

- **SURFACE ANESTHESIA** (Topical)
  - Ear,Nose, mouth, bronchial tree, nasopharynx,cornea, GIT and urinary tracts
    - Lidocaine, tetracaine, Benzocaine
    - EMLA cream (**E**utectic **M**ixture of **L**ocal **A**nesthetics)
      lidocaine 2.5% + prilocaine 2.5%
      permits anesthetic penetration of keratinized layer of skin as deep as 5mm, producing localized numbness.

Clinical Applications

- **INFILTRATION ANESTHESIA**
  - Direct injection into tissues to reach nerve branches and terminals.
  - Can be superficial as well as deep.
  - Used in minor surgery.
  - Immediate onset with variable duration.
  - This type involve skin region as deep as intraabdominal tissue.

.Most LA's used

Clinical Applications

- **NERVE BLOCK** or **FIELD BLOCK**
  - Interruption of nerve conduction upon injection into the region of nerve plexus or trunk.
  - Used for surgery, dentistry, analgesia.
  - Less anesthetic needed than for infiltration
  - Given within specific nerve area such as brachial plexus, within intercostal nerves,abdominal nerves are targeted, cervical plexus when neck region is targeted.

    .Most LA's used

Clinical Applications

- **SPINAL ANESTHESIA**
  - Injection into subarachnoid space below level of L2 vertebra to produce effect in spinal roots and spinal cord.
  - Use hyperbaric or hypobaric solutions depending on area of blockade.
  - Used for surgery to abdomen, pelvis or leg when can't use general anesthesia.
  - Can be employed in pts of hepatic, renal & CVS diseases
    - Lidocaine, tetracaine

Clinical Applications

- EPIDURAL AND CAUDAL ANESTHESIA

  – Injection into epidural space usually at lumbar or sacral levels or near dura matter where nearly most nerves pass closely. Areas supplied by these nerves are targeted e.g.

  .ligamentum flavum(post)

  .spinal periosteum(laterally), dura(ant).

  – Lower part of the body. Pelvic region

  – For painless child birth.

Clinical Applications

- Unwanted effects similar to that of spinal (pain, hematoma, introduction of foreign particle, hypotension – Rx: raise foot-end of bed or give sympathomimetics, headache – Rx: small bore needle & blood patch, cauda equina syndrome, rarely respiratory paralysis)

  - Lidocaine, bupivacaine, ropivacaine