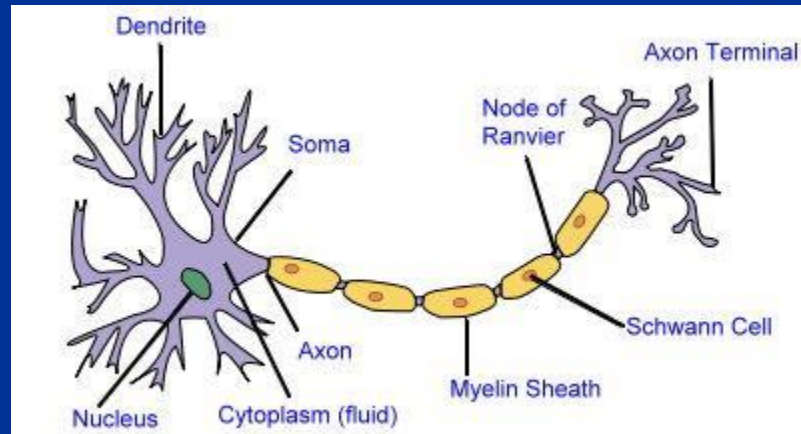


LOCAL ANAESTHETIC DRUGS

MODERATOR-DR.SIDHARTH VERMA
PRESENTING BY-DR RAJEEV



DEFINATION



LA are the drugs that cause reversible loss of sensory perception specially of pain in a restricted area of the body, when applied topically or local injection.

LA if applied to a mixed nerve—sensory and motor impulses are interrupted—resulting in muscular paralysis and loss of autonomic control.

Some Clinical Examples of their Use

- **Topically:** Nasal mucosa and wound margins
- **Infiltration:** Vicinity of peripheral nerve endings and major nerve trunks
- **Epidural** or Subarachnoid spaces: surrounding spinal nerves
- **Regional anesthesia:** Intravenous injection in arm or leg (Bier block)



Common Uses of Local Anaesthetics:



Excision



Dermatology



Dentistry



Spinal Anaesthesia

SCIENCEPHOTOLIBRARY

Local Vs General Anaesthesia

	General	Local
Site of action	CNS	Peripheral nerves
Area	Whole body	Restricted areas
Consciousness	Lost	Unaltered
Preferential use	Major surgery	Minor surgery
Use in non-cooperative patients	Possible	Not possible
Poor health patient	Risky	Safer
Care for vital functions	Essential	Not needed



HISTORY

- Thousands of years - South American indigenous peoples have chewed the leaves of *Erythroxylon coca*
- Found in Ancient Peruvian mummies



Isolation and naming

- Cocaine alkaloid was first isolated by Friedrich Gaedcke in 1855
- Albert Niemann, 1856 improved purification process and named it cocaine
- Richard Willstätter in 1898 first synthesised and described the structure of the cocaine molecule

What are the drugs? (Classification)

- **Injectable anaesthetic:**

- *Low potency, short duration* – **Procaine** and Chlorprocaine
- *Intermediate potency* – **Lidocaine (Lignocaine)** and Prilocaine
- *High potency and long duration* – **Tetracaine, Bupivacaine,** Ropivacaine, Etidocaine, Mepivacaine and Dibucaine (Cinchocaine)

- **Surface anaesthetic:**

- **Soluble** – **Cocaine**, Lidocaine, Tetracaine and Benoxinate
- **Insoluble** – Benzocaine, Butylaminobenzoate and Oxethazine

- **Miscellaneous drugs:**

- Clove oil, phenol, chlorpromazine and diphenhydramine etc.



Another Classification ?

- Local anesthetics are also classified according to Chemical Structure!
- What is it ?



ESTER LINKAGE

- Short acting
- Metabolized in the plasma and tissue fluids
Except cocaine it is metabolised in liver
- Excreted in urine

High incidence of allergic reaction because of para aminobenzoic acid.

AMIDE LINKAGE

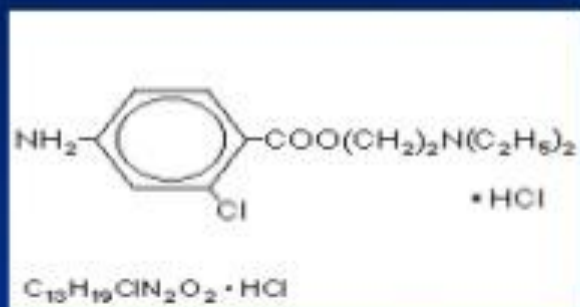
- Longer acting
- Metabolized by liver enzymes
- Excreted in urine

Lower incidence of allergic reaction



Chemistry of LAs – contd.

ESTER LINKAGE



PROCAINE

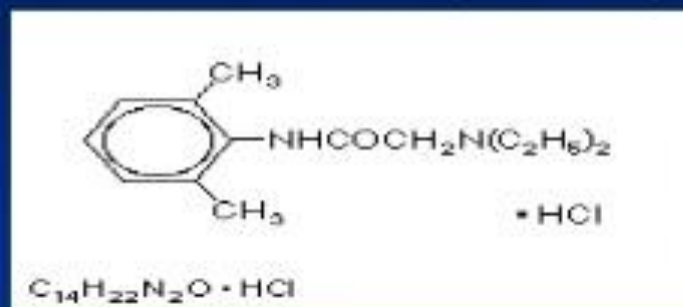
procaine (Novocaine)

tetracaine (Pontocaine)

benzocaine

cocaine

AMIDE LINKAGE (2 EYES!!)



LIDOCAINE

lidocaine (Xylocaine)

mepivacaine (Carbocaine)

bupivacaine (Marcaine)

etidocaine (Duranest)

ropivacaine (Naropin)

Molecular structure

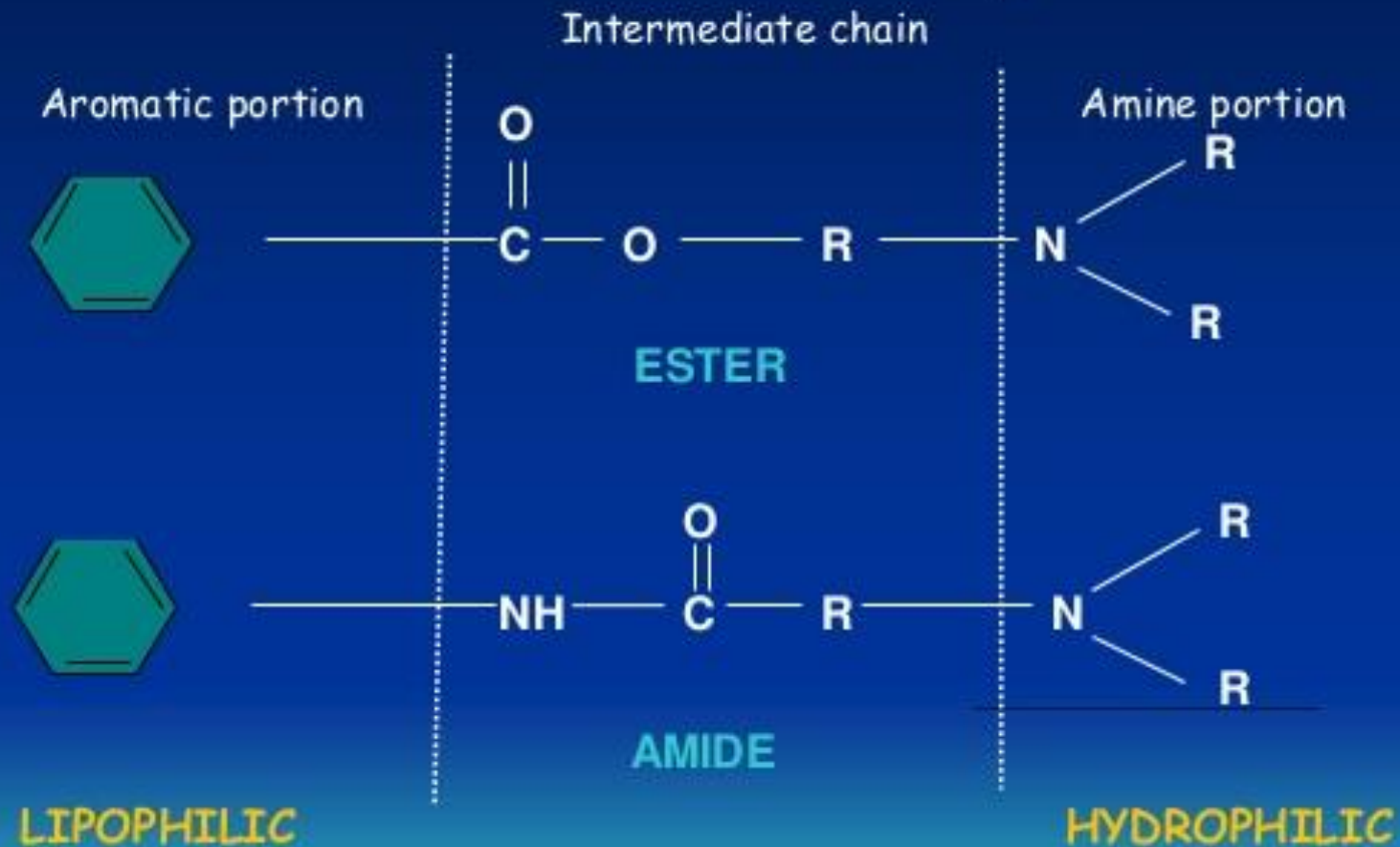
Local Anesthesia consist of a lipophilic and a hydrophilic portion seperated by a connecting hydrocarbon chain.

Hydrophilic group is tertiary amine such as diethylamine where as the lipophilic portion is usually an unsaturated aromatic ring such as paraaminobenzoic acid.

The lipophilic portion is essential for anesthetic activity and therapeutically useful local anesthetic require a delicate balance between lipid solubility and water solubility.

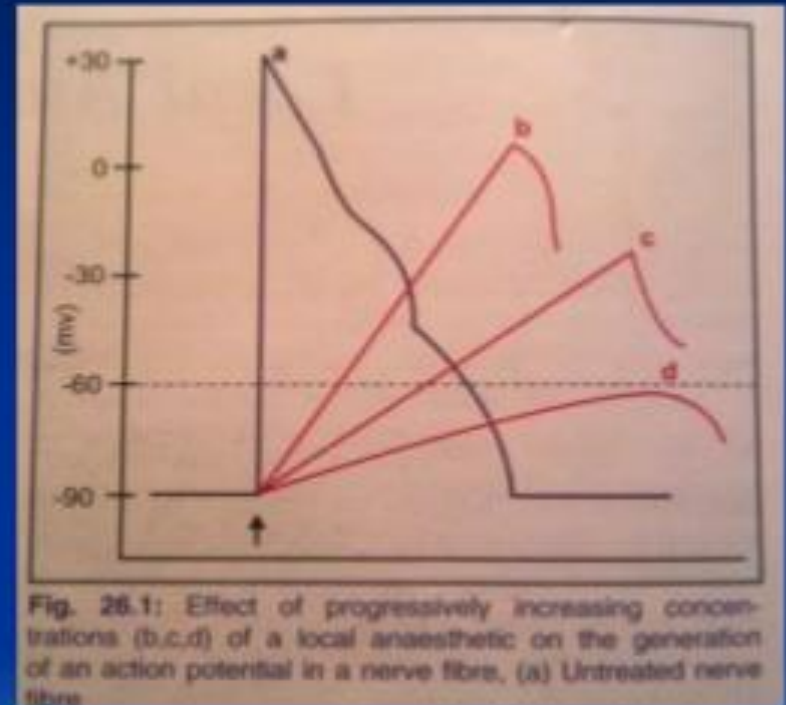


Chemistry of LA – contd. (LAs are Weak Bases)

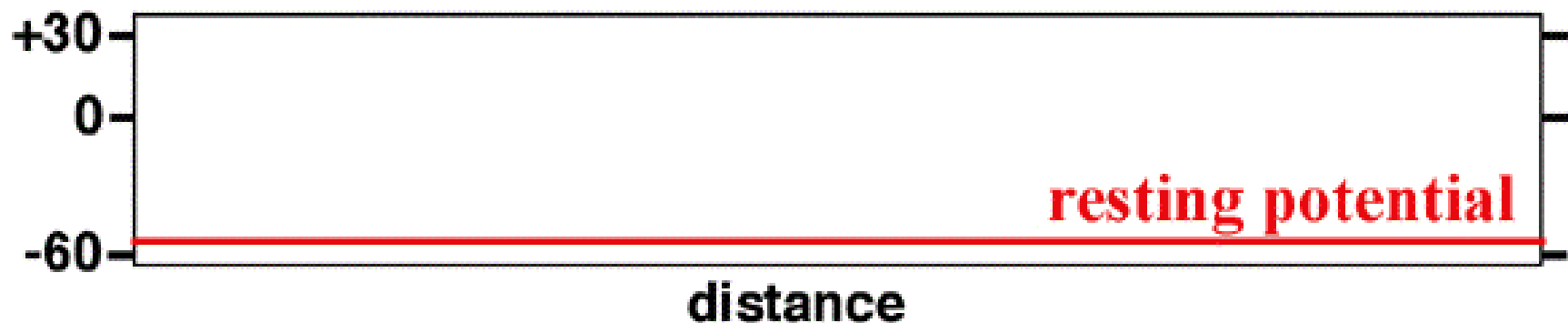
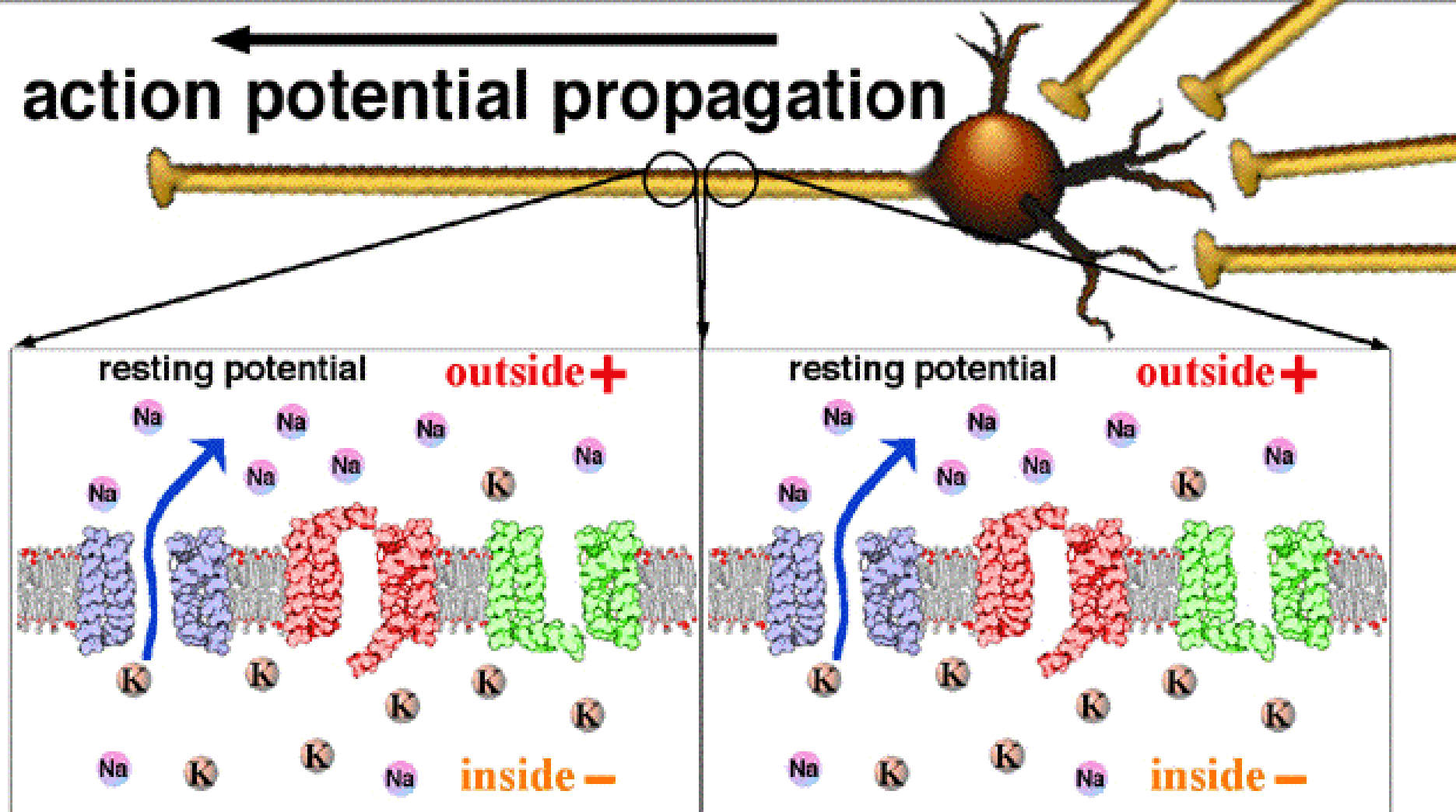


Mechanism - LAs

- As you know, entry of Na^+ is essential for Action potential
- Two things happen:
 - Rate and rise of AP and maximum depolarization decreases – **slowing of conduction**.
 - Finally, local depolarization fails to reach threshold potential – **conduction block**.



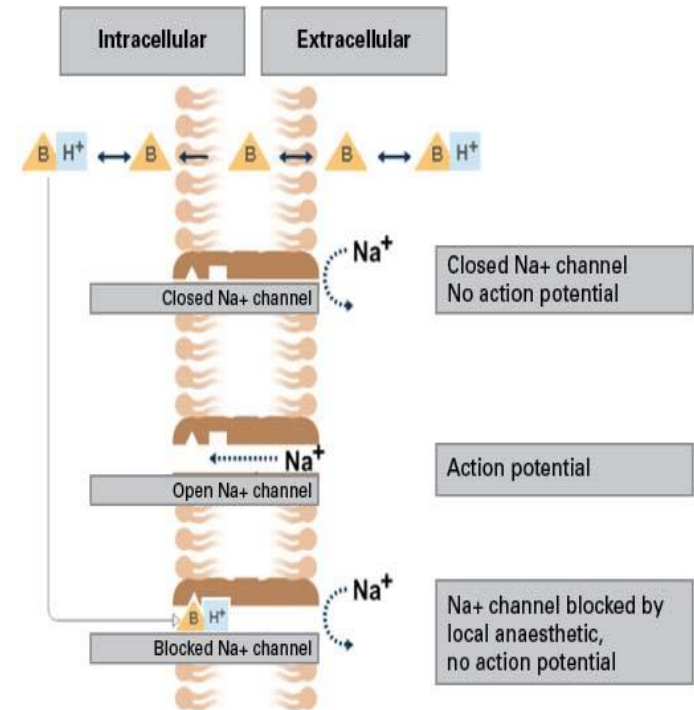
action potential propagation



Mech Of Action

- ◆ Local anesthetics produce anaesthesia by blocking nerve conduction and reducing the influx of sodium ions into the nerve cytoplasm.
- ◆ local anesthetics bind directly to the intracellular voltage-dependent sodium channel and block conduction.
- ◆ Sodium ions cannot influx into the neuron, thus the potassium ions cannot efflux, thereby inhibiting the depolarization of the nerve and hence action potential
- ◆ Block primarily open and inactive sodium channels, at specific sites within the channel

Mechanism of action ■ local anesthetics



CHANGE PAIN®

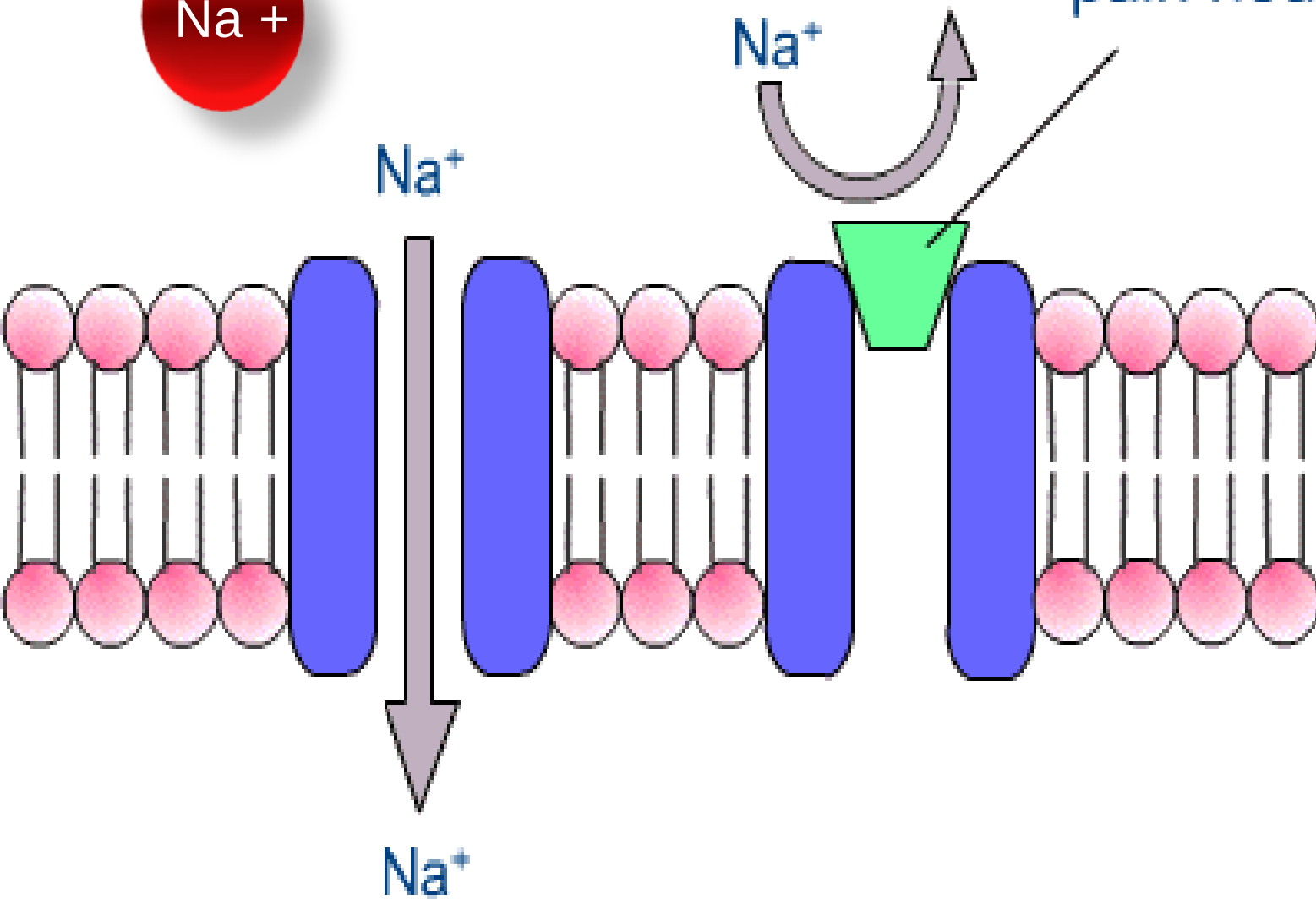
© Grünenthal GmbH

Na⁺

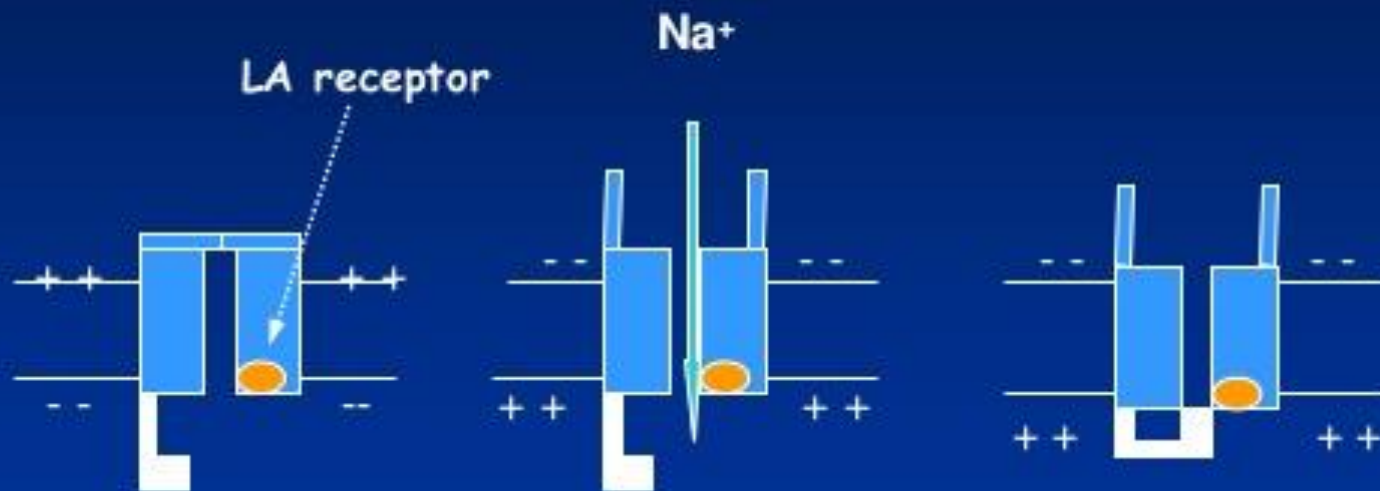
Na⁺

lignocaine blocks
sodium ion channels in
pain neurons

Na⁺



Mechanism of LA – contd.



Resting
(Closed⁺⁺)

Open
(brief)

Inactivated

LA have highest
affinity for the
inactivated form

Very slow
repolarization in
presence of LA

Refractory period

Influencing factor of LA action

Lipid solubility

- All local anesthetics have weak bases. Increasing the lipid solubility leads to faster nerve penetration, block sodium channels, and speed up the onset of action.

Influence of pH

- Lower pKa (7.6 – 7.8) – faster acting (lidocaine, mepivacaine)
- Higher pKa (8.1 – 8.9) – slower acting (procaine, tetracaine, bupivacaine)

Addition of vasoconstrictors

- Cause decrease systemic absorption & increases duration of action.

Adrenaline used as a vasoconstrictors used in concentration 1:2,00,000.

Xylocaine with adrenaline should not be used for ring block of finger, toes pinna, penis may cause ischemia & necrosis

Sodabibarbonate Adding causes change in pH to more alkaline making more drug in non ionized form to bind sodium channels.



(pK_a) Acid dissociation constant / Acid-ionization constant

- pK_a is the pH at which a local anesthetic agent is in 50% ionized and 50% non ionized form.
- LA with Pka closest to physiological pH will have a greater fraction of non ionized base that more readily permeates the nerve cell membrane, generally facilitating a more rapid action.



Actions of LA - Local

- All LAs have effects on nerves acting via Na^+ channel – sensory endings, nerve trunks, NM junctions, ganglion and receptors
- Injected near Mixed nerve – anaesthesia of skin and paralysis of voluntary muscles
- Sensory and Motor fibres are equally sensitive – depends on diameter and types of fibres (gr. C & gr A etc.)
 - Smaller fibers are more sensitive than larger ones
 - Frequency dependence
 - Myelinated nerves are blocked earlier than non-myelinated ones
- Autonomic fibres are more susceptible than somatic ones



Functions lost with LA

Answer

- Pain perception
- Temperature
- Touch sensation
- Proprioception
- Skeletal muscle tone

- **The order of blockade:**
 - Initially gr. `C` fibres are blocked – pain and sympathetic vasoconstrictors
 - Then gr. `A` fibres
- **Pain** – temperature – touch - pressure and vibration –motor fibres (Muscle)
- **Tongue:** bitter – sweet – sour - salt



SYSTEMIC EFFECT OF LA

- 1. CNS** It is the 1st system involved in local anaesthesia toxicity. CNS is involved at much lower doses as compared to CVS. There is a sequence of excitation followed by depression as inhibitory neurons are more sensitive than excitatory neurons.

Increases plasma conc LA crosses blood brain barrier & produce CNS changes, restlessness, vertigo, tinnitus, slurring of speech & skeletal muscle twitching.

Twitching 1st seen in face & extremities followed by seizures. Seizure is due to inhibition of release of neurotransmitter gamma-aminobutyric acid.



CVS

LA are cardiac depressants.

At high doses decrease automaticity, excitability, contractility, conductivity & arrhythmias.

Hypotension due to sympathetic blockage but at high dose cause relaxation of smooth muscles and cardiovascular collapse.
cocaine has sympathetmimetic property produce tachycardia & increase bp

Bupivacain is more cardiotoxic and produced ventricular tachycardia.
lignocaine has little effect on contractility & conductivity.



Undesired effects of LA – contd.

Methemoglobinemia

- Some LA metabolites have significant oxidizing properties
- This may cause a significant conversion of hemoglobin to methemoglobin & compromise ability to carry oxygen.
- May be a problem if cardiopulmonary reserve is limited.
- Treatment with oxygen & methylene blue (converts methemoglobin to hemoglobin)
- Prilocaine , Benzocaine , Lidocaine have been implicated.



Undesired effects of LA – contd.

- **Hypersensitivity:**

- Common with ester-linked LA due to paraaminobenzoic acid
- Rashes, angio-edema, dermatitis and rare anaphylaxis
- Sometimes typical asthmatic attack

- **Neurotoxicity:**

- LA can cause concentration-dependent nerve damage to central and peripheral NS
- Mechanism(s) not clear
- Permanent neurological injury is rare
- May account for transient neurological symptoms after spinal anesthesia
 - Cauda equina syndrome



Pharmacokinetic of LA

- **Absorption:**

- Surface anesthetics from mucus membrane and abraded areas
- Depends on Blood flow to the area, total dose and specific drug characteristics
- Procaine has poor penetration in mucus membrane
- Procaine is negligibly bound to plasma protein but amides are bound to *alpha*₁ acid glycoprotein

- **Distribution:**

- Widely distributed in the body: (lipophilic)
- Enters brain, heart, liver and kidney
- Followed by muscle and other viscera



Pharmacokinetic of LA – contd.

- **METABOLISM**

- Ester type LA

- Hydrolysis by cholinesterase in plasma to PABA derivatives
 - pseudo cholinesterase or butyrylcholinesterase
 - Generally, short acting and low systemic toxicity
 - Prolonged effects seen with genetically determined deficiency or altered esterase (cholinesterase inhibitors)

- Amide type LA

- Bound to alpha1 acid glycoprotein
 - Hydrolyzed by liver microsomal enzymes (P450)
 - Longer acting & more systemic toxicity than esters
 - High first pass metabolism on oral ingestion



Treatment of systemic toxicity of local Anaesthesia;

Include : 1. Airway management,
2. Circulatory support,
3. Removal of LA from receptor site.

- Treatment of LA induced seizures includes ventilation with oxygen because arterial & metabolic acidosis occurs within sec.
- Diazepam used to suppress LA induced seizures
- Propofol can be given if hemodynamic is stable
- If not respond to initial treatment muscle relaxant succinylcholine or NDMR can be given to prevent hypoxia & seizures.



- Use of **LIPID EMULSION** at earliest sign of toxicity is recommended after airway management.
- Initial bolus of 1.5ml/kg lipid emulsion followed by 0.25ml/kg per minute of infusion for 10 min till circulatory stability .
- Epinephrine used lower dose of 10 to 1200 microgm during resuscitation.
- Ca channel + beta blocker avoided
- No response to treatment should undergo cardiopulmonary bypass



Individual LA - Cocaine

- Natural alkaloid from *Erythroxylon coca*
- Medical use limited to surface or topical anesthesia (corneal or nasopharyngeal)
 - Constriction of corneal vessels and sloughing and drying
- A toxic action on heart may induce rapid and lethal cardiac failure – reuptake inhibition of Adr. And NA
- CNS: Stimulation of vasomotor, vomiting and temperature centre etc.
 - Initially euphoria followed by dysphoria (DA reuptake)
- Avoid adrenaline because cocaine already has vasoconstrictor properties. (EXCEPTION!!!)
- A marked pyrexia is associated with cocaine overdose
- Not used presently



Main physiological effects of **COCAINE**

Systemic:

- Increased temperature

Pupils:

- Dilation

Sense of balance:

- Vertigo

Blood vessels:

- Constriction
- Increased blood pressure

Heart:

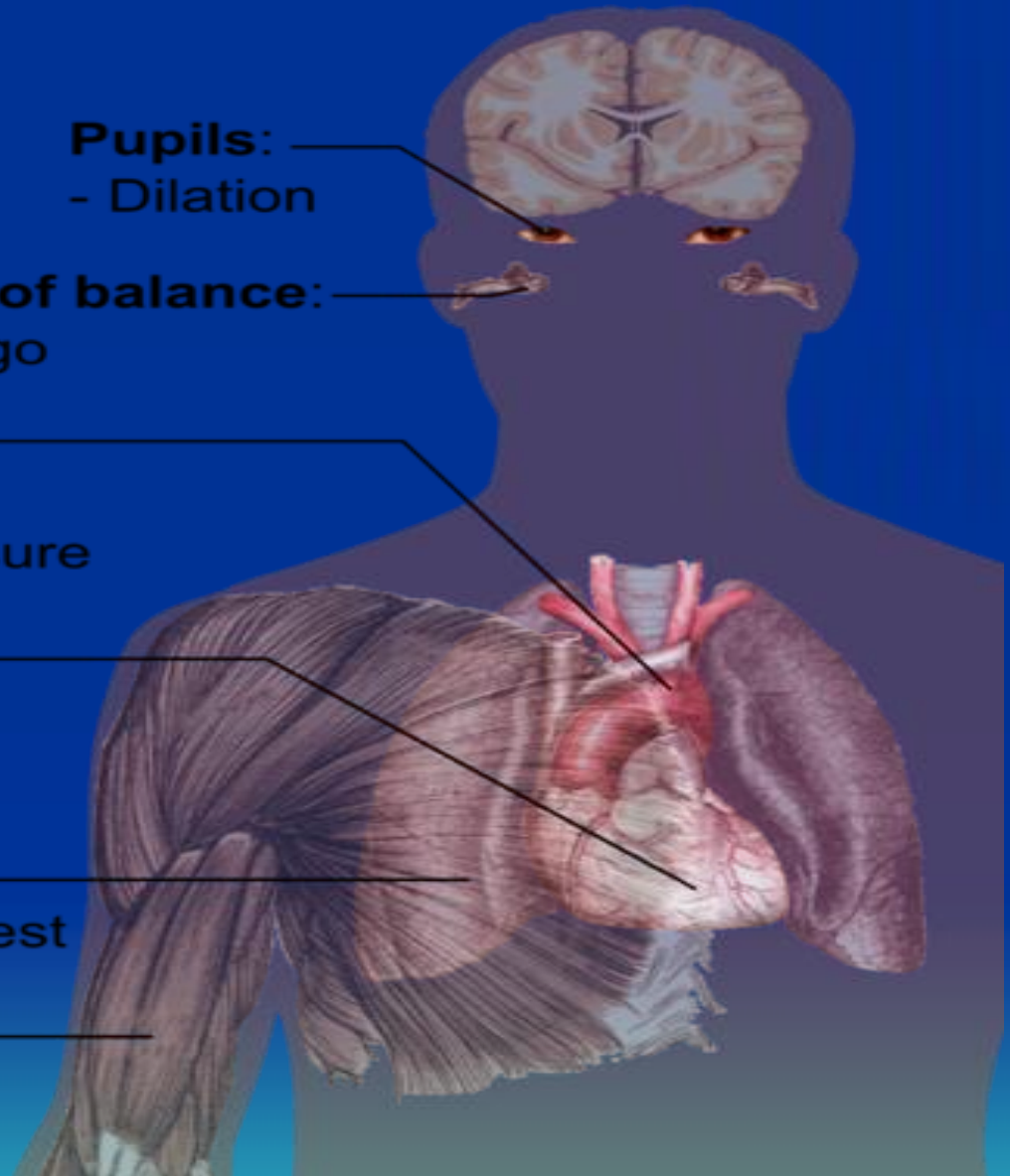
- Increased heart rate
- Risk of cardiac arrest

Lungs:

- Risk of respiratory arrest

Muscles:

- Tremor
- Twitches



Side effects of chronic use of Cocaine

Brain:

- Increased risk of strokes
- Reduced attention
- Insatiable hunger
- Insomnia/Hypersomnia
- Lethargy

Systemic:

- Fever
- Eosinophilia

Nose:

- Rhinorrhea (discharge)

Throat:

- Soreness
- Hoarse voice

Teeth:

- Abrasion

Lungs:

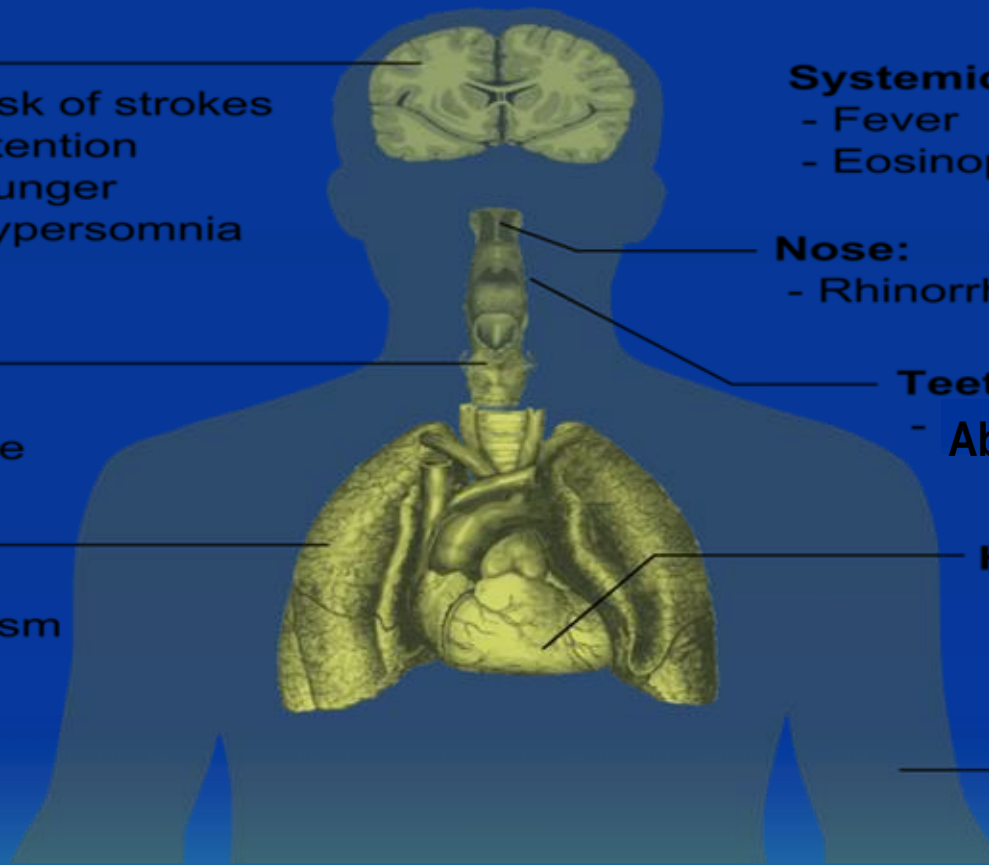
- Hemoptysis
- Bronchospasm
- Dyspnea
- Infiltrates
- Eosinophilia
- Chest pain
- Asthma

Heart:

- Increased risk of infarction

Skin:

- Pruritus



Esters – contd.

Procaine (Novocaine)

- Topically ineffective - disadvantage
- Used for infiltration because of low potency and short duration but most commonly used for spinal anesthesia
- Short local durationproduces significant vasodilation. Adrenaline used to prolong effect
- Systemic toxicity negligible because rapidly destroyed in plasma
- Procaine penicillin



Individual LA - Amides

LIDOCAINE (Xylocaine) Most widely used and popular LA

- Effective by all routes – topical, infiltration, spinal etc.
- Faster onset (3 Vs 15 min), more intense, longer lasting (30 – 60 min.), than procaine
- Addition of Adr in 1:200,000 prolongs the action for 2 Hrs
- More potent than procaine but about equal toxicity
- Quicker CNS effects than others (drowsiness, mental clouding, altered taste and tinnitus)
- Overdose (muscle twitching, cardiac arrhythmia, fall in BP, coma and respiratory arrest)
- Antiarrhythmic
- Available as Injections, topical solution, jelly and ointment etc.



Xylocaine Viscous 2% oral solution and spray

Lidocaine viscous solution and spray is a local anaesthetic that is applied topically to treat painful mucous membranes or throat pain associated with oral diseases and for procedures involving the insertion of instruments into the respiratory or digestive tracts. e.g.

- Bronchoscopy,
- Esophagoscopy ,
- Laryngoscopy in difficult intubation.

Available in 2%, 4 % ,10 %.

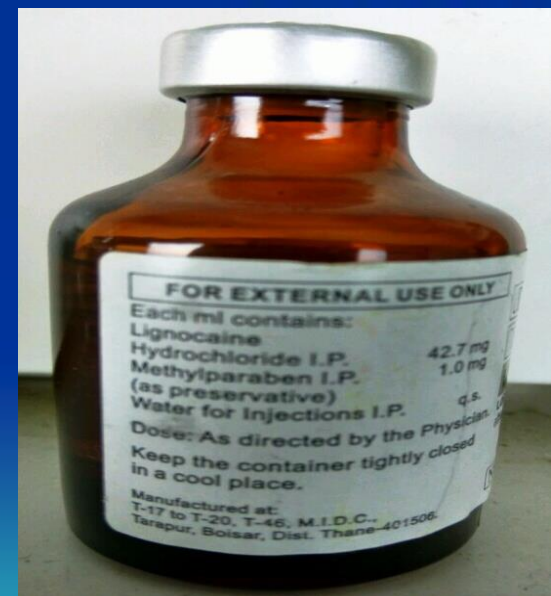
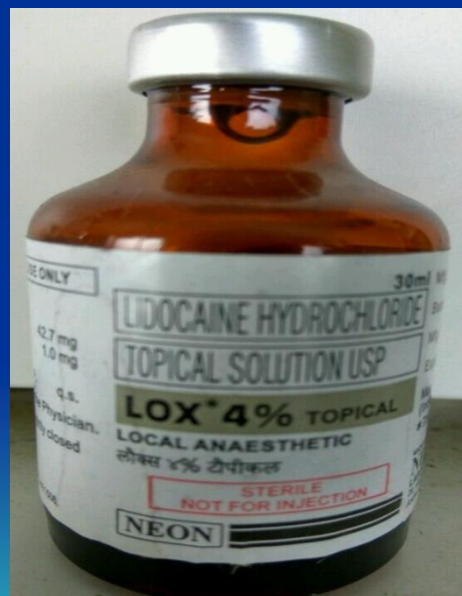
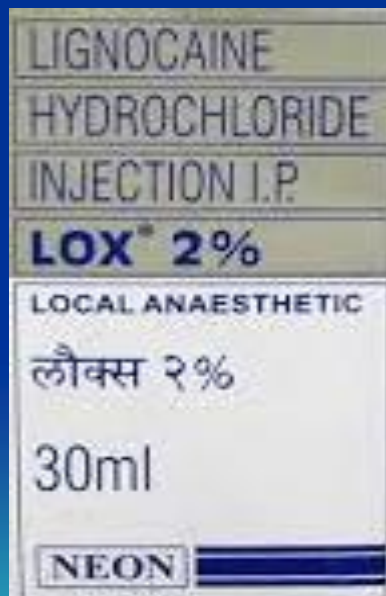
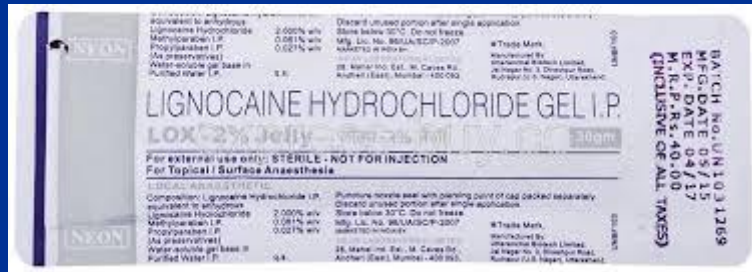
SIDE EFFECTS:

Mild nausea, stinging, and burning may occur at site of application

Allergic or anaphylactic reactions.

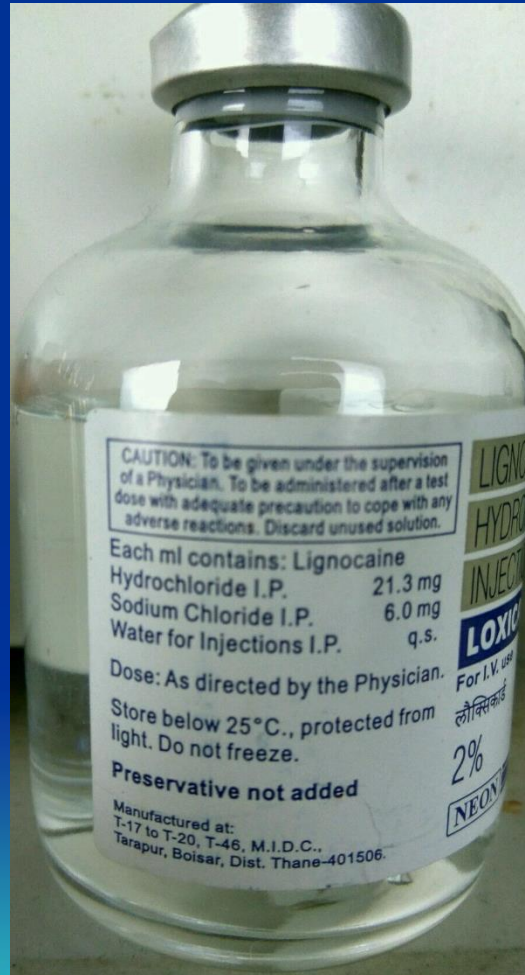


Some variant of lignocaine



LOXICARD

- Loxicard is an antiarrhythmic agent of class IB, local anesthetic
- Treatment and prevention of ventricular arrhythmias (extrasystoles, tachycardia, atrial flutter, atrial fibrillation)
- Used during induction before giving propofol to decrease pain on injection
- Given I/V route



Individual LA (Amides)

Bupivacaine (Marcaine)

- No topical effect
- Slower onset and one of longer duration agents (8 Hrs.)
- Used for infiltration, spinal, nerve block and epidural
- Unique property analgesia without significant motor blockade (*popular drug for analgesia during labor*)
- High lipid solubility, high distribution in tissues and less in blood (*benefit to fetus*)
- More cardio toxic than other LA (prolong QT interval)
 - not given IV
- Available as 0.25%, 0.5% inj.

Contains 1 mg methyl paraben as antiseptic preservative

Each ml contains: Bupivacaine Hydrochloride I.P. equivalent to Anhydrous Bupivacaine Hydrochloride 5.0 mg Sodium Chloride I.P. 8.0 mg Methylparaben I.P. 1.0 mg (as preservative) Water for Injection I.P. q.s. Dose: As directed by the Physician. Store in a cool place, protected from light. MAXIMUM 10 WITHDRAWALS MADE IN INDIA BY: NEON LABORATORIES LIMITED 28, Mahal Ind. Est., M. Caves Rd., Andheri (East), Mumbai - 400 093.	Rx 20ml BUPIVACAINE HYDROCHLORIDE INJECTION I.P. ANAWIN* LOCAL ANAESTHETIC एनाविन 0.5% NEON
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BUPIVACAIN HEAVY

Contain Bupivain hydrochloride 5mg

Dextrose 80mg

No preservative

Uses only for spinal anesthesia

Dextrose make solution hyperbaric heavier than specific gravity of csf

Specific gravity of csf - 1.003-1.008



Conclusion

Anesthetic	pKa	Onset	Duration (with Adrenaline) in minutes	Max Dose (with adrenaline)
Procaine	9.1	Slow	45 - 90	8mg/kg – 10mg/kg
Lidocaine	7.9	Rapid	120 - 240	4.5mg/kg – 7mg/kg
Bupivacaine	8.1	Slow	4 hours – 8 hours	2.5mg/kg – 3mg/kg



Individual LA (Amides) – contd.

EMLA = eutectic mixture of local anesthetics

- Eutectic = two solid substances mixed together in equal quantities by weight form a eutectic mixture
- the melting point of the mixture is lower than the melting points of the individual components
- EMLA = lidocaine and prilocaine becomes an oily mixture



EMLA application



Individual LA (Amides) – contd.

lidocaine/prilocaine combination is indicated for dermal anaesthesia

- Specifically it is applied to prevent pain associated with intravenous catheter insertion, blood sampling, superficial surgical procedures; and topical anaesthesia of leg ulcers for cleansing or debridement
- it can also be used to numb the skin before tattooing.
- EMLA cream is also used in the treatment of premature ejaculation



Individual LA (Amides) – contd.

TAC: (LET)

- tetracaine 0.5%, adrenaline 1 in 2000 and cocaine 10%
- topical anesthetic mixture found to be effective for nonmucosal skin lacerations to the face and scalp
- applied directly to the wound using a cotton-tipped applicator with firm pressure that is maintained for 20 to 40 minutes
- maximum dose for children-0.05ml/Kg
- toxicity due to cocaine



Levobupivacaine

Is a local anaesthetic drug belonging to the amino amide group. It is the *S*-isomer of bupivacaine.

Since it not contain *R* isomers it is less cardio toxic & neurotoxic than bupivacaine.

Compared to bupivacaine, levobupivacaine is less vasodilation and has a longer duration of action.

Used in infiltration, nerve block epidural and intrathecal anaesthesia in adults & infiltration analgesia in children

contraindicated for I/V regional anaesthesia (IVRA).



Ropivacaine

Is a local anaesthetic drug belonging to the amino amide group. Ropivacaine was developed after Bupivacaine to reduce the cardiotoxicity, The butyl group of Levobupivacaine was replaced by propyl group.

Cardiotoxicity & CNS toxicity is much lesser than bupivacaine & slight lesser than levobupivacaine because of rapid reversal of sodium channel secondly rapid clearance from circulation.

Max safe dose is 3mg/kg

It can used for intravenous regional anesthesia.



Tumescent anaesthesia

Is a technique commonly used in cosmetic and dermatologic procedures.

It involves subcutaneous infiltration of large volumes of tumescent fluid containing lidocaine (0.05% or 0.1%), saline, and epinephrine (1:1,000,000) to produce anaesthesia, they causes the targeted tissue to become swollen and firm and permits procedures to be performed on patients without subjecting them to the inherent risks of local anaesthesia and blood loss.

Used for liposuction.



USES OF LOCAL ANESTHESIA					
Aesthetic Agent	Clinical uses	Concentration	Onset	Duration (Min)	Recommended Max Single dose (mg)
LIDOCAINE	TROPICAL	4	FAST	30-60	300
	INFILTRATION	0.5-1	FAST	60-240	300 OR 500 WITH EPINEPHRINE
	IVRA	0.25-0.5	FAST	30-60	300
	PNB	1-1.5	FAST	60-180	300 OR 500 WITH EPINEPHRINE
	SPINAL EPIDURAL	1.5-0.5	FAST	30-60	100
		1.5-2	FAST	60-120	300 OR 500 WITH EPINEPHRINE
BUPIVACAIN	INFILTRATION	0.25	FAST	120-480	175 OR 225 WITH EPINEPHRINE
	PNB	0.25-0.5	SLOW	0.25-0.5	175 OR 225 WITH EPINEPHRINE
	SPINAL EPIDURAL	0.5-0.75	FAST	60-240	20
		0.5-0.75	MODERATE	0.5-0.75	175 OR 225 WITH EPINEPHRINE
LEVOBUPIVACAINE	INFILTRATION	0.25	FAST	120-480	150
	PNB	0.25-0.5	SLOW	840-1020	150
	SPINAL EPIDURAL	0.5-0.75	FAST	60-360	20
		0.5-0.75	MODERATE	300-540	150
ROPIVACAINE	INFILTRATION	0.2-0.5	FAST	120-360	200
	PNB	0.5-1	SLOW	300-480	250
	EPIDURAL	0.5-1	MODERATE	120-360	200
PROCAINE	SPINAL	10	FAST	30-60	1000
MEPIVACAINE	INFILTRATION	0.5-1	FAST	60-240	400 OR 500 WITH EPINEPHRINE
	PNB	1-1.5	FAST	120-240	400 OR 500 WITH EPINEPHRINE
	SPINAL EPIDURAL	2-4	FAST	60-120	100
		1.5-2	FAST	60-180	400 OR 500 WITH EPINEPHRINE

IVRA: INTRAVENOUS REGIONAL ANESTHESIA

PNB: PERIPHERAL NERVE BLOCK

CLINICAL APPLICATIONS (TECHNIQUES) OF LOCAL ANAESTHESIA

1. **Surface anaesthesia:**

- Mucous membranes and abraded skin
- Nose, mouth, bronchial tree, cornea and urinary tracts
 - Lidocaine, tetracaine

2. **Infiltration anaesthesia:**

- Direct injection into tissues to reach nerve branches and terminals
- Used in minor surgery = incisions, hydrocele, herniorrhaphy etc.

3. **Field block:**

- Injection of LA subcutaneously
- Aim is to anaesthetize the region distal to the site of injection
- Examples – forearm, anterior abdominal wall, scalp and lower extremity

4. **Nerve Block:**

- LA is injected around the nerve trunks or plexuses
- Area of anaesthesia is large in comparison to the amount of drug used
- Lasts longer than the field or infiltration methods
- Flooding technique for plexus block
- Examples: Trigeminal nerve blocks (face) , Ophthalmic nerve block (eyelids and scalp), Supraorbital nerve block (forehead)



Clinical applications of LA – contd.

Spinal anaesthesia:

- Site of injection – Subarachnoid space between L 2-3 or L 3-4
- Site of action – nerve root in the cauda equina
- Level of anaesthesia – vol. & speed of injection; baricity of drug soln. with CSF and posture of patient
- Order of anaesthesia – sympathetic > motor
- Uses – lower limbs, pelvis, lower abdomen, prostatectomy fracture setting and obstetric procedures
- Problems - Spinal headache, hypotension, bradycardia and respiratory depression, cauda equina syndrome and nausea-vomiting
- Drugs - Lidocaine, tetracaine



Clinical applications of LA – contd.

- Epidural and Caudal Anaesthesia:
 - Site of injection – sacral hiatus (caudal) or lumbar, thoracic or cervical region
 - Catheters are used for continuous infusion
 - Unwanted effects similar to that of spinal except less likely because longitudinal spread is reduced -
 - Drugs - Lidocaine, bupivacaine, ropivacaine
- Regional anaesthesia (Intravenous)
 - Injection of LA in a vein of a tourniquet occluded limb
 - Mostly limited to upper limb
 - Orthopaedic procedures



Newer Techniques of LA

IONTOPHORESIS

A technique of introducing ionic medicinal compounds into the body through the skin by applying a local electric current.





THANK YOU