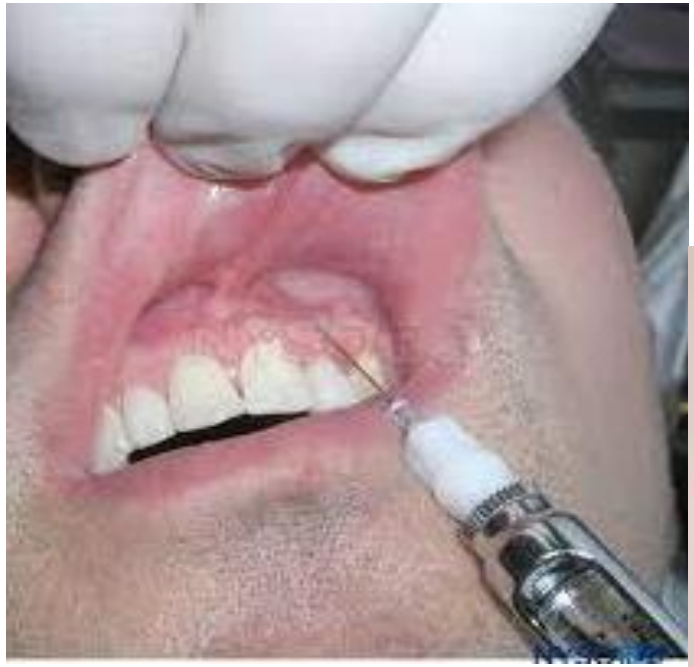
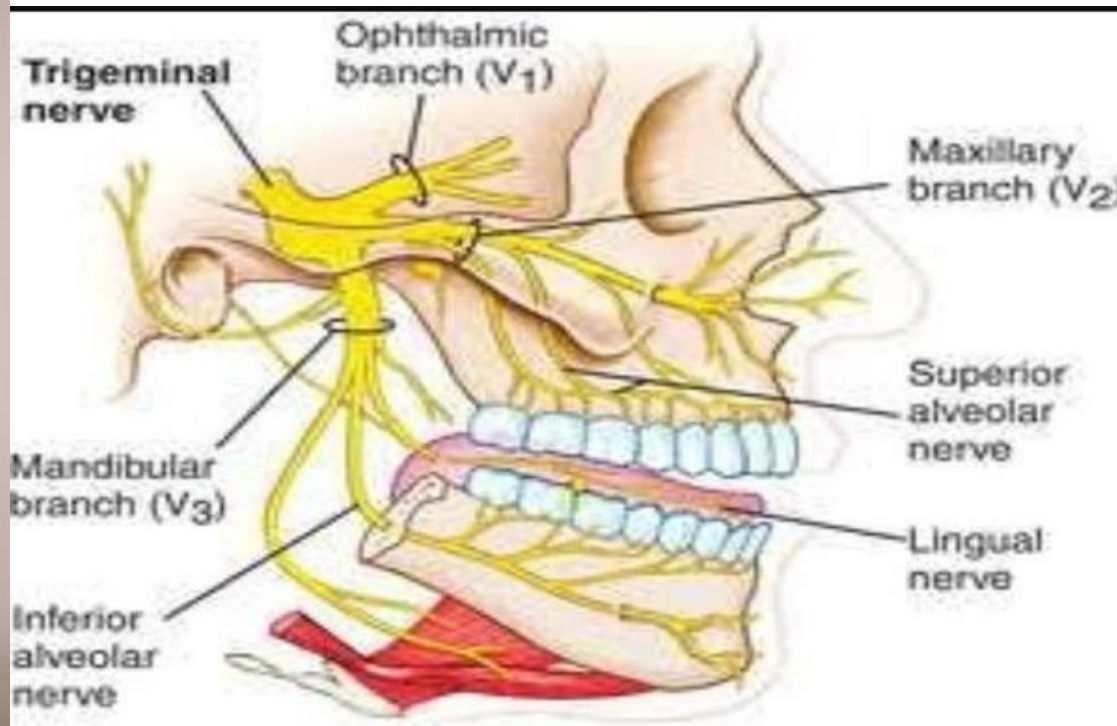
LOCAL ANAESTHESIA IN DENTISTRY

Pharmacology of Local Anesthesia





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Pharmacology of Local Anesthetics

Local anaesthetics are the most commonly used pharmaceuticals in dentistry.
Local anesthetics produce **anesthesia by inhibiting excitation of nerve endings or by blocking conduction in peripheral nerves .**

They **interfere reversibly** with the generation of **the action potential** and with **cellular impulse conduction** by **blockading the sodium channels** in the nerve cell. This results in a **local insensibility to pain stimuli**.

Local anesthetics, when used for the **management of pain**, differ from most other drugs commonly used in medicine and dentistry in one important manner. Virtually all **other drugs**, regardless of the route through which they are administered, must ultimately enter the **circulatory system in sufficiently high concentrations** (e.g., attain therapeutic blood levels in their target organ[s]) **before they can exert a clinical act**ion.

Local anesthetics, however, when used for **pain control**, *cease* to **provide a clinical effect** when they are absorbed from the **site of administration into the circulat**ion.

One prime factor involved in the termination of action of local anesthetics used for pain control is their redistribution from the nerve fiber into the **cardiovascular system (CVS)**. The presence of a local anesthetic in the circulatory system means that the drug will be **transported to every part of the body**.

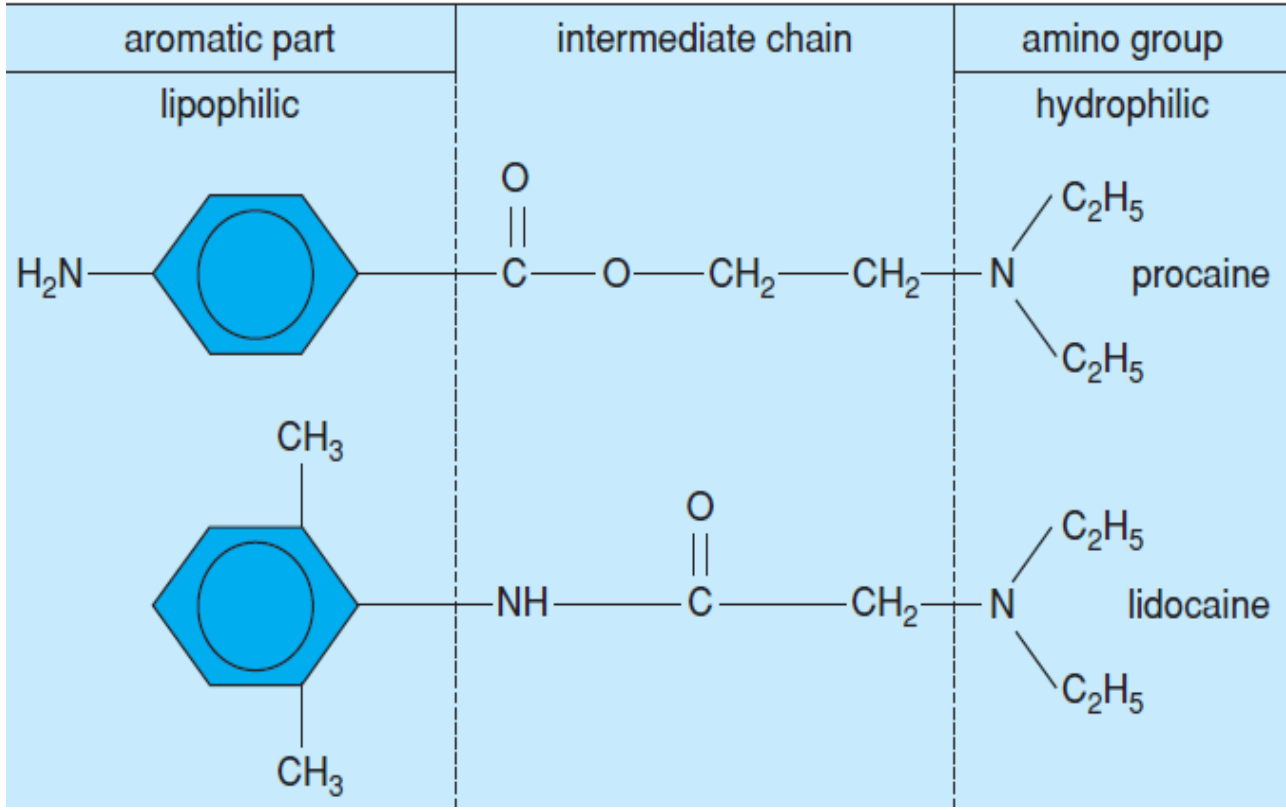
Local anesthetics have the ability to alter the functioning of some of these cells.

Pharmacokinetics of Local Anesthetics

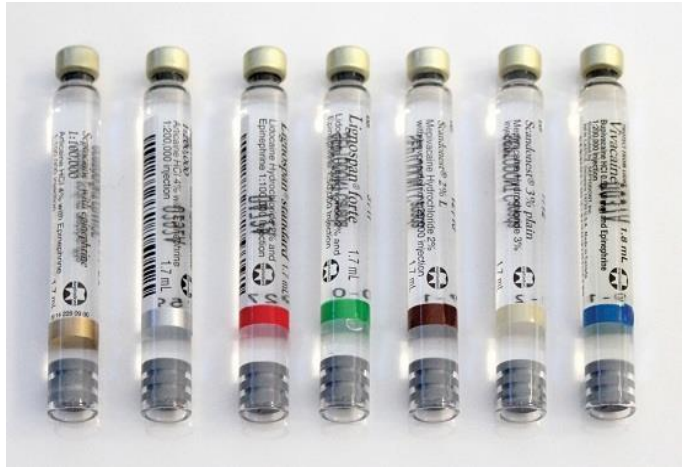
Local anaesthetics share several common characteristics in their molecular structure . **A lipophilic group** can be identified which determines **lipid solubility**.
Another part contains a **hydrophilic group** that determines the **degree of water solubility**.

Usually the lipophilic part of the molecule is an aromatic structure that contains a **benzene ring**.

The **hydrophilic part** contains **a secondary or a tertiary amine**. Both parts, present at the **opposite ends of the molecule**, are connected by an **intermediate sect**ion. This intermediate section consists of an **ester** or an **amide** group and a relatively short chain of **four to five carbon atoms**



Molecular structure of an ester-linked (procaine) and amide-linked local anaesthetic (lidocaine).



Local anaesthetics are distributed throughout all body tissues. In general, **tissues with a high vascular perfusion (e.g. lung) absorb local anaesthetics most rapidly while tissues with a low vascular perfusion show a slower rate of uptake**.

Plasma protein binding influences the rate of tissue uptake, the blood concentration of local anaesthetic agents following regional anaesthesia is **determined by the absorption**, **tissue redistribution**, **metabolism** and **excretion characteristics of the various agents.**

Absorption is related to the site of injection, dosage employed, use of vasoconstrictors and physicochemical profile of the specific agent.

Local anaesthetics are distributed throughout all body tissues. In general, tissues with a high vascular perfusion (e.g. lung) absorb local anaesthetics most rapidly while tissues with a low vascular perfusion show a slower rate of uptake. Plasma protein binding influences the rate of tissue uptake. Local anaesthetics are primarily bound to α-1-acid glycoproteins.

The metabolism of local anaesthetics varies according to their chemical classification. The amino esters are hydrolysed in plasma by the enzyme cholinesterase while the amino amides are primarily metabolized in the liver by microsomal enzymes.

Local anaesthetics and their metabolites are excreted primarily by the kidneys. Less than 5% of the parent compound is excreted in an unchanged form.

The elimination of local anaesthetics is influenced by a variety of factors such as age, clinical status of the patient, and concomitant administration of other drugs. In general, neonates and geriatric patients eliminate local anaesthetics more slowly.

A disturbance of the calcium binding, with the **closure of the sodium channel as a result**. The strength of the effect of **local anaesthetics** on sodium channels is dependent on the **frequency of the action potential**.
On the one hand, when the **sodium channel is open** it is more accessible for the local anaesthetic.
On the other hand, **local anaesthetics have a higher affinity with open sodium channels**.
The total process is called **conduction blockade** or **membrane stabilisation** and **consists of a decrease in sodium conduction** and a **reduction in the rate of depolarisation**.
In addition, the threshold potential level will no longer be reached, so an action potential cannot occur anymore.
However, the resting potential, the threshold potential and the repolarisation of the cell membrane will not or hardly be affected.

Pharmacokinetics of local anesthetics :

Pharmacokinetics (PK) is defined as the **movement of drugs through the body**, whereas **Pharmacodynamics (PD)** is defined as the **body's biological response to drugs**. In other words, PK describes a **drug's absorption, distribution, metabolism, and excretion (also known as ADME)** and **PD** describes **how biological processes in the body respond to or are impacted by a drug**. Put in the simplest terms, pharmacokinetics is what the body does to the drug and pharmacodynamics is what the drug does to the body
Local anesthetics are distributed throughout all body tissues.
In general, **tissues with a high vascular perfusion (e.g. lung) absorb local anaesthetics most rapidly while tissues with a low vascular perfusion show a slower rate of uptake**.

Classification of Local Anesthetics

Esters

Esters of benzoic acid
Butacaine
Cocaine
Ethyl aminobenzoate (benzocaine)
Hexylcaine
Piperocaine
Tetracaine

Esters of *p*-aminobenzoic acid
Chloroprocaine
Procaine
Propoxycaine

Amides

Articaine
Bupivacaine
Dibucaine
Etidocaine
Lidocaine
Mepivacaine
Prilocaine
Ropivacaine

Quinoline

Centbucridine

A ccidental intra-arterial injection of a drug (e.g.,thiopental) or injection of e**pinephrine or norepinephrine** into a fingertip or toe. Intra-arterial administration of an irritating drug such as thiopental may produce **arteriospasm,**with an attendant decrease in tissue perfusion that if **prolonged could lead to tissue death**, **gangrene**, and loss of the affected limb. In this situation, procaine is administered intra-arterially in an attempt to break the arteriospasm and reestablish blood flow to the affected limb. Tetracaine, chloroprocaine, and propoxycaine also possess vasodilating properties to differing degrees but not to the degree of procaine.
Cocaine is the only local anesthetic that consistently produces vasoconstriction..

The initial action of cocaine is vasodilation, followed by an intense and prolonged vasoconstriction.
It is produced by inhibition of the uptake of catecholamines (especially norepinephrine) into tissue binding sites.
This results in an excess of free norepinephrine,leading to a prolonged and intense state of vasoconstriction.
This inhibition of the reuptake of norepinephrine has not been demonstrated with other local anesthetics, such as **lidocaine and bupivacaine**.

A significant clinical effect of vasodilation is an increasein the rate of absorption of the local anesthetic into the blood, thus decreasing the duration and quality (e.g., depth) of pain control, while increasing the anesthetic blood (or plasma) concentration and its potential for overdose (toxicreaction). The rates at which local anesthetics are absorbed into the bloodstream and reach their peak blood level vary according to the route of administration

Plasma protein binding influences the rate of tissue 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 differ**, and some (e.g., **cocaine**). may produce **vasoconstriction.** To some degree, these effects may be **concentration dependent**.

Relative **vasodilating va**lues of **amide local anesthetics .Ester local anesthetics** are also potent **vasodilating drugs**.

Procaine, the most potent vasodilator among local anesthetics

is, on rare occasion, injected clinically to induce **vasodilation** when peripheral blood flow has been compromised.

Oral Route OF LA

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. After absorption of lidocaine from the gastrointestinal tract into the enterohepatic circulation, a fraction of the drug dose is carried to the liver, where approximately 72% of the dose is biotransformed into inactive metabolites.

This has seriously hampered the use of lidocaine as an oral antidysrhythmic drug. In 1984

Astra Pharmaceuticals and Merck Sharp & Dohme introducedan analogue of lidocaine, tocainide hydrochloride, that is effective orally.

The chemical structures of tocainide and lidocaine are presented in

Topical Route OF LA

Local anesthetics are absorbed at differing rates after application to mucous membrane: in the tracheal mucosa, absorption

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.**

Skeletal muscle, although not as highly perfused as these areas, contains the greatest percentage of local anesthetic of any tissue or organ in the body because it constitutes the largest mass of tissue in the body 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:

1. the rate at which the drug is absorbed into the **CVS**
2. the rate of distribution of the drug from the vascular compartment to the tissues (more rapid in healthypatients 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.**

Time to Achieve Peak Blood Level

Route	Time (min)
Intravenous	1
Topical	5 (approximately)
Intramuscular	5–10
Subcutaneous	30–90

Percentages of Cardiac Output Distributed to Different Organ Systems

Region	Percentage of Cardiac Output Received
Kidney	22
Gastrointestinal system, spleen	21
Skeletal muscle	15
Brain	14
Skin	6
Liver	6
Bone	5
Heart muscle	3
Other	8

Modified from Mohrman DE, Heller LJ. *Cardiovascular Physiology*. 7th ed. New York: Lange Medical Books/McGraw-Hill; 2010.)

The rate at which a local anesthetic is removed from the blood is described as its *elimination half-life*.

Simply stated, the elimination half-life is the time necessary for a 50% reduction in the blood level (one half-life is equivalent to 50% reduction; two half-lives are equivalent to 75% reduction; three half-lives are equivalent to 87.5% reduction; four half-lives are equivalent to 94% reduction; five half-lives are equivalent to 97% reduction; six half-lives are equivalent to 98.5% reduction) .

All local anesthetics readily cross the blood-brain barrier.They also readily cross the **placenta and enter the circulatory system of the developing fetus**

Half-Life of Local Anesthetics

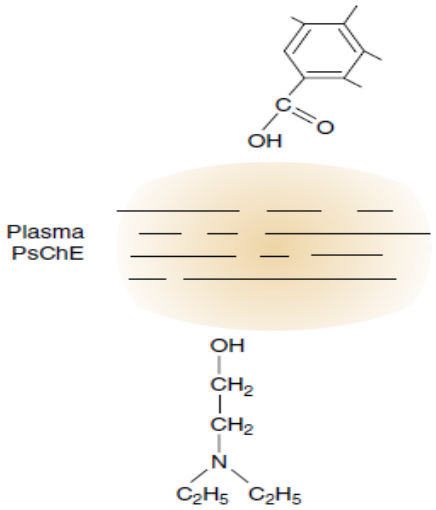
Drug	Half-Life (h)
Chloroprocaine[a]	0.1
Procaine[a]	0.1
Tetracaine[a]	0.3
Articaine[b]	0.5
Cocaine[a]	0.7
Prilocaine[b]	1.6
Lidocaine[b]	1.6
Mepivacaine[b]	1.9
Ropivacaine[b]	1.9
Etidocaine[b]	2.6
Bupivacaine[b]	3.5
Propoxycaine[a]	NA

[a]Ester.
[b]Amide.
NA, Not available.

Metabolism (Biotransformation,Detoxification)

A significant difference between the two major groups of local anesthetics, the esters and the amides, is the means by which the body biologically transforms the active drug into one that is pharmacologically inactive.

Metabolism (alsoknown as *biotransformation* or *detoxification*) of local anesthetics is important because the overall toxicity of a drug depends on a balance between its rate of absorption into the bloodstream at the site of injection and its rate of removal from the blood through the processes of tissue uptake and metabolism.



Metabolic hydrolysis of procaine. *PsChE*, Pseudocholinesterase. (From Tucker GT. Biotransformation and toxicity of local anesthetics. .

The aromatic part of the ester-type local anaesthetics is derived from **para amino benzoic acid (PABA**).
Ester anaesthetics are **metabolised in plasma** by the enzyme **pseudo cholinesterase**, which generates PABA **analogues and amino alcohol**.
The PABA analogues are excreted in the **urine mainly unaltered**; the **amino alcohol** is further **metabolised** in the **liver**.
Approximately 2% of ester anaesthetics are excreted unchanged by the kidneys. The PABA analogues are responsible for the **allergic reactions** that frequently occur with the use of **local anaesthetics of the ester type**.

Anaesthetics of the amide type are **metabolised in the liver** first by the **cytochrome P450 system**. This reaction is followed by **conjugation, resulting in highly water-soluble metabolites** that are excreted by the kidneys.
Between 70 and 90% of the amide anaesthetic is metabolised, and **10–30% is excreted by the kidneys unchanged**.

The velocity of **degradation in the liver** is reciprocally related to **the toxicity**.

Prilocaine is metabolised fastest and is **consequently the least toxic amide-type local anaesthetic**.

Patients with severe liver insufficiency degrade amide-type local anaesthetics at a delayed rate, which increases the **risk of a toxic effect (and spontaneous respiration resumes**.
Persons with **atypical pseudocholinesterase are unable to hydrolyze succinylcholine at a normal rate, resulting in the duration of apnea being prolonged.**

Atypical pseudocholinesterase is a **hereditary trait**. Any familial history of adverse events during general anesthesia should be **carefully evaluated** by the doctor before **dental care commences**.

A confirmed or strongly suspected history, in the patient or biological family, of atypical pseudocholinesterase represents a relative contraindication to **administration of ester-type local anesthetics.**

There are **absolute** and **relative contraindications to the administration** of drugs.
An *absolute contraindication* implies that under no circumstance should the drug in question be administered to the patient as the possibility of **potentially toxic** or **lethal reactions is increased**, whereas a *relative contraindication* means that the drug in question may be administered to the patient after careful weighing of the **risk associated** with use of the drug versus the potential benefit to be gained, and if an acceptable alternative drug is not available. **However, the smallest clinically effective dose should always be used because the likelihood of adverse reaction to this drug is increased in the patient.**

Amide Local Anesthetics

The biotransformation of amide local anesthetics is more complex than that of ester local anesthetics. 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 (primarily)** and the **liver.** The rates of biotransformation of **lidocaine, mepivacaine, etidocaine, and bupivacaine are similar.**

Therefore liver function and hepatic perfusion significantly influence the rate of biotransformation of an amide local anesthetic. Approximately 70% of a dose of injected lidocaine undergoes biotransformation in patients with normal liver function.
Patients with lower-than-usual hepatic blood flow (hypotension, congestive heart failure). or poor liver function (cirrhosis) are **unable to biotransform amide local anesthetics at a normal rate**. This slower-than-normal biotransformation results in **higher anesthetic blood levels** and **increased risk of toxicity**.

Significant liver dysfunction (American Society of Anesthesiologists [ASA] physical status classification system class 4 or 5) or **heart failure (ASA class 4 or 5)** represents a **relative contraindication to the administration of amide local anesthetic drugs**.

Articaine has a shorter half-life than other **amides (27 minutes vs. 90 minutes)** because a significant portion of its biotransformation occurs in the blood by the **enzyme plasma cholinesterase**. The biotransformation products of certain local anesthetics can possess significant clinical activity if they are permitted to accumulate in the blood.

This may be seen in renal or cardiac failure and during periods of prolonged drug administration. A clinical example is the production of methemoglobinemia in patients receiving large doses of prilocaine

Prilocaine, the parent compound, does not produce methemoglobinemia, but orthotoluidine, a primary metabolite of prilocaine, does induce the formation of methemoglobin, which is responsible for methemoglobinemia. When methemoglobin blood levels become elevated, clinical signs and symptoms are observed.

Another example of **pharmacologically active meta**bolites is the sedative effect occasionally observed after **lidocaine** administration.
Lidocaine does not **produce sedation**; however, **two metabolites**— **monoethylglycinexylidide** and **glycinexylidide**— are thought to be responsible for this clinical action. The metabolic pathways of lidocaine and prilocaine are shown in

Excretion

The kidneys are the primary excretory organ for both the local anesthetic and its metabolites. A proportion of a given dose of local anesthetic is excreted unchanged in the urine. This proportion 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. Procaine appears in the urine as PABA (90%) with 2% unchanged. Ten percent of a cocaine dose is found in the urine unchanged.

Hydrolysis Rate of Esters

Drug	Rate of Hydrolysis (μmol/mL/h)
Chloroprocaine	4.7
Procaine	1.1
Tetracaine	0.3

Lidocaine Disposition in Various Groups of Patients

Group	Lidocaine Half-Life (h)	Mean Total Body Clearance (mL/kg/min)
Normal	1.8	10
Heart failure	1.9	6.3
Hepatic disease	4.9	6
Renal disease	1.3	13.7

Data from Thomson PD, Melmon KL; Richardson JA, et al. Lidocaine pharmacokinetics in advanced heart failure, liver disease, and renal failure in humans. *Ann Intern Med*. 1973;78:499–513.

Amides are usually present in the **urine as the parentcompound** in a greater percentage than the esters, primarily because of their more complex process of biotransformation.
Although the percentages of parent drug found in urine differ from study to study, **less than 3% lidocaine**, 1% mepivacaine, and **1% etidocaine** is found **unchanged in the urine**.
Patients with significant **renal impairment may be unable to eliminate the parent local anesthetic compound** or its major metabolites from the blood, resulting in **slightly elevated blood levels** and therefore **increased potential for toxicity**. This may occur with the **esters or amides**, and is especially likely **with cocaine**. Thus significant renal disease (ASA class 4 or 5) represents a relative contraindication to the administration of local anesthetics. This includes patients undergoing **renal dialysis** and those with **chronic glomerulonephritis** or pyelonephritis

Systemic Actions of Local Anesthetics:

Local anesthetics are chemicals that reversibly block action potentials in all excitable membranes .

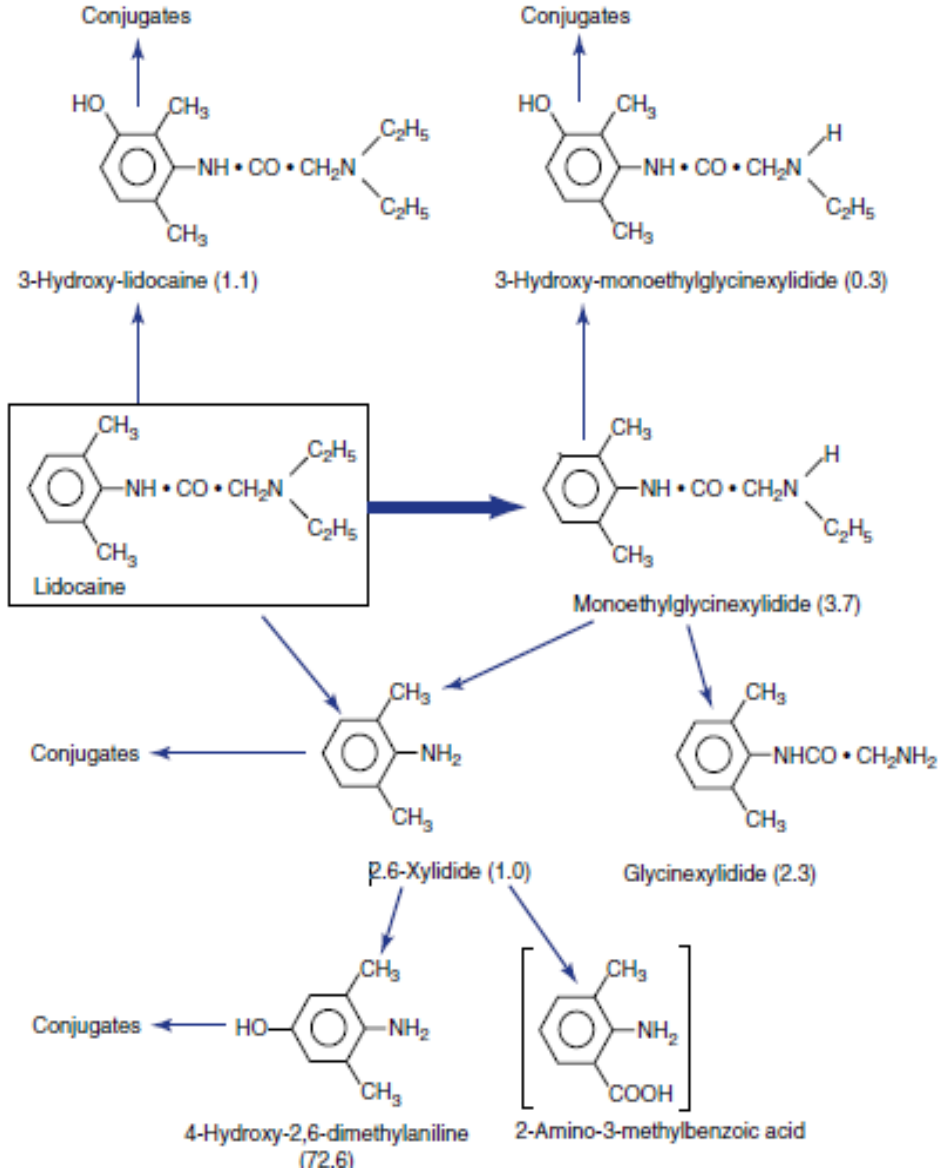
The central nervous system (CNS) and the CVS therefore are especially susceptible to their actions. Most of the systemic actions of local anesthetics are related to their blood or plasma level in a target organ (CNS, CVS). The higher the blood level, the greater will be the clinical action.

Centbucridine (a quinoline derivative) has proved to be five to eigh times as potent a local anesthetic as lidocaine,with an equally rapid onset of action and an equivalent duration.

Centbucridine works by reducing the **excitations in the nerve ending** as well as **prohibiting any further electrical conduction in the peripheral nerves**, in and around the **area where the anesthetic is applied**.

The drug is able to achieve this by **reducing the influx of sodium ions through cell membranes of neuron cells by closing the voltage gated sodium channels** and other **sodium specific ion channels present in these cells.**

Temporary side effects like **dizziness**, **headache**, **pins** and **needles**, twitchiness of **the muscles** and **continued numbness** in the area may occur upon usage of **Centbucridine**



Metabolic pathways of lidocaine. Percentages of the dose found in urine are indicated in parentheses.

It is great importance is the finding that it does not adversely affect the CNS or CVS, except in very high doses. It has been used both by injection and by topical application in ophthalmic surgery but not, as yet, in dentistry. Local anesthetics are absorbed from their site of administration into the circulatory system, which effectively dilutes them and carries them to all cells of the body.

The resulting **blood level of the local anesthetic** depends on **its rate of uptake** from the site of administration into the circulatory system (**increasing the blood level**), and on the rates of distribution in tissue and biotransformation (in **the liver**), processes that remove the drug from the blood (**decreasing the blood level**).

Central Nervous System:

Local anesthetics **readily cross the blood-brain barrier**. Their pharmacologic action on the CNS is **one of depression**.

At low (**therapeutic, nontoxic**) blood levels, no CNS effects of any clinical significance l

At higher (**toxic,overdose**) levels the primary clinical manifestation is **a generalized tonic-clonic convulsion.** Between these two extremes exists a spectrum of other clinical signs and symptoms.

It is important to note that individual patients may respond either **more positively** or **more negatively** to **doses** or **blood levels of a drug** that are considered to be **"normal" (e.g., within an acceptable range**).

However, approximately 15% of persons are "**hyperresponders**"to an "average" dose of a given drug.

Preconvulsive Signs and Symptoms of Central Nervous System Toxicity

Signs (Objectively Observable)	Symptoms (Subjectively Felt)
Slurred speech	Numbness of tongue and circumoral region
Shivering	Warm, flushed feeling of skin
Muscular twitching	Pleasant dreamlike state
Tremor of muscles of face and distal extremities	
Generalized lightheadedness	
Dizziness	
Visual disturbances (inability to focus)	
Auditory disturbance (tinnitus)	
Drowsiness	
Disorientation	

Within this 15% there is a normal distribution curve, so yet another 15% of these persons would be considered as "**extreme hyperresponders**." In such an individual an "**average**" or "**normal**" dose of a drug could result in the manifestation of **significant signs and symptoms of toxicity (overdose).**

Anticonvulsant Properties

The "classic" overdose reaction to a local anesthetic is a **generalized tonic-clonic convulsion**. Some local anesthetics (e.g., procaine, lidocaine, mepivacaine, prilocaine, and even cocaine) have demonstrated anticonvulsant properties.

These occur at a blood level considerably below that at which the same drugs produce seizure activity. Values for anticonvulsive blood levels of **lidocaine** are shown in **Procaine**, **mepivacaine**, and **lidocaine** have been used intravenously to **terminate or decrease the duration of both grand mal and petit mal seizures**.
Of the local anesthetics tested, ***lidocaine appeared to be the most promising anticonvulsant***
as it exhibits the **widest therapeutic range:** a threefold
margin between **seizure-protecting** and seizure-inducing doses. **The anticonvulsant blood level of lidocaine (about 0.5 to 4 µg/mL) is very close to its cardio therapeutic range**
It has been demonstrated to be effective in temporarily arresting seizure activity in most human epileptic patients.
It was especially effective in **interrupting status epilepticus at therapeutic doses** of 2 to 3 mg/kg when given intravenously at a rate of 40 to 50 mg/min.
This use of local anesthetics has been essentially dormant since then as more effective anticonvulsants have been introduced into clinical practice.

Mechanism of Anticonvulsant Properties of Local Anesthetics

Epileptic patients possess hyperexcitable cortical neurons at a site within the brain where the convulsive episode originates
(called the *epileptic focus*). Local anesthetics, by virtue of their depressant actions on the CNS, raise the seizure threshold by decreasing the excitability of these neurons, thereby preventing or terminating seizures.

Preconvulsive Signs and Symptoms

With a further increase in the blood level of the local anesthetic to above its therapeutic level, adverse reactions may be observed. **Because the CNS is much more susceptible than other systems to the actions of local anesthetics**, it is not surprising that the initial **clinical signs and symptoms of overdose (toxicity) are of CNS origin**.
With lidocaine, this second phase is observed at a level between **4.5 and 7 µg/ mL** in the average normal **healthy patient**.
Initial clinical signs and symptoms of **CNS toxicity are usually excitatory in nature** .
Lidocaine and procaine differ somewhat from other local anesthetics in that the usual progression of signs and symptoms just noted may not be seen.

Lidocaine and procaine frequently produce an initial mild sedation or drowsiness (more common with lidocaine). Because of this potential, "air crew/SOD (special operational duty) members cannot fly for at least 8 hours after receiving a **local or regional anesthetic agent**." Sedation may develop in place of the excitatory signs. If excitation or sedation is observed during the **first 5 to 10 minutes after intraoral administration of a local anesthetic**, it **should serve as a warning to the clinician of a rising local anesthetic blood level** and the **possibility (if the blood level continues to rise) of a more serious reaction, including a generalized convulsive episode**.

Convulsive Phase

Further increase in local anesthetic blood level leads to signs and symptoms consistent with a generalized tonic-clonic convulsive episode.

Signs & Symptoms of Local Anesthetic Overdose

Minimal to Moderate Overdose Levels

Signs
- Talkativeness
- Apprehension
- Excitability
- Slurred speech
- Generalized stutter, leading to muscular twitching and tremor in the face and distal extremities
- Euphoria
- Dysarthria
- Nystagmus
- Sweating
- Vomiting
- Failure to follow commands or be reasoned with
- Elevated blood pressure
- Elevated heart rate
- Elevated respiratory rate

Symptoms (Progressive With Increasing Blood Levels)
- Lightheadedness and dizziness
- Restlessness
- Nervousness
- Sensation of twitching before actual twitching is observed (see "Generalized stutter" under "Signs")
- Metallic taste
- Visual disturbances (inability to focus)
- Auditory disturbances (tinnitus)
- Drowsiness and disorientation
- Loss of consciousness

Moderate to High Overdose Levels

- Tonic-clonic seizure activity followed by
  - Generalized central nervous system depression
  - Depressed blood pressure, heart rate, and respiratory rate

From Malamed SF. *Medical Emergencies in the Dental Office*. 7th ed. St Louis: Mosby; 2015.

Vasoconstrictors

Vasoconstrictors like adrenaline in local anaesthetics are associated with more drug interactions than any other drug in Dentistry with an incidence of adverse reactions ranging from 2.5%-11%. Therefore, understanding the **physiological** and **pharmacological effects**, **interactions with other drugs**, and **dosages are important in day to day dental practice**.

Local anaesthetics are vasodilators, hence the addition of a **vasoconstrictor like adrenaline provides the following advantages: improves the anaesthetic onset** and **duration**, **reduces bleeding**, and **decreases the systemic absorption rate of local anaesthetics by reducing the plasma concentration**.

However, **adrenaline** is unstable and therefore an **antioxidant is added to prevent it oxidizing**. Sodium bisulphite is the **preservative most commonly added to local anaesthetics**.

Of course, **patients allergic to sulphites will now react to a local anaesthetic containing sodium bisulphites**

Vasoconstrictors are extremely important in the clinical use of local anaesthetics. Without these compounds, the clinical use of local anaesthetics in dentistry would be **hampered by their limited duration of action**, as most anaesthetics **produce vasodilatation**. Exceptions are **mepivacaine and prilocaine**.
All clinically effective injectable local anesthetics are vasodilators.

The degree of vasodilation ranges from significant (**procaine)** to minimal (**prilocaine, mepivacaine**) as well as with both the injection site and individual patient response.

After deposition of a local anesthetic into tissues, blood vessels (arterioles and capillaries primarily) in the **area dilate**, resulting in increased perfusion at the site, leading to the following reactions:
1. an increased rate of absorption of the local anesthetic into the cardiovascular system, which in turn removes it from the injection site (redistribution of the drug);
2. higher plasma levels of the local anesthetic, with an attendant increase in the risk of local anesthetic toxicity (overdose);
3. decrease in both the depth and the duration of anesthesia because the local anesthetic is removed from the site of injection more rapidly;
4. increased bleeding at the site of treatment as a result of increased perfusion.

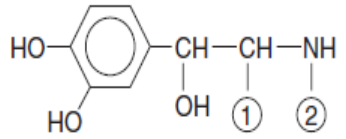
Vasoconstrictors are drugs that **constrict blood vessels** and **thereby control tissue perfusion**. They are added to local anesthetic solutions to oppose the inherent vasodilatory actions of the local anesthetics.
Vasoconstrictors are important additions to a local anesthetic solution for the following reasons:
1. By constricting blood vessels, vasoconstrictors 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. compares blood levels of local anesthetic both with and without a vasoconstrictor.
3. Local anesthetic blood levels are lowered, thereby decreasing the risk of local anesthetic toxicity from over administration of the drug. (**Overdose from rapid intravascularinjection can still occur.**)
4. More local anesthetic diffuses into the nerve, where it remains longer, thereby increasing (in some cases significantly,

Effects of a Vasoconstrictor (Epinephrine 1:200,000) on Peak Local Anesthetic Levels in Blood

Local Anesthetic	Dose (mg)	Peak Level (μg/mL)	
		Without Vasoconstrictor	With Vasoconstrictor
Mepivacaine	500	4.7	3
Lidocaine	400	4.3	3
Prilocaine	400	2.8	2.6
Etidocaine	300	1.4	1.3

Data from Cannall H, Walters H, Beckett AH, Saunders A. Circulating blood levels of lignocaine after peri-oral injections. *Br Dent J*. 1975;138:87–93.

in others minimally4) the duration of action of most local anesthetics.
5. Vasoconstrictors decrease bleeding at the site of administration.
Their inclusion in the local anesthetic solution is useful when increased bleeding is anticipated (e.g., during a surgical procedure).
The vasoconstrictors commonly used in conjunction with injected local anesthetics are chemically identical or similar to the sympathetic nervous system mediators epinephrine and norepinephrine.
The actions of the vasoconstrictors so resemble the response of adrenergic nerves to stimulation that they are classified as sympathomimetic, or adrenergic, drugs. These drugs have many clinical actions besides vasoconstriction.Sympathomimetic drugs may also be classified **according to their chemical structure and mode of action**



	①	②
Epinephrine	H	CH_3
Levonordefrin	CH_3	H
Norepinephrine	H	H

Chemical Structure

Classification of sympathomimetic drugs by chemical structure is related to the presence or absence of a catechol nucleus.
Catechol is also known as ***o*-dihydroxybenzene**. Sympathomimetic drugs that have hydroxyl (OH) substitutions at the third and fourth positions of the aromatic ring are termed ***catechols.***
If they also contain an amine group (NH_2) attached to the aliphatic side chain, they are called ***catecholamines.***
Epinephrine, **norepinephrine**, and **dopamine** are the naturally **occurring catecholamines of the sympathetic nervous system.**
Isoproterenol and **levonordefrin** are **synthetic catecholamines**.

Vasoconstrictors that do not possess OH groups at the third and fourth positions of the aromatic molecule are not catechols but are amines because they have an NH_2 group attached to the aliphatic side chain.

Therefore, the vasoconstrictors adrenaline (also known as **epinephrine**) and **felypressin** are added to the local anaesthetics used in dentistry.

Adrenaline is an **endogenous compound**, released into the blood by the **adrenal medulla**, with a half-life of only a **few minutes**.
Nervous or anxious people may have increased blood levels of adrenaline from fear of dental treatment. Vasoconstriction by adrenaline is achieved by **stimulation of α1-adrenergic receptors of the smooth muscles of the vessel wall**. **The maximum dose of adrenaline for adults is 200 µg**.

Felypressin (octapressin) is a synthetic analogue of poly peptide vasopressin vasoconstrictor , derived from **vasopressin (antidiuretic hormone).** The vasoconstrictive activity of **felypressin** mainly originates from inducing constriction of the venous part of the circulation.
The duration of action is longer than that of adrenaline For adults, **the maximum dose of felypressin is 5.4 µg**.

Modes of Action:

Three categories of sympathomimetic amines are known:
direct-acting drugs, which exert their action directly on **adrenergic receptors**; **indirect-acting drugs**, which act by releasing norepinephrine from adrenergic **nerve terminals**; and **mixed-acting drugs,** with both **direct** and **indirect actions**

Categories of Sympathomimetic Amines

Direct Acting	Indirect Acting	Mixed Acting
Epinephrine	Tyramine	Metaraminol
Norepinephrine	Amphetamine	Ephedrine
Levonordefrin	Methamphetamine	
Isoproterenol	Hydroxyamphetamine	
Dopamine		
Methoxamine		
Phenylephrine		

Catecholamines	Noncatecholamines
Epinephrine	Amphetamine
Norepinephrine	Methamphetamine
Levonordefrin	Ephedrine
Isoproterenol	Mephentermine
Dopamine	Hydroxyamphetamine
	Metaraminol
	Methoxamine
	Phenylephrine

Adrenergic Receptors

Adrenergic receptors are found in most tissues of the body.

The concept of adrenergic receptors was proposed byAhlquist in 1948, and is well accepted today.

Ahlquist recognized **two types of adrenergic receptors**,termed ***alpha* (α)** and ***beta* (β),** on the basis of **inhibitory** or **excitatory actions** of **catecholamines on smooth muscle**.

Stimulation of α receptors by a **sympathomimetic drug usually produces a response that includes contraction of smooth muscle in blood vessels (vasoconstriction).** On the basis of differences in their **function and location**, **α receptors** have been subcategorized.

Whereas **α1 receptors** are excitatory postsynaptic, **α2 receptors** are inhibitory postsynaptic.

Stimulation of **β receptors** produces smooth muscle relaxation (vasodilation and bronchodilation) and **cardiac stimulation (increased heart rate and strength of contraction).**

Beta receptors are further divided into β1 and β2 receptors:

β1 receptors are found in the heart and small intestine and are responsible for cardiac stimulation and lipolysis;

B2 receptors, found in the bronchi of the lungs, **vascular beds**, and **uterus**, produce **bronchodilation** and **vasodilation.** the differences in degrees of α and β receptor activity of three commonly used vasoconstrictors.

lists the systemic effects, based on α and β receptor activity, of **epinephrine** and **norepinephrine.**

Adrenergic Receptor Activity of Vasoconstrictors

Drug	α_1	α_2	β_1	β_2
Epinephrine	+++	+++	+++	+++
Norepinephrine	++	++	++	+
Levonordefrin	+	++	++	+

Relative potency of drugs is indicated as follows: +++, high; ++, intermediate; and +, low.

From Jastak JT, Yagiela JA, Donaldson D. *Local Anesthesia of the Oral Cavity*. Philadelphia: WB Saunders; 1995.

Release of Catecholamines

Other sympathomimetic drugs, such as **tyramine** and **amphetamine**, act indirectly by causing the release of the **catecholamine norepinephrine** from storage sites in

Adrenergic nerve terminals. In addition, these drugs may exert direct action on α and β receptors.
The clinical actions of this group of drugs therefore are **quite similar** to the actions of norepinephrine.
Successively repeated doses of these drugs will be less effective than those given previously because of depletion of **norepinephrine from storage sites**. This phenomenon is termed ***tachyphylaxis*** and is not seen with drugs that act directly on **adrenergic receptors**.

Dilutions of Vasoconstrictors

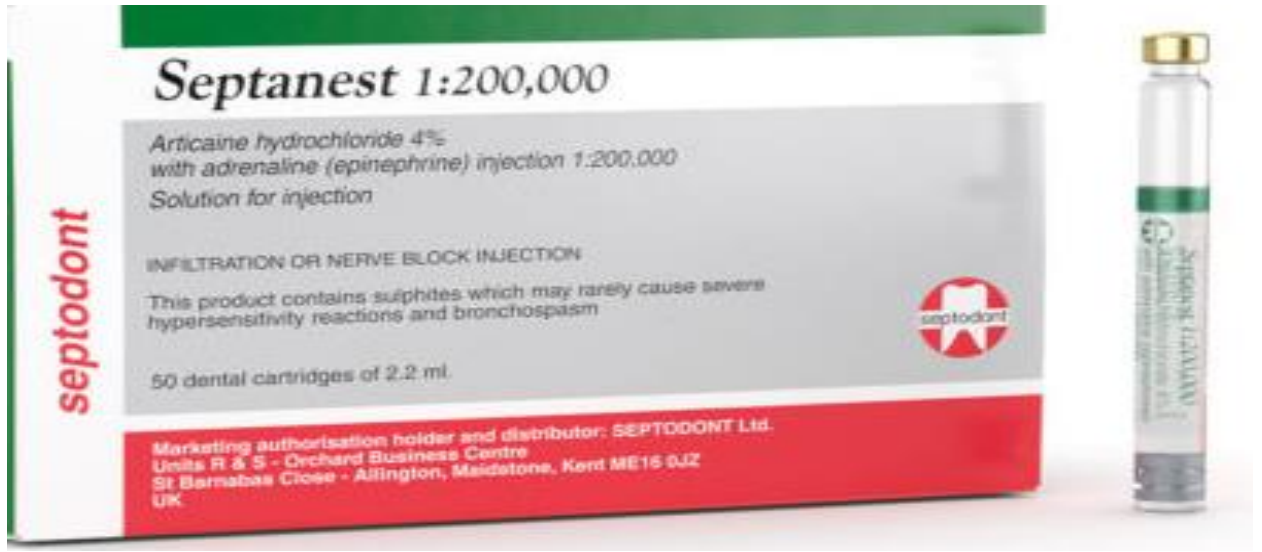
The use of vasoconstrictors can have **negative effects**, both **locally** and **systemically.** The dilution of vasoconstrictors is commonly referred to as a ***ratio*** **(e.g., 1:1000**). Because the maximum doses of vasoconstrictors are presented in **milligrams,** or more commonly today in **micrograms**, the following interpretations should enable the reader to convert these terms readily:
A concentration of 1:1000 means that 1 g (1000 mg) of drug is contained in 1000 mL of solution.
Therefore, a 1:1000 dilution contains 1000 mg in 1000 mL or 1.0 mg per milliliter of solution (1000 μg/mL).
Vasoconstrictors, as used in dental local anesthetic solutions,are much more dilute than the 1:1000 concentration described in the preceding paragraph. To produce these more dilute, clinically safer, yet effective concentrations, the 1:1000 dilution must be diluted further.
This process is asfollows:
• To produce a 1:10,000 concentration, **1 mL of** a **1:1000** solution is added to 9 mL of solvent (e.g., **sterile water**); therefore 1:10,000 = 0.1 mg/mL (100 μg/mL).
• To produce a 1:100,000 concentration, 1 mL of a1:10,000 concentration is added to 9 mL of solvent; therefore 1:100,000 = 0.01 mg/mL (10 μg/mL).

The milligram per milliliter and microgram per millilitervalues of the various vasoconstrictor dilutions used in medicine
and dentistry are shown in Table 3.4.The genesis of vasoconstrictor dilutions in local anesthetics
began with the discovery of epinephrine in 1897
by Abel. In 1903 Braun10 suggested using epinephrine as a
chemical tourniquet to prolong the duration of local anesthetics.
Braun recommended the use of a 1:10,000 dilution of epinephrine, ranging to as dilute as **1:100,000**, with cocaine in nasal surgery **(a highly vascular area).**
It appears at present that an epinephrine concentration of **1:200,000** provides comparable results, with fewer systemic side effects.
The 1:200,000 dilution, which contains 5 µg/mL (or 0.005mg/mL), has become widely used in both **medicine** and **dentistry**, and is currently found for **articaine**, **prilocaine**,**lidocaine** (although not in North America), **etidocaine**, and **bupivacaine**.

Concentrations of Clinically Used Vasoconstrictors

Dilution	Milligrams per Milliliter	Micrograms per Milliliter	Amount per 1.8-mL Cartridge (µg)	Therapeutic Use
1:1000	1.0	1000		Epinephrine—emergency medicine (IM/SC in anaphylaxis)
1:2500	0.4	400		Phenylephrine
1:10,000	0.1	100		Epinephrine—emergency medicine (IV/ET in cardiac arrest)
1:20,000	0.05	50	90	Levonordefrin—local anesthetic
1:30,000	0.033	33.3	73 (2.2-mL cartridge)	Norepinephrine—local anesthetic
1:50,000	0.02	20	36	Epinephrine—local anesthetic
1:80,000	0.0125	12.5	27.5 (2.2-mL cartridge)	Epinephrine—local anesthetic (United Kingdom)
1:100,000	0.01	10	18	Epinephrine—local anesthetic
1:200,000	0.005	5	9	Epinephrine—local anesthetic
1:400,000	0.0025	2.5	4.5	Epinephrine—local anesthetic

ET, Endotracheal; *IM*, intramuscular; *IV*, intravenous; *SC*, subcutaneous.



In several European and Asian countries, lidocaine with epinephrine concentrations of 1:300,000 and 1:400,000 is available in dental cartridges.

Although it is the most used vasoconstrictor in local anesthetics in both **medicine** and **dentistry**, epinephrine is *not* an ideal drug. The benefits to be gained from adding epinephrine (or any vasoconstrictor for that matter) to a local anesthetic solution must be weighed against any risks that might be present.

Epinephrine is absorbed from the **site of injection**, just as is the local anesthetic. Measurable epinephrine blood levels are obtained, influencing **the heart** and **blood vessels**. Resting plasma epinephrine levels (39 pg/mL) are doubled after administration of one cartridge of lidocaine with epinephrine 1:100,000.

Elevation of epinephrine plasma levels is **linearly dose dependent** and persists from several minutes to 30 minutes after administration.

Contrary to a **previously held position** that **intraoral administration of usual volumes of epinephrine produces no cardiovascular response**, and that patients are more at risk from endogenously released epinephrine than they are from exogenously administered epinephrine, evidence now demonstrates that epinephrine plasma levels equivalent to those achieved **during moderate to heavy exercise** may occur **after intraoral injection**.

These are associated with moderate increases in **cardiac output** and **stroke volume** (see the following section). Blood pressure and heart rate, however,are minimally affected at usual doses.

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 after usual **precautions** (e.g., aspiration, slow injection) have been taken, sufficient epinephrine can be absorbed to cause **sympathomimetic reactions** such as **apprehension, tachycardia**,**sweating**, and **pounding in the chest (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. Intravenous administration of 0.015 mg of epinephrine with lidocaine results in an increase in the heart rate ranging from 25 to 70 beats per minute, with elevations in systolic blood pressure from 20 to 70 mmHg.

Occasional rhythm disturbances may be observed, and premature ventricular contractions are most often noted.

Other vasoconstrictors used in **medicine and dentistry** include **norepinephrine, phenylephrine**, **levonordefri**n, and **felypressin**.

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.

Although it is currently available in some countries in local anesthetic solutions, the use of norepinephrine as a vasopressor in dentistry is diminishing and cannot be recommended.

The use of a **mixture of epinephrine and norepinephrine** is to be **absolutely avoided**.

Phenylephrine, a pure **α-adrenergic agonist**, theoretically possesses advantages over other vasoconstrictors. However, in clinical trials, peak blood levels of lidocaine were actually higher with **phenylephrine** 1:20,000 (lidocaine blood level 2.4 μg/mL) than with epinephrine 1:200,000 (1.4 μg/mL).

The cardiovascular effects of levonordefrin most closely resemble those of norepinephrine.24 Felypressin was shown to be about as effective as epinephrine in reducing cutaneous blood flow. **Epinephrine remains the most effective and the most used vasoconstrictor in medicine and dentistry.**

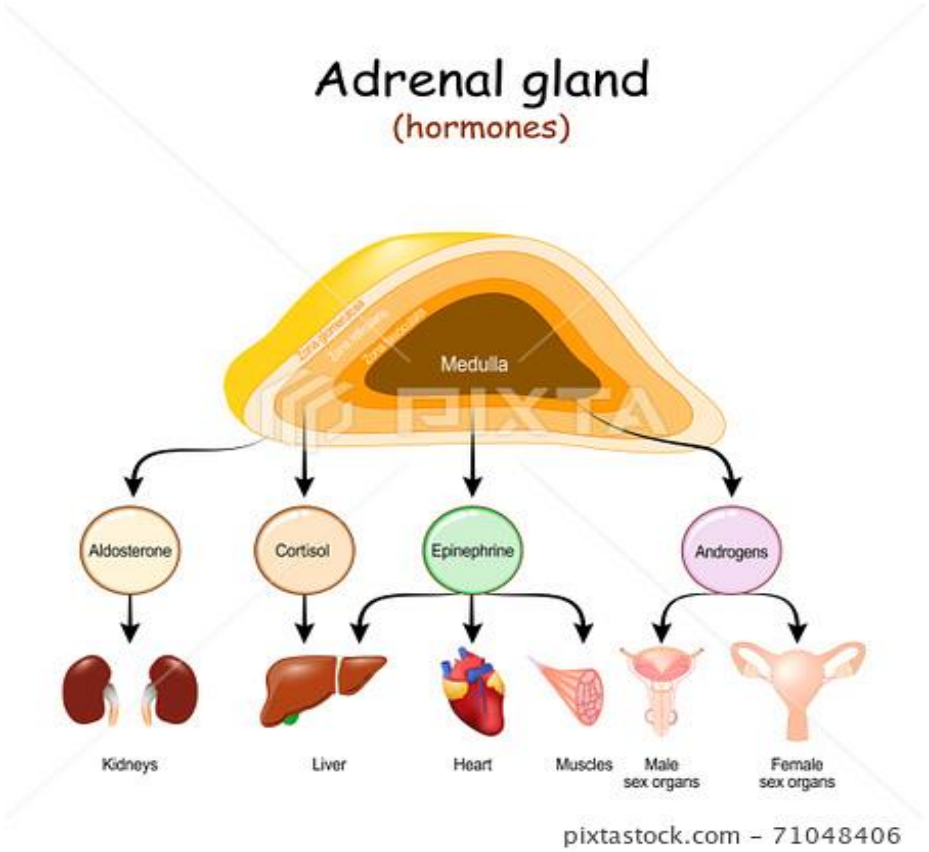
Epinephrine(Adrenalin).

Chemical Structure

Epinephrine as the acid salt is highly soluble in water. Slightly acid solutions are relatively stable if they are protected from air. Deterioration (through oxidation) is hastened by heat and the presence of heavy metal ions. Sodium bisulfite is commonly added to epinephrine solutions to delay this deterioration.

Source

Epinephrine is available as a **synthetic** and is also **obtained** from the **adrenal medulla** of animals (epinephrine constitutes approximately **80% of adrenal medullary secretions**).
It exists in both **levorotatory** and **dextrorotatory** forms; the levorotatory form is approximately 15 times as potent as the dextrorotatory form



Mode of Action:

Epinephrine is a nonselective adrenergic agonist, stimulating **α1-, α2-, β1-, and β2-adrenergic receptors**. The degree of stimulation varies with the concentration of epinephrine at the specific receptor.

Systemic Actions

Myocardium :

Epinephrine stimulates **β1** receptors of the myocardium. There is a positive inotropic (**force of contraction**) and a positive chronotropic (**rate of contraction**) effect. Both **cardiac output** and **heart rate are increased**.
Pacemaker Cells .**Epinephrine stimulates β1 receptors** and **increases the irritability of pacemaker cells**, leading to an increased incidence of **dysrhythmias**. **Ventricular tachycardia** and **premature ventricular contractions** are common.

Coronary Arteries :

Epinephrine produces dilation of the coronary arteries,increasing coronary artery blood flow.

Blood Pressure:

Systolic blood pressure is increased.
Diastolic pressure is decreased with small doses of epinephrine because of the greater sensitivity to **epinephrine of β2 receptors compared** with **α receptors** in blood vessels supplying skeletal muscle.
Diastolic blood pressure is increased with larger doses of epinephrine because of constriction of blood vessels supplyingthe skeletal muscles caused by **α-receptor stimulation.**

Cardiovascular Dynamics

The overall action of epinephrine on the heart and cardiovascular system is one of direct stimulation:

- increased systolic and diastolic pressures
- increased cardiac output
- increased stroke volume
- increased heart rate
- increased strength of contraction
- increased myocardial oxygen consumption

These actions lead to an overall *decrease* in cardiac efficiency.

2% lidocaine with epinephrine 1:100,000 in hypertensive patients. A decrease in systolic blood pressure in patients with the diastolic blood pressure decreased after the injections.

2% mepivacaine with epinephrine 1:100,000 . There were no statistically significant differences in heart rate and blood pressure monitored before and after injection.

Articaine, either 1:100,000 or 1:200,000, via intraosseous injection in patients with irreversible pulpitis
Reported no significant changes in blood pressure, heart rate, or ECG.

Another study demonstrated that there were no significant changes in heart rate, systolic blood pressure, diastolic blood pressure, oxygen saturation (Spo2), and ECG in the patients studied.

The reduced blood flow decreases the **pH of the tissue**, which shifts the equilibrium reaction towards the ionised form of the **anaesthetic.** This reduces the penetration of the local anaesthetic in the **nerve** and **diminishes the anaesthetic effect**. In addition, **decreased blood flow may have a negative effect on wound healing**.

A third **local disadvantage** is that a 'rebound' effect may occur as soon as the vasoconstrictor has worn off, due to the accumulation of degradation products; because of increased blood flow, there is an increased risk of secondary hemorrhage. After intravasal injection of an adrenaline-containing local anaesthetic, blood pressure and heart frequency will increase (dangerously).

Other adrenergic agonist vasoconstrictor

- Nor-adrenaline and phenylphrine have prominent alpha activity comparing to beta activity which may result in **severe vasoconstriction** (increase blood pressure) and ischemia.
- It is contraindicated in patients with cardiac problem.

It is contraindicated in terminal extremities

Metabolism of catecholamines

Catecholamines are metabolized by multiple pathways involving oxidative deamination catalyzed by **monoamine oxidase (MAO)**, O-methylation by **catechol O-methyltransferase** (COMT) and **conjugation** by **sulfotransferases** or **glucuronidases**

Side effects and overdose of adrenaline

CNS: Fear apprehension palpitation

CVS: Cardiac stimulant effects , increase blood pressure and rebound bleeding at prolonged dental procedure.

<u>Causes of rebound bleeding</u>:Adrenaline selectivity on receptor: Low concentration β effect. High concentration α effect

Felypressin:

Felypressin is a non-catecholamine vasoconstrictor that is chemically related to **vasopressin**, the posterior pituitary hormone

It is an **analogue** of the naturally occurring **Vasopressin(**Vasopressin is a hormone of the posterior pituitary that is secreted in response to **high serum osmolarity**.

Excitation of atrial stretch receptors inhibits vasopressin secretion.

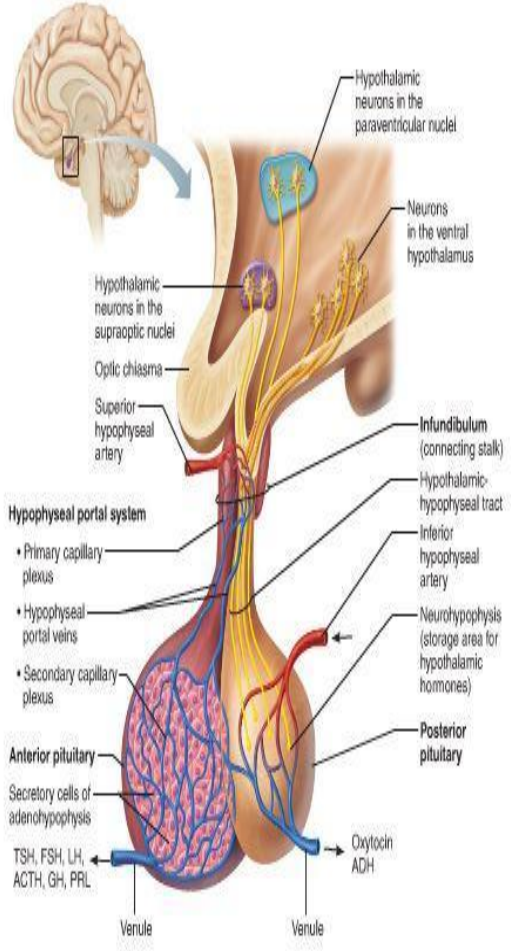
Vasopressin is also released in **response to stress**, **inflammatory signals**, and **some medications**.

Hypotension, **morphine**, **nicotine**, **angiotensin II**, **glucocorticoids**, and **IL-6 all** stimulate release of vasopressin)**.**

•Bind to **vasopressin V_1 receptor** in the vascular smooth muscle producing **vaso-constriction** and **reduce local blood flow.**

•**Less potent** than the **catecholamines** & **poorer control of bleeding** during operative procedures.

•Acts on the **venous side** rather than the **arterial side.**



Vasopressin (Felypressin)

Available concentration = 0.03 IU/ml in combination with prilocaine 2% or 3%

MRD= 0.27 IU Uses of small amount available in dental cartridge is better than exposing the patient to failure anesthesia which produce pain and bleeding that can stimulate fear and increase intrinsic adrenaline that may have more dangerous effect than extrinsic adrenaline

- **Dose: 0.03 IU/ml (0.54 µg/ml)** Synthetic analogue of **posterior pituitary hormone** (Octopressin)(Vasopressin is a hormone of the posterior pituitary that is secreted in response to high serum osmolarity. Excitation of atrial stretch receptors inhibits vasopressin secretion. Vasopressin is also released in response to stress, inflammatory signals, and some medications. Hypotension, morphine, nicotine, angiotensin II, glucocorticoids, and IL-6 all stimulate release of vasopressin)
- Act on **V1 receptor** that is found on **venous site of microcirculation**
- It **posses mild hemostatic effect** and used only when other **vasoconstrictor contraindicated**
- **Less potent** than the **catecholamines** & **poorer control of bleeding** during operative procedures.
- Acts on the **venous side** rather than the **arterial side.**

Consideration

❖Maximum Recommended Dosage (MRD) for cardiovascular disease patient = 0.04 mg of adrenaline = 2 dental cartridge of 2ml 1:100000 concentration adrenaline

❖Controversy still exists on using adrenaline in controlled cardiovascular diseased patient.

❖**Uses of small amount available in dental cartridge** is better than exposing the patient to failure anesthesia which produce pain and bleeding that can **stimulate fear** and **increase intrinsic adrenaline** that may have **more dangerous** effect than **extrinsic adrenaline**

Preservative agent of LA

➢Maintains sterility of the solution

➢Caprylhydrocuprienotoxin used for this purpose

Methylparaben used in the past but nowadays omitted ?

Reducing agent (in vasoconstrictor containing solution)

▪Antioxidant (reducing agent) used to prevent **oxidation of vasoconstrictor** that may deteriorate on exposure to sunlight (brown discoloration)

▪**Sodium metabisulfite** used for this purpose

▪On exposure to oxygen it will diffuse through the rubber of the cartridge where sodium metabisulfite will be converted to sodium metabisulfate (oxidized)

▪Oxidized instead of vasoconstrictor

▪Why is an old solution more acidic? Painful ? Irritant?

Selection of a Local Anesthetic agent

The decision to inject local anesthetic agents to achieve profound anesthesia is **dependent upon many factors**, **particularly the depth** and **duration of anesthesia required**, and **the possible need for hemostasis**.

To maximize the safety of local anesthetic injections, it is necessary to weigh the **risks against** the **benefits for each patient**, for each anesthetic agent, for **use of a vasoconstrictor**, and **for the delivery technique for the selected agent**

local anesthetics available are currently used in dentistry.

lidocaine, **mepivacaine**, **prilocain**e, and the combination of **procaine** and **propoxycaine**. **bupivacaine** and **etidocaine** .**The hybrid(ester/amide) molecule articaine .Articaine** is classified as an intermediate-duration local anesthetic..

With the availability of these local anesthetics, in various combinations with and without vasoconstrictors, it is possible for a doctor to select a local anesthetic solution that possesses the specific pain-controlling properties necessary to provide pain-free treatment for virtually all dental patients.

It is strongly suggested that the reader—the potential administrator of these drugs—become familiar with this material, including contraindications to the administration of certain local anesthetic combinations

Local Anesthetics Available in North America (February 2019)

Local Anesthetic (+ Vasoconstrictor)	Duration of Action[a]
Articaine hydrochloride	
4% + epinephrine 1:100,000	Intermediate
4% + epinephrine 1:200,000	Intermediate
Bupivacaine hydrochloride	
0.5% + epinephrine 1:200,000	Long
Lidocaine hydrochloride	
2% + epinephrine 1:50,000	Intermediate
2% + epinephrine 1:100,000	Intermediate
Mepivacaine hydrochloride	
3%	Short
2% + levonordefrin 1:20,000	Intermediate
2% + epinephrine 1:100,000	Intermediate
Prilocaine hydrochloride	
4%	Short (infiltration); intermediate (nerve block)
4% + epinephrine 1:200,000	Intermediate

[a]The classification of duration of action is approximate, for extreme variations may be noted among patients. Short-duration drugs provide pulpal or deep anesthesia for <30 min, intermediate-duration drugs provide it for about 60 min, and long-duration drugs provide it for longer than 90 min.

Thank You!