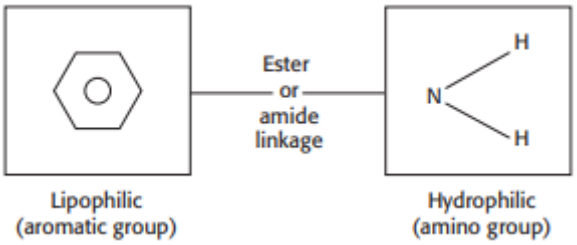
Anesthetics

- **General anesthetics.**
- **Local anesthetics.**

Local Anesthetics: are drugs that cause reversible blockade of the nerve impulse transmission, causing reversible absence of pain sensation without inducing loss of consciousness, they also cause transient interruption of the motor and autonomic functions when administered in sufficient doses. The order of blockade of nerve function proceeds in the following manner—pain, temperature, touch, pressure and finally skeletal muscle power.

Classification of Local Anesthetics:

All currently used local anesthetics are weak bases consist of three parts: a lipophilic aromatic ring connected to a terminal hydrophilic amide group (that influences the speed of onset and potency of the drug) by either an ester or amide linkage (that influences the duration and effects of the drug).

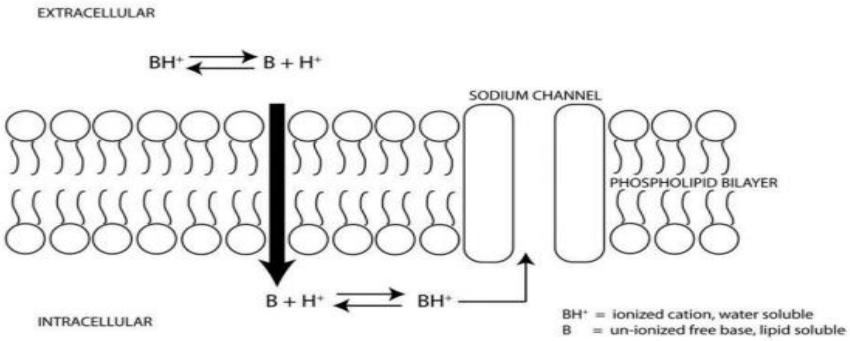


Depending on this intermediate chain, LAs are classified as either esters or amides

- Esters: procaine, propoxycaine, benzocaine and tetracaine.
- Amides: lidocaine, mepivacaine, prilocaine, bupivacaine, ropivacaine and etidocaine.

Mechanism of Action of Local Anesthetics:

Main site of action of local anesthetics is the cell membrane. The local anesthetics in 'unionized' form easily penetrate the nerve sheath and the axon membrane. Within the axoplasm, the molecules become 'ionized' and block the voltage-gated Na+ channels.



Sodium ion channels are blocked to prevent the transient increase in permeability of the nerve membrane to Na+ that is required for an action potential. When propagation of action potentials is prevented, sensation cannot be transmitted from the source of stimulation to the brain.
Action of local anesthetic is pH dependent and the penetrability of LA is increased at alkaline pH (i.e. when the unionized form is more). Penetrability is very poor at acidic pH. In infected tissues, pH is low, which causes ionization of the drug. This reduces the penetration of LA through the cell membrane, thus decreases the effectiveness of LAs. Therefore, LAs are less effective in inflamed and infected areas.
LAs block small fibers first followed by larger fibers.
Myelinated fibers are blocked earlier than non-myelinated nerve of the same diameter.
Sensory fibers are blocked earlier than motor fibers because of their high firing rate and longer duration of action potential.
Fibers in the centre are blocked later than ones located in the circumference of the nerve bundle.

Physical Properties and Clinical Actions of Local Anesthetics:

• Lipid solubility: increased lipid solubility results in increased LA potency. Amide LAs have better lipid solubility and more potency than ester LAs.
• Protein binding: higher protein binding leads to longer duration of action.
• The dissociation constant (pKa): higher pKa results in more ionized form which can not cross the membrane leading to longer onset of action.

Pharmacokinetics:

With the exception of cocaine, local anesthetics are absorbed poorly, if at all, from the gastrointestinal tract after oral administration. In addition, most local anesthetics (especially lidocaine) undergo a significant hepatic first-pass effect after oral administration.
The rate of systemic absorption of injected LAs depends on many variables like the affinity of the anesthetic solution for the local tissues, tissue blood flow, the effect of the anesthetic on the local circulation, and the use of a vasoconstrictor.
Topical route could be through the skin or through mucosal surfaces such as the mouth, genitals, and conjunctiva. The penetration of mucosal surfaces is easier than that of keratinized surfaces due to the absence of stratum corneum. LAs are distributed to all tissues throughout the body after their absorption into the bloodstream with higher concentrations in the highly vascular organs such as the brain, heart, liver, kidney, and lungs. The toxicity of LAs is directly related to the amount of accumulation in these tissues.
Ester LAs are hydrolyzed rapidly by plasma pseudocholinesterase into para-aminobenzoic acid (PABA) and other derivatives, and small amount of the drug is eliminated unchanged. PABA is a potent allergen that can cause, although rare, allergy for ester anesthetics.
Metabolism of amide LAs occurs in the liver by the mixed-function oxidase system primarily via CYP 3A4 and CYP 1A2 isoforms. Hepatic blood flow and hepatic function affect the rate of amides metabolism and any condition that lowers hepatic blood flow can retard the metabolism of amides and enhance the chance for toxicity.
Plasma albumin has weak affinity to LAs despite its abundance, however, alpha-1-acidic glycoprotein which is less abundant binds to LAs more potently. Plasma protein binding of LAs

remains largely unchanged with aging in spite of the decreased levels of albumin because alpha-1-acid glycoprotein levels are minimally changed. Likewise, despite a 20-40% reduction in hepatic blood flow in geriatric patients, LAs metabolism remains unchanged with aging unless complicated by significant hepatic disease.
Amides clearance depends on hepatic metabolism, and an accumulation of metabolites may occur in renal failure.

Adverse effects:

1. Central Nervous System (CNS): LAs initially cause CNS stimulation followed by depression. They are restlessness, tremor, headache, drowsiness, confusion and convulsions followed by respiratory depression, coma and death.
2. CVS: Bradycardia, hypotension, cardiac arrhythmias, rarely cardiovascular collapse and death. Bupivacaine is highly cardiotoxic.
3. Allergic reactions: These are skin rashes, itching, erythema, urticaria, wheezing, bronchospasm and rarely anaphylactic reaction. The incidence of allergic reactions is more with ester-linked LAs than with amide-linked LAs(?). Allergic cross-reactivity occurs within the same LAs group but never with the opposite group.

Allergic reactions may be attributed to the additives contained in the LAs such as metabisulfite or methylparaben which are well-known allergens. Sodium metabisulfite is an anti-oxidant commonly used along with vasoconstrictors like adrenaline while methylparabens are bacteriostatic preservatives necessary for multidose vials and were used in the dental cartridges in the past. Latex allergy due to the latex plunger and diaphragm in the cartridge has theoretical but not clinical significance.
Most reactions to LAs are psychogenic in origin and they are misdiagnosed as allergic reactions. Psychogenic reactions manifestations are various like fainting, hyperventilation, nausea and vomiting with signs that mimic these of allergic reactions like urticarial, edema and bronchospasm

4. methaemoglobinaemia: Methemoglobinemia is a condition in which there is a decrease in the oxygen-carrying capacity of circulating hemoglobin due to oxidation of some or all of the four iron species to be in the oxidized ferric [Fe3+] state instead of the reduced ferrous [Fe2+] state. This conversion to the ferric state leads to methemoglobin formation. Methemoglobinemia is more commonly caused by prilocaine.

Some Important Local Anesthetics

- ***Lidocaine (lignocaine):(Xylocaine)***

Lidocaine injections are indicated for production of local or regional anesthesia.
Lidocaine (2%) with adrenaline (1:80,000) is mostly used local anesthetic in dentistry which produces good soft tissue and pulpal anesthesia. The pulpal anesthesia is obtained within 2-3 minutes after injection.
Lidocaine is the only amide marketed as a single agent for topical anesthesia in dentistry. Formulations of lidocaine hydrochloride include a 2% gel, a 2% viscous solution, a 4% solution, and in Canada a 10% topical spray. Lidocaine base is marketed in a 2.5% and 5% ointment and solution and a 10% aerosol spray. A mucosal adherent patch 2 cm long × 1 cm wide and containing

46.1 mg of lidocaine is also available. Addition of adrenaline does not prolong the duration of surface anesthesia (?)
Lidocaine is used i.v. as antiarrhythmic drug to treat ventricular arrhythmia.

- ***Mepivacaine***

Mepivacaine is a rapid onset, amide LA used in dentistry in the form of 2% solution containing levonordefrin in a concentration of 1:20000, 3% solution without any vasoconstrictor (plain mepivacaine). It is also available in the form of 2% solution containing 1:100000 epinephrine. In dentistry, mepivacaine is the third most widely used LA only after articaine and lidocaine.
It is used in epidural and spinal blocks but mepivacaine is slowly metabolized by the fetus, making it a poor choice for epidural anesthesia in the parturient.

- ***Tetracaine***

An ester type of LA; has long duration but slow onset of action. It is used to numb the eyes, nose, or throat.

- ***Bupivacaine***

It is a widely used LA. It is potent and has a long duration of action. It produces more sensory than motor blockade; hence it is very popular for obstetric analgesia. It is highly cardiotoxic and may precipitate ventricular arrhythmias. It is one of the more painful agents during injection.

- ***Ropivacaine***

It is less potent and less cardiotoxic than bupivacaine. Its duration of action is similar to bupivacaine. It is used for regional anesthesia.

- ***Prilocaine***

It is an amide type of LA. It has intermediate onset and duration of action. It has poor vasodilatory effect, hence can be used without a vasoconstrictor.

- ***Articaine***

It is an amide local anesthetic used in dentistry for infiltration and nerve block anesthesia. It acts rapidly and has a duration of action of 1 h. It is expensive. It is also available with adrenaline. The adverse effects are methaemoglobinaemia, paraesthesia and neuropathies.

- ***Benzocaine***

Surface anesthetic of ester type. Its pronounced lipophilicity has relegated its application to topical anesthesia. It causes minimal systemic toxicity. It is available as ointment and lozenges; used for hemorrhoids, anal fissure and sore throat.

- ***Procaine:***

It is the first useful injectable local anesthetic. It is ester type LA.
Today, procaine is of some importance in the immediate management of inadvertent intra-arterial injection of a drug; its vasodilating properties are used to aid in breaking arteriospasm.
It is an ingredient of some long-acting intramuscular formulations of penicillin.

Components of Local Anesthetics Used in Dentistry:

1. Anesthetic agent.
2. Vehicle (sterile water with sodium chloride to maintain the osmotic pressure between the tissues of the body and the anesthetic solution).
3. Buffers (sodium hydroxide and hydrochloric acid to adjust the pH and reduce the oxidation of the vasoconstrictor).
4. Antioxidants (sodium metabisulfite) to prevent oxidation of the vasoconstrictor.
5. Vasoconstrictors (epinephrine or levonordefrin).

Combination of Vasoconstrictor with Local Anesthetics:

All clinically used LAs (except cocaine?) have a vasodilatory effect due to direct relaxation of the peripheral arteriolar smooth muscle fibers which results in faster absorption and shorter duration of action therefore a vasoconstrictor is added to the LA to counteract this vasodilation.
The commonly used vasoconstrictor with a local anesthetic is adrenaline.

Addition of a vasoconstrictor to the LA has the following advantages:

1. Slow absorption from the local site, which results in prolonged duration of action of local anesthesia.
2. Decreased bleeding in the surgical field.
3. Slow absorption of LA reduces its systemic toxicity.
4. Reduce the necessary concentration of the anesthetic agent for achieving adequate anesthesia.

Disadvantages and Contraindications of Combining Vasoconstrictor with LA:

1. Intense vasospasm and ischemia in tissues with end arteries may cause gangrene of the part (e.g. fingers, toes, penis, ear lobule, tip of the nose, etc.). Hence, use of vasoconstrictors is contraindicated in these sites.
2. Absorption of adrenaline can cause systemic toxicity—tachycardia, palpitation, rise of BP and precipitation of angina or cardiac arrhythmias. Hence, combined preparation (LA with adrenaline) should be avoided in patients with hypertension, congestive cardiac failure (CCF), arrhythmias, ischemic heart disease and uncontrolled hyperthyroidism.
3. May delay wound healing by reducing the blood flow to the affected area.

There is some concern about systemic consequences that occur as a result of vasoconstrictors use due to inadvertent intravascular injection and cardiovascular side effects especially in patients with cardiovascular disease. Dentists usually tend to use plain LAs for patients with cardiovascular disorders to avoid adverse effects and complications caused by vasoconstrictors. Patients with significant cardiovascular disease, thyroid dysfunction, diabetes, or sulfite sensitivity and those receiving monoamine oxidase inhibitors, tricyclic antidepressants, or phenothiazines may require a medical consultation to determine the need for a local anesthetic without vasoconstrictor.
Stress can cause an increase in the release of epinephrine and other catecholamines by 20 to 40 folds. Secondary endogenic catecholamines released due to stress on the patient during the dental procedure can cause greater adverse cardiovascular effects than that are caused by the dose of

epinephrine actually used in the anesthetic solution. The administration of plain LA does not provide sufficient anesthesia and/or produce the desired hemostasis, which can cause bleeding and trans-operative pain with subsequent release of endogenic catecholamines more than those found in the therapeutically used LA, which can be reflected in the hemodynamic factors under study. The typical concentrations of vasoconstrictors contained in local anesthetics are not contraindicated in cardiovascular disease so long as preliminary aspiration is practiced, the agent is injected slowly, and the smallest effective dose is administered.

Reversal of Soft Tissue Local Anesthesia:

Phentolamine mesylate is used in dentistry as the only commercially available agent for reversal of local anesthesia**.** Phentolamine mesylate acts as a competitive antagonist, blocking the effects of epinephrine by blocking α-adrenoceptors leading to smooth muscle relaxation, hence it acts as a vasodilator, which allows faster dissipation of the LA into the vasculature. When the LA diffuses into the cardiovascular system away from the injection site, less of the LA will be available to block sodium channels, thus diminishing anesthesia which in turn accelerates return of normal sensation**.**