Lec. 9 **Pharmacology of local anesthesia** **د.ابرار نزار**

Classification of local anesthetic

(A) On the Basis of Occurrence in Nature

1. Naturally occurring, e.g. cocaine

2. Synthetic compounds. a. Nitrogenous compounds e.g. procaine, benzocaine, lignocaine.

b. Non-nitrogenous compounds, e.g. benzyl alcohol, and propanediol

3. Miscellaneous drugs with local anesthetic action, e.g. clove oil, phenol, chlorpromazine, certain anti-histaminics such as diphenhydramine.

(B) On the Basis of Chemical Structure

1.Esters

These can be further classified as:

i. Esters of benzoic acid, e.g. cocaine, benzocaine

ii. Esters of para-aminobenzoic acid, e.g. procaine, chloroprocaine, and propoxycaine.

2.Amides e.g. Bupivacaine, lidocaine, mepivacaine, and prilocaine.

3. Quinoline e.g. Centbucridine

(C) On the Basis of Duration of Action

1. Short-acting: Articaine, lidocaine, mepivacaine, prilocaine, etc.

2. Long-acting: Bupivacaine, etidocaine, bucricaine, etc.

• Active forms of local anesthetics

Typically all local anesthetics are amphipathic, that is, they possess both ***lipophilic*** and ***hydrophilic*** characteristics, generally at opposite ends of the molecule. The typical local anesthetic structure is:
1-The lipophilic part is the largest portion of the molecule. Aromatic in structure, it is derived from benzoic acid, aniline, or thiophene.
2-An intermediate hydrocarbon chain containing an ester or an amide linkage.
**Local anesthetics may be classified as amino esters or amino amides according to their chemical linkages.
3-The hydrophilic part is an amino derivative of ethyl alcohol or acetic acid.
**Local anesthetics without a hydrophilic part are not suited for injection but are good topical anesthetics (e.g., benzocaine).
**Local anesthetics are available as acid salts (usually hydrochloride) for clinical use. (e.g., lidocaine HCl, articaine HCl), dissolved in sterile water or saline
**The local anesthetic salt, both water soluble and stable, is dissolved in sterile water or saline. In this solution, it exists simultaneously as:

a- uncharged molecules (RN), also called the *base,* and
b- positively charged molecules (RNH+), called the *cation***.**

$\mathbf{RNH^+ \rightleftharpoons RN + \mathit{H}^+}$

**The two factors involved in the action of a local anesthetic:
(1) diffusion of the drug through the nerve sheath via the uncharged, lipid-soluble, free base form (RN) of the anesthetic.
(2) binding at the receptor site in the ion channel.
In the presence of a high concentration of hydrogen ions (low pH), the equilibrium shifts to the left, and most of the anesthetic solution exists in ***cationic*** form: $\mathbf{RNH^+ > RN + \mathit{H}^+}$
As hydrogen ion concentration decreases (higher pH), the equilibrium shifts toward the free base form: $\mathbf{RNH^+ < RN + \mathit{H}^+}$
The relative proportion of ionic forms also depends on the pKa, or dissociation constant, of the specific local anesthetic.
**** Acidification of tissue decreases local anesthetic effectiveness. Inadequate anesthesia results when local anesthetics are injected into inflamed or infected areas. The pH of normal tissue is 7.4, whereas the inflammatory process produces acidic products rendering the pH of an inflamed area to be 5-6.
**** Elevating the pH (alkalinization) of a local anesthetic solution, speeds its onset of action, increases its clinical effectiveness, and makes its injection more comfortable.

Induction of local anesthesia

During the induction phase of anesthesia, the local anesthetic moves from its extra-neural site of deposition toward the nerve (as well as in all other possible directions). This process is termed *diffusion*. The unhindered migration of molecules or ions through a fluid medium is significantly influenced with the ***concentration gradient*** of the local anesthetic. Anatomical barriers restrict the diffusion process, the perineurium is the greatest barrier to penetration of local anesthetics.
** The greater the initial concentration of the local anesthetic, the faster the diffusion of its molecules and the more rapid its onset of action
** Fibers near the surface of the nerve (mantle fibers) tend to innervate more proximal regions (e.g., the molar area with an inferior alveolar nerve block), whereas fibers in the core bundles innervate the more distal points of nerve distribution (e.g., the incisors and canine with an inferior alveolar block).

Recovery from anesthesia

The extra-neural concentration of local anesthetic is continually depleted by *diffusion, dispersion, and uptake of the drug*, whereas the intraneural concentration of local anesthetic remains relatively stable. The ***concentration gradient is reversed***, the intra-neural concentration exceeds the extra-neural concentration, and anesthetic molecules begin to diffuse out of the nerve.
**Fasciculi in the mantle begin to lose the local anesthetic much sooner than do the core bundles. Local anesthetic within the core then diffuses into the mantle, so that the first nerve fibers to entirely lose anesthesia are those centermost in the nerve. Mantle fibers remain anesthetized the longest, and core fibers the shortest, time.

Tachyphylaxis

Tachyphylaxis is defined as increasing tolerance to a drug that is administered repeatedly. It is much more likely to develop with local anesthetic, if nerve function is allowed to return before

reinjection (e.g., if the patient complains of pain). The duration, intensity, and spread of anesthesia with reinjection are greatly reduced. It is affected by multiple factors. (Table 1)

Table 1

Explanation of tachyphylaxis للاطلاع	
Probable factor	Explanation
Edema Localized hemorrhage Clot formation Transudation	These factors isolate the nerve from contact with the local anesthetic solution.
hypernatremia	raises the sodium ion gradient, thus counteracting the decrease in sodium ion conduction brought about by the local anesthetic.
decreased pH	Is brought about by the first injection of the acidic local anesthetic. The ambient pH in the area of injection may be somewhat lower, so that fewer local anesthetic molecules are transformed into the free base (RN) on reinjection.

Constituents of local anesthetic dental cartridge

It contains primarily the local anesthetic drug, and also the other ingredients, which are as follows:

1. Local anesthetic drug
2. Vasopressor/vasoconstrictor drug
3. Preservative for vasopressor: a specific agent, an antioxidant, that acts as a preservative for vasoconstrictors. The most frequently used antioxidant is sodium-bisulfite or sodium metabisulfite.
4. Sodium chloride (NaCl) or Ringer's solution: to make the solution isotonic with the tissues of the body. Hypertonic solution produces tissue edema, paresthesia, sometime lasting for several months following drug administration.
5. Distilled water
6. General preservatives: These are added to increase the shelf-life; and include:

(i) Methylparaben, (ii) Thymol, and (iii) Chlorbutol

• Pharmacokinetic and Pharmacodynamic of local anesthetics

Uptake

When injected into soft tissues, local anesthetics exert pharmacologic action on blood vessels in the area. All local anesthetics possess a degree of vasoactivity, most producing dilation of the vascular bed into which they are deposited, although the degree of vasodilation may vary, and some may produce vasoconstriction.

Distribution

Once absorbed into the blood, local anesthetics are distributed throughout the body to all tissues. Highly perfused organs (and areas), such as the brain, head, liver, kidneys, lungs, and spleen, initially will have higher anesthetic blood levels than less highly perfused organs. The plasma concentration of a local anesthetic in certain target organs has a significant bearing on the potential toxicity of the drug. ***The blood level of the local anesthetic*** is influenced by the following factors:

1. Rate at which the drug is absorbed into the cardiovascular system.
2. Rate of distribution of the drug from the vascular compartment to the tissues (more rapid in healthy patients than in those who are medically compromised [e.g., congestive heart failure], thus leading to lower blood levels in healthier patients)
3. Elimination of the drug through metabolic or excretory pathways
The latter two factors serve to decrease the blood level of the local anesthetic.

Metabolism

A significant difference between the two major groups of local anesthetics, the esters and the amides

A) Ester Local Anesthetics

Ester local anesthetics are hydrolyzed in the plasma by the enzyme pseudocholinesterase. The rate at which hydrolysis of different esters occurs varies considerably. The rate of hydrolysis has an impact on the potential toxicity of a local anesthetic. Chloroprocaine, the most rapidly hydrolyzed, is the least toxic, whereas tetracaine, hydrolyzed 16 times more slowly than chloroprocaine, has the greatest potential toxicity. Procaine undergoes hydrolysis to para-aminobenzoic acid (PABA), which is excreted unchanged in the urine, and to diethylamine alcohol, which undergoes further biotransformation before excretion. Allergic reactions that occur in response to ester local anesthetics usually are not related to the parent compound (e.g., procaine) but rather to PABA, which is a major metabolic product of many ester local anesthetics.

B) Amide Local Anesthetics

The biotransformation of amide local anesthetics is more complex than that of the esters. The primary site of biotransformation of amide local anesthetics is the liver. Virtually the entire metabolic process occurs in the liver for lidocaine, mepivacaine, etidocaine, and bupivacaine. Prilocaine undergoes primary metabolism in the liver, with some also possibly occurring in the lung. Articaine, a hybrid molecule containing both ester and amide components, undergoes metabolism in both the blood and the liver.

Excretion

The kidneys are the primary excretory organ for both the local anesthetic and its metabolites. A percentage of a given dose of local anesthetic is excreted unchanged in the urine. This percentage varies according to the drug. Esters appear only in very small concentrations as the parent compound in the urine because they are hydrolyzed almost completely in the plasma.
Amides usually are present in the urine as the parent compound in a greater percentage than the esters, primarily because of their more complex process of biotransformation.

- **Systemic actions of local anesthetics**

Most of the systemic actions of local anesthetics are related to their blood or plasma level in the target organ (CNS, CVS). The higher the level, the greater will be the clinical action.

Central Nervous System

Local anesthetics readily cross the blood–brain barrier. Their pharmacologic action on the CNS is seen as **depression**. At low (therapeutic, nontoxic) blood levels, no CNS effects of any clinical

significance have been noted. At higher (toxic, overdose) levels, the primary clinical manifestation is a generalized tonic–clonic convulsion. Other CNS effects include: Anticonvulsant properties, analgesia and mood elevation.

Anticonvulsant Properties

Some local anesthetics (e.g., procaine, lidocaine, mepivacaine, prilocaine, even cocaine) have demonstrated anticonvulsant properties. Procaine, mepivacaine, and lidocaine have been used intravenously to terminate or decrease the duration of both grand mal and petit mal seizures. The anticonvulsant blood level of lidocaine (about 0.5 to,4 μg/mL) is very close to its cardiotherapeutic range. It was especially effective in interrupting status epilepticus.

Cardiovascular System

Local anesthetics have a direct action on the myocardium and peripheral vasculature. In general, however, the cardiovascular system appears to be more resistant than the CNS to the effects of local anesthetic drugs.

Direct Action on the Myocardium

Local anesthetics modify electrophysiologic events in the myocardium in a manner similar to their actions on peripheral nerves. Local anesthetics produce a myocardial depression that is related to the local anesthetic blood level. Local anesthetics decrease the electrical excitability of the myocardium, decrease the conduction rate, and decrease the force of contraction.

Direct Action on the Peripheral Vasculature

The primary effect of local anesthetics on blood pressure is hypotension. This action is produced by direct depression of the myocardium and smooth muscle relaxation in the vessel walls by the local anesthetic.

Cocaine is the only local anesthetic drug that consistently produces vasoconstriction at commonly employed dosages.

Ropivacaine causes cutaneous vasoconstriction, whereas its congener

Bupivacaine produces vasodilation.

All other local anesthetics produce a peripheral vasodilation through relaxation of smooth muscle in the walls of blood vessels. This leads to increased blood flow to and from the site of local anesthetic deposition. Increased blood perfusion produce the following:

i. Increases the rate of drug absorption, in turn leading to higher plasma level with increased risk of overdose toxicity.
ii. Decreased depth and duration of local anesthetic action,
iii. Increased bleeding in the treatment area.

Other systemic actions of local anesthetic include:

a. Local tissue toxicity and irritation

b. Respiratory depression due to either direct smooth muscle relaxation or generalized CNS depression.

It is necessary to select a suitable local anesthetic depending on factors listed in table 2.

Table 2
Factors in Selection of a Local Anesthetic for a Patient
1. Length of time pain control is necessary 2. Potential need for posttreatment pain control 3. Possibility of self-mutilation in the postoperative period 4. Requirement for hemostasis 5. Presence of any contraindications (absolute or relative) to the local anesthetic solution selected for administration

• **Vasoconstrictors**

Vasoconstrictors are drugs that constrict blood vessels and thereby control tissue perfusion. They are added to local anesthetic solutions to oppose the inherent vasodilatory actions of the local anesthetics. Vasoconstrictors are important additions to a local anesthetic solution for the following reasons:

1. Decrease blood flow (perfusion) to the site of drug administration.
2. Absorption of the local anesthetic into the cardiovascular system is slowed, resulting in lower anesthetic blood levels.
3. Decreasing the risk of local anesthetic toxicity.
4. More local anesthetic enters into the nerve, where it remains for longer periods, thereby increasing the duration of action of most local anesthetics.
5. Decrease bleeding at the site of administration; better visibility (e.g., during a surgical procedure).

**The vasoconstrictors commonly used in conjunction with injected local anesthetics are:

I. Epinephrine and Norepinephrine, chemically identical or similar to the sympathetic nervous system mediators.
II. Felypressin, a synthetic analog of the polypeptide vasopressin (antidiuretic hormone).

• **Mode of action of vasoconstrictors**

Three categories of sympathomimetic amines are known:

1. direct-acting drugs, which exert their action directly on adrenergic receptors; two types of adrenergic receptor, termed alpha (α) and beta (β), based on inhibitory or excitatory actions of catecholamines on smooth muscle.
2. indirect-acting drugs, which act by releasing norepinephrine from adrenergic nerve terminals; and
3. mixed-acting drugs, with both direct and indirect actions

*In patients with preexisting cardiovascular or thyroid disease, the side effects of absorbed Epinephrine must be weighed against those of elevated local anesthetic blood levels. It is currently thought that the cardiovascular effects of conventional epinephrine doses are of little practical concern, even in patients with heart disease. However, even following usual precautions (e.g., aspiration, slow injection), sufficient epinephrine can be absorbed to cause sympathomimetic reactions such as apprehension, tachycardia, sweating, and palpitation the so-called epinephrine reaction.

*Intravascular administration of vasoconstrictors and their administration to sensitive individuals (hyperresponders), or the occurrence of unanticipated drug–drug interactions, can however produce significant clinical manifestations.
*Norepinephrine, lacking significant β2 actions, produces intense peripheral vasoconstriction with possible dramatic elevation of blood pressure, and is associated with a side effect ratio nine times higher than that of epinephrine.
* Felypressin, synthetic analog of the polypeptide vasopressin (antidiuretic hormone), it acts as a direct stimulant of vascular smooth muscle. Its actions appear to be more pronounced on the venous than on the arteriolar microcirculation. In CNS it has no effect on adrenergic nerve transmission; thus, it may be safely administered to hyperthyroid patients and to anyone receiving MAO inhibitors or tricyclic antidepressants. It has both antidiuretic and oxytocic actions, the latter contraindicating its use in pregnant patients.
* Other vasoconstrictors used in medicine and dentistry include phenylephrine and levonordefrin.

• Dilutions of vasoconstrictors

The dilution of vasoconstrictors is commonly referred to as a *ratio* (e.g., 1 to 1000 written 1:1000). Because maximum doses of vasoconstrictors are presented in milligrams, or more commonly today as micrograms (μg), the following interpretations should enable the reader to convert these terms readily:
**A concentration of 1:1000 means that 1 g (1000 mg) of solute (drug) is contained in 1000 mL of solution. Therefore, a 1:1000 dilution contains 1000 mg in 1000 mL or 1.0 mg/mL of solution (1000 μg/mL).

• Specific agents

Lidocaine HCl

Classification: Amide.

Metabolism: In the liver, by the microsomal fixed-function oxidases

Excretion: Via the kidneys; less than 10% unchanged, more than 80% various metabolites

Effective Dental Concentration: 2%. (i.e. 2gm of lidocaine in 100 ml of solution= 20mg/ml)

**Calculation of milligrams of local anesthetic per dental cartridge (1.8 ml cartridge) is displayed in table 3.

Two Percent (2%) Lidocaine HCl Without a Vasoconstrictor (Lidocaine Plain) Its vasodilating properties severely limit the duration and the depth of pulpal anesthesia (5 to 10 minutes). This vasodilatory effect leads to (1) higher blood levels of lidocaine, with an attendant increase in the risk of adverse reactions, along with (2) increased perfusion in the area of drug deposition. Few clinical indications are known for the use of 2% lidocaine *without a vasoconstrictor* in the typical dental practice.

Two Percent (2%) Lidocaine With Epinephrine 1:100,000 Administration of 2% lidocaine with epinephrine 1:100,000 decreases blood flow into the area of injection. Duration of action is increased: approximately 60 minutes of pulpal anesthesia and 3 to5 hours of soft tissue

anesthesia. In addition to the lower blood level of lidocaine, less bleeding occurs in the area of drug administration. The epinephrine dilution is 10 μg/mL = 18 μg per cartridge.

The maximum recommended dose (MRD)

The MRD for a local anesthetic is defined as **the highest amount of an anesthetic drug that can be safely administered without complication to a patient while maintaining its efficacy.** Doses of local anesthetic drugs are presented in terms of milligrams of drug per unit of body weight—as milligrams per kilogram (mg/kg) or as milligrams per pound (mg/lb). Accordingly, the maximum recommended number of cartridges are calculated for each type of local anesthetic. (Table 4)

Maximum doses are unlikely to be reached in most dental patients, especially adults of normal body weight, for most dental procedures. The maximum recommended dose calculated should always be decreased in medically compromised, debilitated or elderly persons.

The Maximum Recommended dose for lidocaine with or without a vasoconstrictor is 4.4 mg/kg body weight.

Table 3

Calculation of milligrams of local anesthetic per dental cartridge (1.8 ml cartridge)

Local Anesthetic	**Percent Concentration**	**mg/mL**	**× 1.8 mL = mg/Cartridge**
Articaine	4	40	72
Bupivacaine	0.5	5	9
Lidocaine	2	20	36
Mepivacaine	2	20	36
	3	30	54
Prilocaine	4	40	72

Table 4

Recommended Maximum Local Anesthetic Doses

Drug/Solution	Maximum Amount (mg/kg)	Number of Cartridges for 70-kg (154-lb) Adult	Number of Cartridges for 20-kg (44-lb) Child
Lidocaine 2% with 1:100,000 epinephrine	5.0	10	3.0
Mepivacaine 2% with 1:20,000 levonordefrin	5.0	10	3.0
Mepivacaine 3% (no vasoconstrictor)	5.0	6	2.0
Prilocaine 4% with 1:200,000 epinephrine	5.0	6	2.0
Articaine 4% with 1:100,000 epinephrine	7.0	6	1.5
Bupivacaine 0.5% with 1:200,000 epinephrine	1.5	10	3.0
Etidocaine 1.5% with 1:200,000 epinephrine	8.0	15	5.0