International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 10 (3): May-June 2020

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences **Review Article……!!!**

Received: 04-04-2020; Revised: 20-04-2020; Accepted: 01-05-2020

LOCAL ANESTHESIA: A REVIEW

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Keywords:

Local anesthetics, Mechanism of action, physicochemical properties

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ABSTRACT

Local anesthetics are a group of structurally related compounds which share as principal mechanism of action the blockade of voltage-gated sodium channels, resulting in reversible interruption of nerve signal transduction. Currently used local anesthetics are divided into amino amides, or amino esters. Each substance has distinct physicochemical properties, and local anesthetics can be administered continuously or together with adjuvants, allowing clinicians to tailor their anesthetic to procedure and patient. Next to sodium channel blockade, local anesthetics interact with other targets, for example calcium and potassium channels, and G-protein coupled receptors. The latter mode of action explains the anti-inflammatory properties of local anesthetics. Clinical application of existing local anesthetics, and development of novel local anesthetics, is hampered by systemic and local toxicity. Among the additives to local anesthetics, epinephrine is helpful in prolonging duration of action of medium-acting local anesthetics, and to reduce systemic absorption of any local anesthetic. Buprenorphine is an effective additive and has local anesthetic properties but causes excessive nausea and vomiting. Dexmedetomidine and clonidine are popular additives as well but can cause dose-dependent systemic side effects such as sedation, bradycardia and hypotension.

INTRODUCTION:

Local anaesthesia is any technique to induce the absence of sensation in a specific part of the body, generally for the aim of inducing local analgesia, that is, local insensitivity to pain, although other local senses may be affected as well. It allows patients to undergo surgical and dental procedures with reduced pain and distress.

A local anaesthetic (LA) is a medication that causes absence of pain sensation. When it is used on specific nerve pathways (local anaesthetic nerve block), paralysis (loss of muscle power) also can be achieved. Local anesthesia, in a strict sense, is anesthesia of a small part of the body such as a tooth or an area of skin.

Local anesthesia has been defined as loss of sensation in a circumscribed area of the body caused by depression of excitation in nerve endings or inhibition of the conduction process in peripheral nerves. An important feature of local anesthesia is that it produces this loss of sensation without inducing loss of consciousness. In this one major area, local anesthesia differs dramatically from general anesthesia.

From a minor procedure with a shot to numb the area to a more serious surgery in which you will be "asleep," knowing the basics about anesthesia may help answer your questions and ease some concerns.

In today's hospitals and surgical centres, highly trained professionals use a wide variety of safe, modern medicine and extremely capable monitoring technology. Anesthesia is broken down into three main categories: local, regional, and general, all of which affect the nervous system in some way and can be administered using various methods and different medications.

Local anesthesia. An anaesthetic drug (which can be given as a shot, spray, or ointment) numbs only a small, specific area of the body (for example, a foot, hand, or patch of skin). With local anesthesia, a person is awake or sedated, depending on what is needed. The medicine used can numb the area during the procedure and for a short time afterwards to help control post-surgery discomfort.

Regional anesthesia. An anaesthetic drug is injected near a cluster of nerves, numbing a larger area of the body (such as below the waist, like epidurals given to women in labour). Regional anesthesia

is generally used to make a person more comfortable during and after the surgical procedure. Regional and general anesthesia are often combined.

General anesthesia. The goal is to make and keep a person completely unconscious (or "asleep") during the operation, with no awareness or memory of the surgery. General anesthesia can be given through an IV (which requires sticking a needle into a vein, usually in the arm) or by inhaling gases or vapours by breathing into a mask or tube.

HISTORY:-

Pharmacology of Local Anaesthetics –

1860 Albert Niemann isolated crystals from the coca shrub – and called it “cocaine” – he found that it reversibly numbed his tongue! Sigmund Freud became awareof the mood altering properties of cocaine, and thought it might be useful in curing morphine addiction. Freud obtained a supply of cocaine (from Merck) and shared it with his friend Carl Koller, a junior intern in ophthalmology at the University of Vienna[1]

1884 Following preliminary experiments using conjunctiva sacs of various animals species, Koller did first eye surgery in humans using cocaine as local anaesthetic

1905 German chemist Alfred Einhorn produced the first synthetic ester typelocal anaesthetic - novocaine (procaine) - retained the nerve blocking properties, but lacked the powerful CNS actions of cocaine.

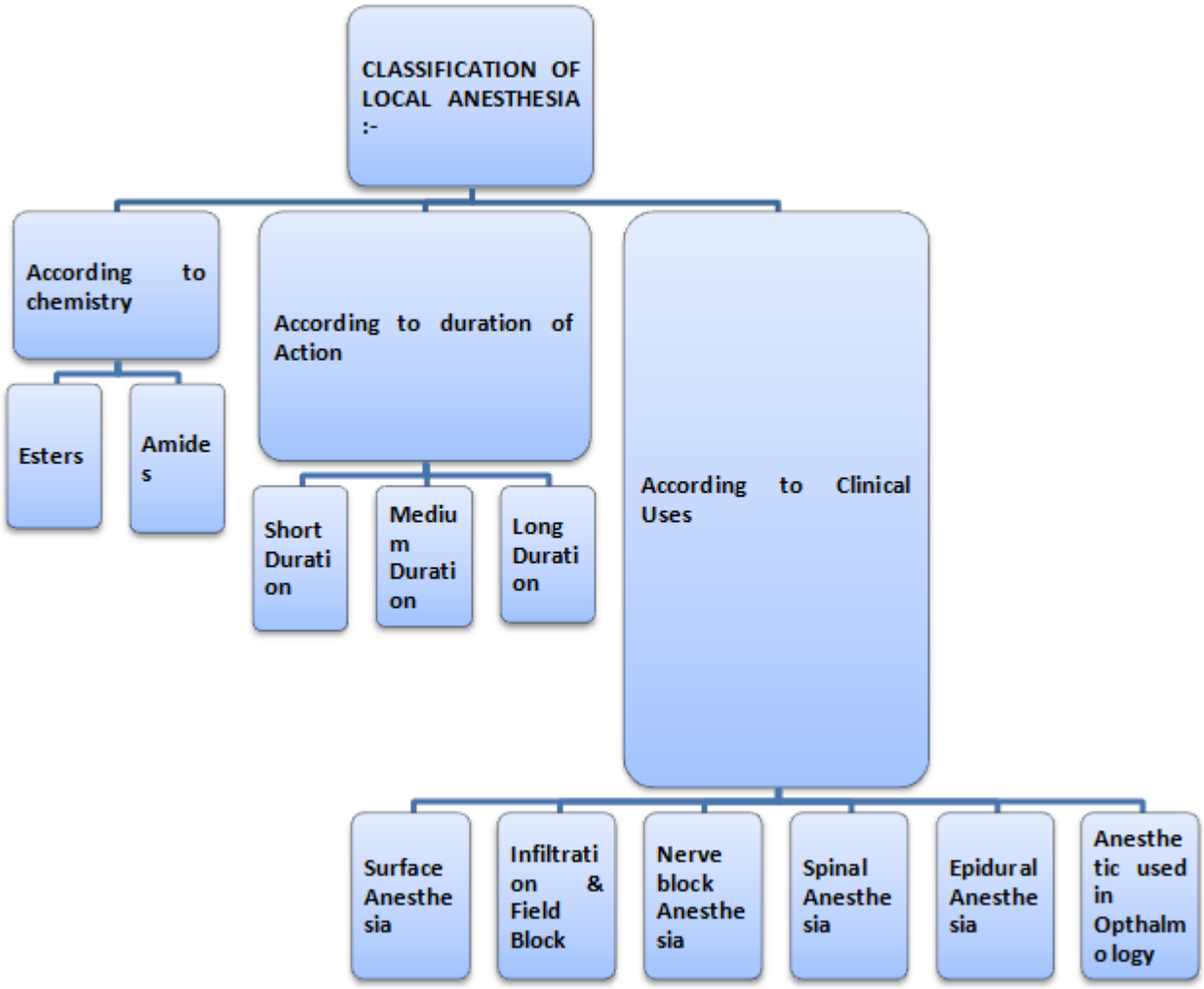
1943 Swedish chemist Nils Löfgren synthesized the first amide-type local anaesthetic - marketed under the name of xylocaine (lidocaine)

MECHANISM OF ACTION:-

All LAs are membrane-stabilizing drugs; they reversibly decrease the rate of depolarization and repolarization of excitable membranes (like nociceptors). Though many other drugs also have membrane-stabilizing properties, not all are used as LAs (propranolol, for example, though it has LA properties).

LA drugs act Mechanism of action mainly by inhibiting sodium influx through sodium-specific ion channels in the neuronal cell membrane, in particular the so-called voltage-gated sodium channels. When the influx of sodium is interrupted, an action potential cannot arise and signal conduction is

CLASSIFICATION OF LOCAL ANESTHESIA:-



inhibited. The receptor site is thought to be located at the cytoplasmic (inner) portion of the sodium channel. Local anaesthetic drugs bind more readily to sodium channels in an activated state, thus onset of neuronal blockade is faster in rapidly firing neurons. This is referred to as state-dependent blockade.

LAs are weak bases and are usually formulated as the hydrochloride salt to render them water-soluble. At a pH equal to the protonated base's pKa, the protonated (ionized) and un protonated (unionized) forms of the molecule exist in equimolar amounts, but only the un protonated base diffuses readily across cell membranes. Once inside the cell, the local anaesthetic will be in equilibrium, with the formation of the protonated (ionized) form, which does not readily pass back

out of the cell. This is referred to as "ion trapping". In the protonated form, the molecule binds to the LA binding site on the inside of the ion channel near the cytoplasmic end [8]

Most LAs work on the internal surface of the membrane - the drug has to penetrate the cell membrane, which is achieved best in the no ionised form. Acidosis such as caused by inflammation at a wound partly reduces the action of LAs. This is partly because most of the anaesthetic is ionized and therefore unable to cross the cell membrane to reach its cytoplasmic-facing site of action on the sodium channel.All nerve fibers are sensitive to LAs, but due to a combination of diameter and myelination, fibers have different sensitivities to LA blockade, termed differential blockade. Type B fibers (sympathetic tone) are the most sensitive followed by type C (pain), type A delta (temperature), type A gamma (proprioception), type A beta (sensory touch and pressure), and type A alpha (motor). Although type B fibers are thicker than type C fibers, they are myelinated, thus are blocked before the unmyelinated, thin C fiber. conduction of nerve impulses is mediated by action potential (AP) generation along axon Cationic form of anesthetic binds at inner surface of Na+ channel – preventing Na+ influx (rising phase of membrane potential) which initiates AP → blockade of nerve impulses (e.g., those mediating pain)

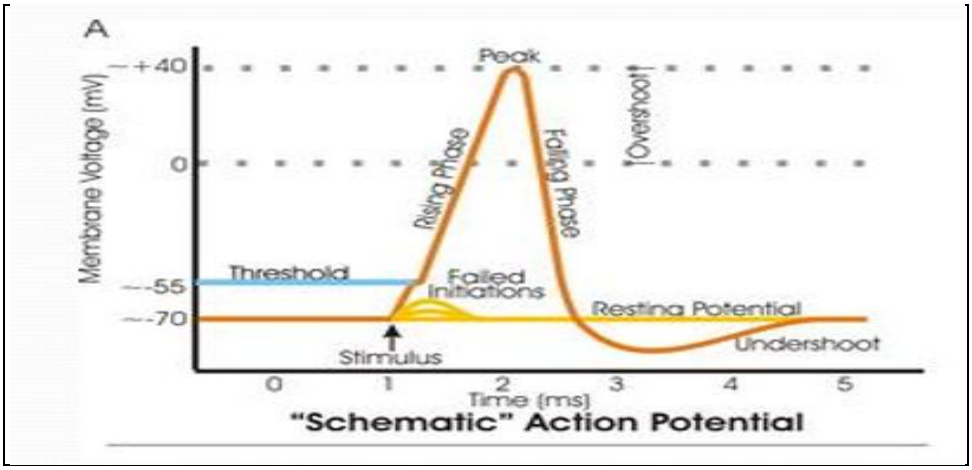


Fig.1: Action potential

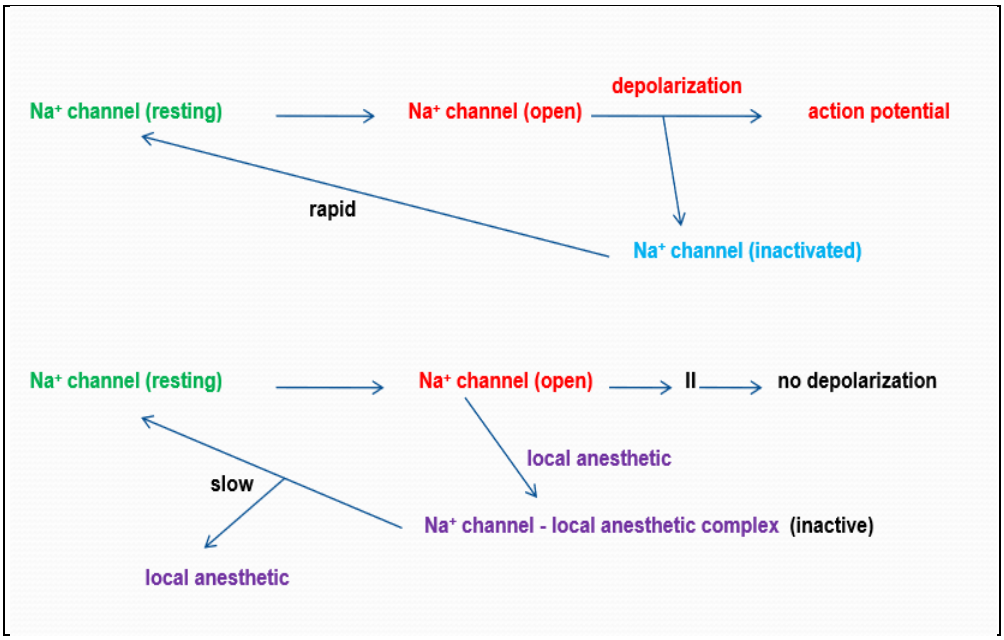


Fig.2: Mechanism of Action of Local anesthetics

Fundamentals of Impulse Generation and Transmission:-

The discovery in the late 1800s of a group of chemicals with the ability to prevent pain without inducing loss of consciousness was one of the major steps in the advancement of the medical and dental professions. For the first time, medical and dental procedures, could be carried out easily and in the absence of pain, a fact that is virtually taken for granted by contemporary medical and dental professionals and their patients. [3]

The concept behind the actions of local anaesthetics is simple:

They prevent both the generation and the conduction of a nerve impulse. In effect, local anaesthetics set up a chemical roadblock between the source of the impulse (e.g., the scalpel incision in soft tissues) and the brain. Therefore the aborted impulse, prevented from reaching the brain, cannot be interpreted by the patient as pain.Fig. 3. Shows the fuse is lit and the flame reaches the dynamite; an explosion occurs, and the patient experiences pain.

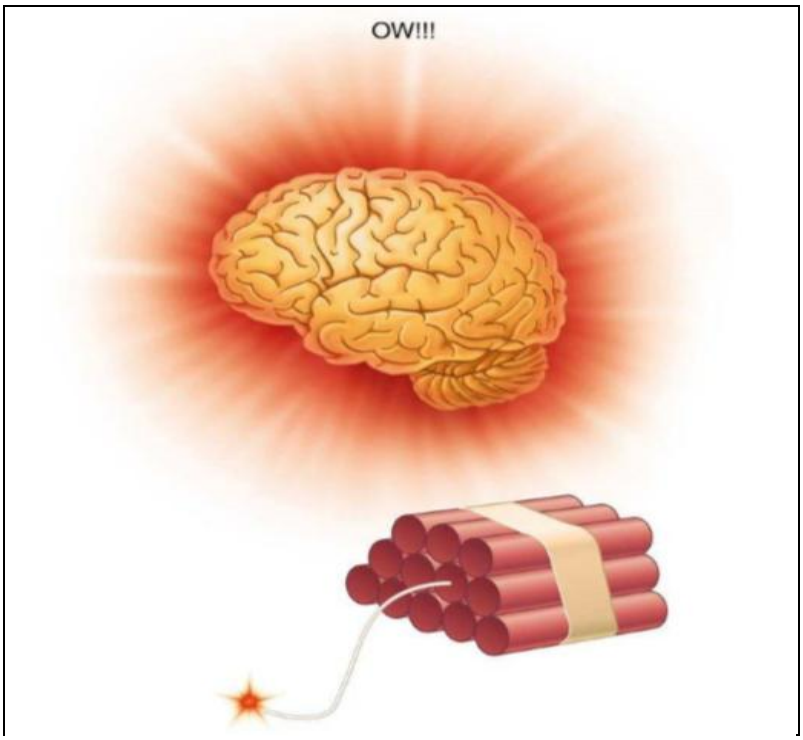


Fig.3: Experiences of pain

Fig.4 shows Local anaesthetic is placed at some point between the pain stimulus and the brain (dynamite). The nerve impulse travels up to the point of local anaesthetic application and then "dies," never reaching the brain, and pain does not occur.

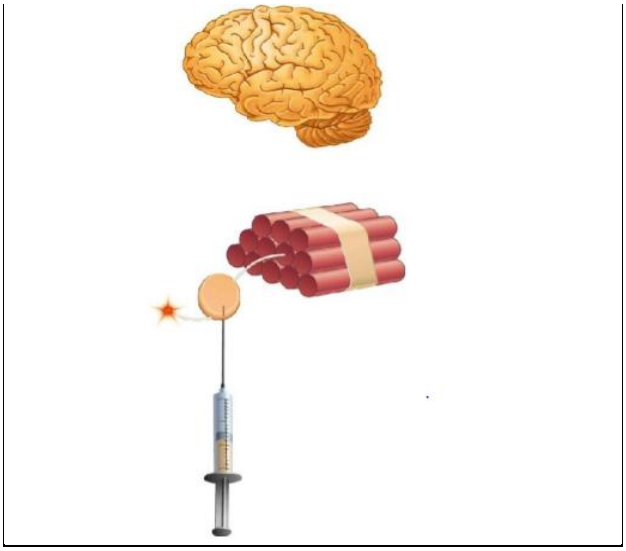


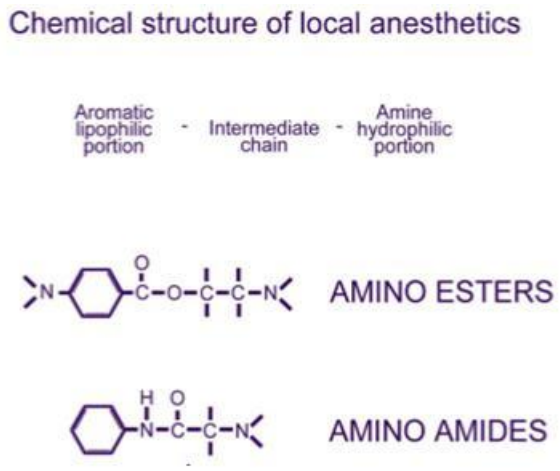
Fig.4: Local anaesthetic MOA

The primary action of local anaesthetics in producing a conductionblock is to decrease the permeability of ion channels to sodium ions(Na+).Local anaesthetics selectively inhibit the peak permeability ofsodium, may be reproduced or transmitted without publisher's priorPermission Violators will be prosecuted. Whose value is normallyabout five to six times greater than the minimum necessary forimpulse conduction. Local anaesthetics reduce this safety factor,decreasing both the rate of rise of the action potential and itsconduction velocity [2].When the safety factor falls below unity, 10 conduction fails and nerve block occurs. Local anaesthetics producea very slight, virtually insignificant decrease in potassium (K+) conductancethrough the nerve membrane. Calcium ions (Ca++), which exist in bound form within the cell membrane, are thought to exert a regulatory role on the movement of sodium ions across the nerve membrane. Release of bound calcium ions from the ion channel receptor site may be the primary factor responsible for increased sodium permeability of the nerve membrane. This represents the first step in nerve membrane depolarization. Local anaesthetic molecules may act through competitive antagonism with calcium for some site on the nerve membrane.

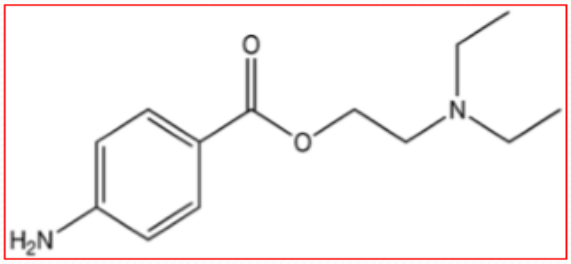
Structure-Activity Relationships:-

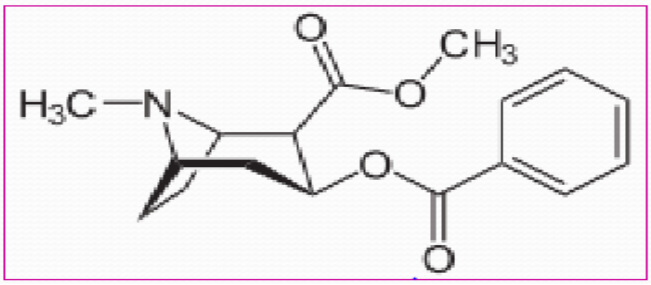
All local anaesthetics contain 3 structural components:

1. An aromatic ring (usually substituted)
2. A connecting group which is either an ester (e.g., novocaine) or an amide (e.g. lidocaine)
3. An ionisable amino group [6].

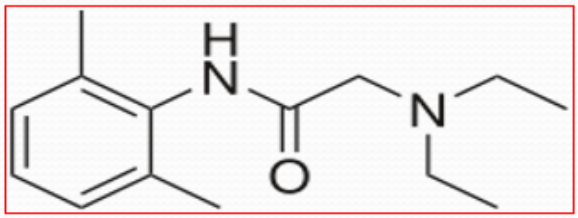


Chemical structures of prototypical ester-and amide-type local anaesthetics – comparison with cocaine (note 3 structural components of procaine) :-





Procaine/novocaine **cocaine**



Lidocaine/xylocaine

Pharmacokinetics of Local Anesthetics:-

Injectable local anaesthetics are subject to absorption; a large fraction of the injected drug is removed by the systemic circulation and distributed to distant organs according to their vascular density. Highly vascular organs (brain, heart, lung, liver, and kidneys) are exposed to unmetabolised local anaesthetic at peak concentration. The local anaesthetic is taken up within each organ according to its tissue-plasma partition coefficient.

Most absorbed local anaesthetic is cleared from the liver. Hepatic clearance is a function of the hepatic extraction ratio and hepatic blood flow. The hepatic extraction ratio, in turn, is dependent on the ratio of free to protein-bound drug. Local anaesthetics bind tightly to plasma proteins greatly limiting the free fraction of available drug. Only the free or unbound fraction that is bioactive [4].

Like most weak bases, local anaesthetics bind mainly to alpha-1-acid glycoprotein. Lignocaine, being moderately protein-bound, has a high hepatic extraction ratio (70–75% per pass). Clearance is therefore flow-limited and is reduced by factors that limit hepatic blood flow. Conversely, bupivacaine and ropivacaine, being highly protein-bound, are cleared <50% per pass; hence, their

clearance depends on free drug concentration. Low cardiac output states may not greatly affect the plasma concentration of the highly protein-bound agents, as their clearance is not flow limited. Intrinsic hepatic disease may alter clearance by altering plasma protein content and degree of protein binding, by decreasing the enzyme activity of the liver, and by reducing hepatic blood flow. Patients with liver disease may have single-shot blocks with normal doses. Doses for continuous infusion and repeat blocks need to be significantly reduced (10–50% relative to the degree of dysfunction) due to the risk of accumulation of the primary compound and its metabolites.

Patients with mild or controlled cardiac failure may not need a dose reduction for single-shot blocks. Doses of ropivacaine and bupivacaine for continuous infusion and repeat blocks need to be reduced, as theirmetabolites will be eliminated slowly.

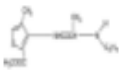
In patients with renal dysfunction, reduced clearance and faster absorption of local anaesthetic lead to an elevation in plasma concentration. Clearance of both bupivacaine and ropivacaine has been shown to be reduced in uraemic patients.The clearance of one of the main metabolites of ropivacaine, 2,6-pipecoloxylidide (PPX), is also decreased in uraemic patients.

Chemical Structure, Physicochemical Properties, and Pharmacologic Properties of Local Anaesthetic Agents:-

Lipid solubility of a local anaesthetic appears to be related to its intrinsic potency. The estimated lipid solubility of various local anaesthetics are presented in Table 1. Greater lipid solubility permits the anaesthetic to penetrate the nerve membrane (which itself is 90% lipid) more easily**.**

The degree of protein binding of the local anaesthetic molecule is responsible for the duration of anaesthetic activity. After penetration of the nerve sheath, a reequilibrium occurs between the base and cationic forms of the local anaesthetic according to the Henderson- Hassel Bach equation. Now, in the sodium channel itself, RNH+ ions bind at the receptor site. Proteins constitute approximately 10% of the nerve membrane, and local anaesthetics (e.g., etidocaine, ropivacaine, bupivacaine) possessing a greater degree of protein binding than others (e.g., procaine) appear to attach more securely to the protein receptor sites and to possess a longer duration of clinical activity.[9]

Table 1: Chemical classes of local anesthetics

	CHEMICAL CONFIGURATION			PHYSICOCHEMICAL PROPERTIES			PHARMACOLOGIC PROPERTIES			
Agent	Aromatic (lipophilic)	Intermediate Chain	Amine (hydrophilic)	Molecular Weight (base)	pKa (36° C)	Onset	Approx Lipid Solubility	Usual Effective Concentration, %	Protein Binding	Duration
Esters										
Procaine				236	9.1	Slow	1.0	2-4	5	Short
Chloroprocaine				271	8.7	Fast	NA	2	NA	Short
Tetracaine				264	8.4	Slow	80	0.15	85	Long
Amides										
Mepivacaine				246	7.9	Fast	1.0	2-3	75	Moderate
Prilocaine				220	7.7	Fast	1.5	4	55	Moderate
Lidocaine				234	7.7	Fast	4.0	2	65	Moderate
Ropivacaine				274	8.1	Moderate	2.8	0.2-0.5	94	Long
Bupivacaine				288	8.1	Moderate	NA	0.5-0.75	95	Long
Etidocaine				276	7.9	Fast	140	0.5-1.5	94	Long
Articaine				320	7.8	Fast	17	4	95	Moderate

PROPERTIES OF LAs:-

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. Its 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.
7. It should 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 sterilized by heat without deterioration.

Medical uses:-

Acute pain

Acute pain may occur due to trauma, surgery, infection, disruption of blood circulation, or many other conditions in which tissue injury occurs. In a medical setting, pain alleviation is desired when its warning function is no longer needed. Besides improving patient comfort, pain therapy can also reduce harmful physiological consequences of untreated pain.[7]

Acute pain can often be managed using analgesics. However, conduction anesthesia may be preferable because of superior pain control and fewer side effects.

For purposes of pain therapy, LA drugs are often given by repeated injection or continuous infusion through a catheter. LA drugs are also often combined with other agents such as opioids for synergistic analgesic action. Low doses of LA drugs can be sufficient so that muscle weakness does not occur and patients may be mobilized.

Some typical uses of conduction anesthesia for acute pain are:

Labor pain (epidural anesthesia, pudendal nerve blocks)

Postoperative pain (peripheral nerve blocks, epidural anesthesia) Trauma (peripheral nerve blocks, intravenous regional anesthesia, epidural anesthesia)

Chronic pain

Chronic pain is a complex and often serious condition that requires diagnosis and treatment by an expert in pain medicine. LAs can be applied repeatedly or continuously for prolonged periods to relieve chronic pain, usually in combination with medication such as opioids, NSAIDs, and anticonvulsants. Though it can be easily performed, repeated local anaesthetic blocks in chronic pain conditions are not recommended as there is no evidence of long-term benefit.

Surgery

Virtually every part of the body can be anesthetized using conduction anesthesia. However, only a limited number of techniques are in common clinical use. Sometimes, conduction anesthesia is combined with general anesthesia or sedation for the patient's comfort and ease of surgery. However, many anaesthetists, surgeons, patients and nurses believe that it is safer to perform major surgeries under local anesthesia than general anesthesia.

Typical operations performed under conduction anesthesia include:

- ***Dentistry :-***(surface anesthesia, infiltration anesthesia or intraligamentary anesthesia during restorative operations such as fillings, crowns, and root canals, or extractions, and regional nerve blocks during extractions and surgeries)
- ***Podiatry:-***(cutaneous, nail avulsions, matricectomy, bunionectomy, hammertoe repair and various other podiatric procedures)
- ***Eye surgery:-***(surface anesthesia with topical anaesthetics or retrobulbar block during cataract removal or other ophthalmic procedures.
- ***ENT operationshead and neck surgery :-***(infiltration anesthesia, field blocks, or peripheral nerve blocks, plexus anesthesia)
- ***Shoulder and arm surgery:-***plexus anesthesia or intravenous regional anesthesia.
- ***Heart and lung surgery :-***epidural anesthesia combined with general anesthesia
- ***Abdominal surgery :-***epidural anesthesia/spinal anesthesia, often combined with general anesthesia during inguinal hernia repair or other abdominal surgery
- ***Gynaecological, obstetrical, and urological operations:-*** (spinal/epidural anesthesia)

- ***Bone and joint surgery:-*** of the pelvis, hip, and leg (spinal/epidural anesthesia, peripheral nerve blocks, or intravenous regional anesthesia)
- ***Surgery of skin and peripheral blood vessels:-*** (topical anesthesia, field blocks, peripheral nerve blocks, or spinal/epidural anesthesia) Diagnostic Tests
- **Diagnostic tests**

  Such as bone marrow aspiration, lumbar puncture (spinal tap) and aspiration of cysts or other structures are made to be less painful upon administration of local anaesthetic before insertion of larger needles.
- **Other uses**

  Local anesthesia is also used during insertion of IV devices, such as pacemakers and implantable defibrillators,
- Ports used for giving chemotherapy medications and haemodialysis access catheters. Topical anesthesia, in the form of lidocaine or procaine (EMLA) is most commonly used to enable relatively painless venipuncture (blood collection) and placement of intravenous cannulae. It may also be suitable for other kinds of punctures such as ascites drainage and amniocentesis. Surface anesthesia also facilitates some endoscopic procedures such as bronchoscopy (visualization of the lower airways) or cystoscopy (visualization of the inner surface of the bladder).

Pharmacological effects and toxicities:-

A. Nerves: decrease or abolition of conduction
B. Vascular smooth muscle: vasodilatation
C. Heart: decreased excitability (reduced pacemaker activity, prolongation of effective refractory period)
D. Central nervous system: increased excitability, followed by generalized depression

A. Effects of local anaesthetics on nerve:-

Na+ channels are present in all nerves and local anaesthetics, at sufficient concentrations, can completely block action potential generation and conduction

- "Differential nerve blockade" – nerve fibres differ markedly in their susceptibility to conduction blockage by local anaesthetics (this is the basis of their clinical use)e.g., small, non-myelinated

neurons mediating pain are much more susceptible that large, myelinated fibres mediating motor functions.

Differential susceptibility of nerves to local anaesthetics

In neuronal conduction, depolarizing current moves along nodes of Ranvier – 2-3 successive nodes must be blocked to completely impair neuronal conduction small fibres have smaller internodal distances -a shorter lengthof nerve fibre needs to be blocked to impair conduction as compared to larger nerve fibres

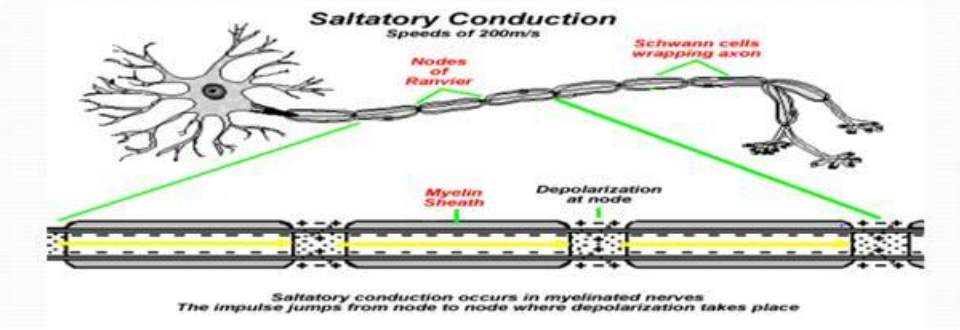


Fig.5: Impulse conduction

Anaesthetic blockade of Na+ channels exhibits "use-dependence"increased frequency of stimulation increased level of blockadehigh stimulation frequency increases # of Na+ channels in the"open" form that preferentially binds anaesthetic∴ neurons withhigh rates of firing (e.g., pain fibres) or ectopic pacemakers in the my ocardium will be highly susceptible to blockade by local anaesthetics.

In excitable tissues with long action potentials, probability of Na+ channels being in (susceptible) "open" form is increased enhanced susceptibility to blockade by local anaesthetics e.g., pain fibres have long action potentials (3 millisecond) versus motor fibres (0.5 millisecond)cardiac muscle has prolonged action potentials relative to other excitable tissues - ∴ myocardium highly susceptible to local anaesthetics (clinically important)

B. Effects of local anaesthetics on vascular smooth muscle:-

Blockade of Na+ channels in vascular smooth muscle by local anaesthetics vasodilatation consequences of vasodilatation: [10]

enhanced rate of removal of anaesthetic from site of administration (decreased duration of anaesthetic action and increased risk of toxicity) hypotension (may be intensified by anestheticinduced cardiodepression)

C. Effects of local anaesthetics on heart:-

Local anaesthetics can reduce myocardial excitability and pacemaker activity and also prolong the refractory period of myocardial tissue – this is the basis of the antiarrhythmic effects of local anaesthetics

Local anaesthetic-induced myocardial depression (compounded by anaesthetic-induced hypotension) can also be a manifestation of toxicity and can lead to cardiovascular collapse and even death!

D. Effects of local anaesthetics on CNS:-

As is the case with CNS depressants generally (e.g., alcohol) local anaesthetics (at toxic doses) produce a biphasic pattern of excitation followed by depression

The excitatory phase likely reflects the preferential blockade of inhibitory neurons and effects can range from mild hyperactivity to convulsions)

The subsequent depressive phase can progress to cardiovascular collapse and even death if unmanaged.

Local anaesthetic toxicity:-

Most common causes:

Inadvertent intravascular injection while inducing nerve block (important to always aspirate before injecting!) — rapid absorption following spraying of mucous membranes (e.g., respiratory tract) with local anaesthetic prior to diagnostic or clinical procedures

Manifestations of local anaesthetic toxicity: allergic reactions, cardiovascular and CNS effects

Allergic reactions: restricted to esters – metabolized to allergenic p-amino benzoic acid (PABA) (∴ amides usually preferred for nerve block)

Cardiovascular: may be due to anaesthetic (cardiodepression, hypotension) or vasoconstrictor (hypertension, tachycardia) ∴ monitor pulse/blood pressure

CNS: excitability (agitation, increased talkativeness – may → convulsions) followed by CNS depression (∴ care in use of CNS depressants to treat convulsions - may worsen depressive phase – convulsions usually well tolerated if brain oxygenation maintained between seizures)[5]

Advantages of LAs:-

1. Relatively atraumatic
2. Patient need not be able to open the mouth
3. Fewer postoperative complications (e.g. trismus)
4. Lower aspiration rate (<10%)than with the inferior alveolar nerve block
5. Provides successful anesthesia where a bifid inferior alveolar nerve and bifid mandibular canals are present
6. Minimal contraindication
7. Haemorrhage could be controlled by vasoconstrictor
8. Co-operative patient simplify the work

Disadvantage of *LAs*:-

1. Difficult to visualize the path of the needle and the depth of insertion
2. No bony contact depth of penetration somewhat arbitrary
3. Potentially traumatic if the needle is too close to the periosteum
4. There are individual variation in response to local anaesthetic drug

CONCLUSIONS:

Local anaesthesia has been the comer stone of modern day pain free dental practice. However, the practitioners limitations is updating about newer drug formulations available and newer techniques to administer the drugs has, still not made the goal of pain free dentistry a reality. The availability and cost factor are not excuses not to adapt newer proven methods, when the benefits outweigh the shortcomings. There is a need in the current evidence based era of dental practice for us to constantly update , evaluate and incorporate newer drugs and techniques into daily practice to provide our patients the best of care at all times. The best way to avoid nearly all complications relating to administration of local anaesthetics is to use the right technique and to have a good knowledge of the anatomy of the trigeminal nerve and the adjacent anatomical structures. However, if complications occur, the dentist should know how best to manage them.

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