

LOCAL ANESTHETICS: A PRACTICAL REVIEW FOR SEDATION DENTISTRY

Relationship to Sedation Dentistry

Drug Interaction Potential

The most common drug that dentists administer are local anesthetics, with or without vasoconstrictor. Theoretically then, the most likely drug interaction with sedation medications will be with local anesthetics. From a practical standpoint, this is not the case. Still, the potential exists for drug interactions between local anesthetics, vasoconstrictors, and the drugs the patient presents with on board.

Increased Toxicity Potential

Given the extensive needs that the “typical” sedation presents with, as well as the desire to resolve as many of their dental needs per visit, the potential for larger doses of local anesthetic and vasoconstrictor exists. In larger amounts, these normally innocuous drugs dentists use every day can pose problems, especially in the non-healthy (\geq ASA II) patient.

Special Needs Of The Sedation Patient

The sedation patient is often anxious because they are a more of a challenge to numb. Conscious sedation will allow for more profound anesthesia to be accomplished, but a better understanding of the pharmacology of local anesthetics as well as more effective techniques will result in a higher success rate of sedation.

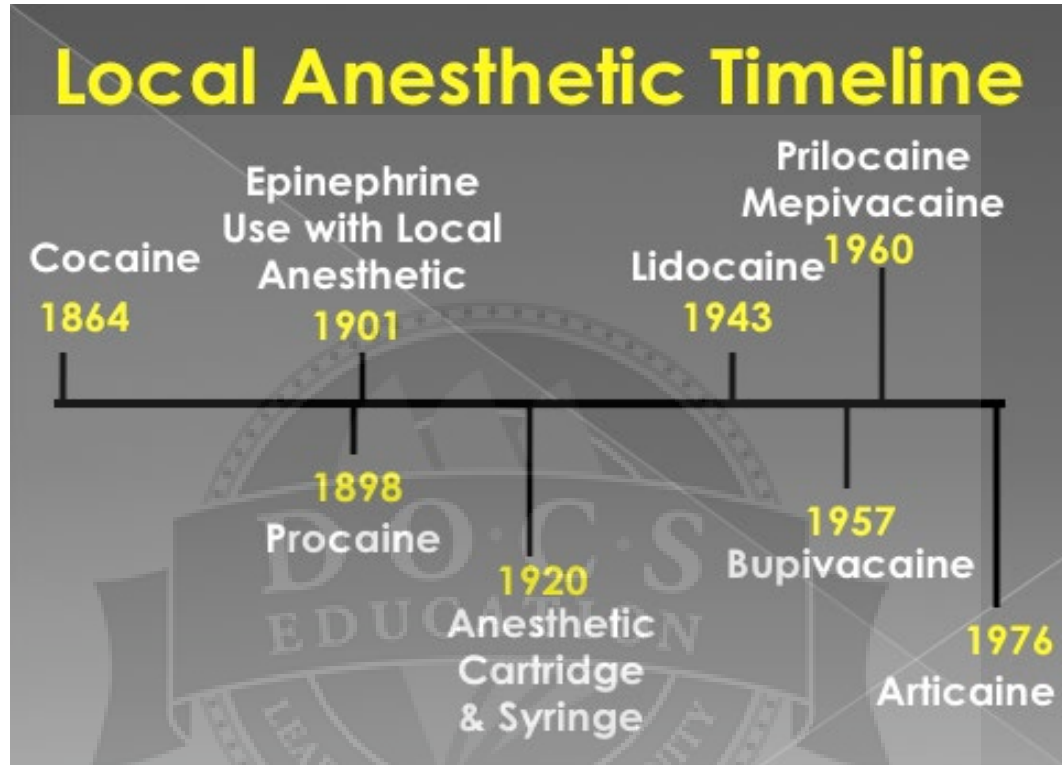
History

Local anesthetics have a long and storied history of use in dentistry. Their action, the reversible blocking of impulse conduction along nerve axons may be the most important discovery in the history of the dental profession.

Cocaine is a naturally occurring compound indigenous to the Andes Mountains, West Indies and Java. It was the first anesthetic to be discovered and is the only naturally occurring anesthetic.

Cocaine was first isolated in 1860 by Albert Neimann. In 1884, Carl Koller introduced it for medicinal use as an ophthalmic anesthetic. Several famous clinicians experimented with its use including Sigmund Freud and William Halstead, both of which became transiently addicted to the drug.

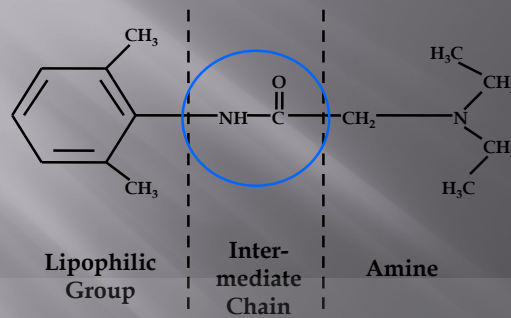
Cocaine, still the only local anesthetic with vasoconstrictor properties, remained the only anesthetic available for the next 30 years until Procaine was synthesized in 1898. Since then, several new compounds have been introduced with more desirable qualities of safety, efficacy, and duration of action.



Chemical Structure

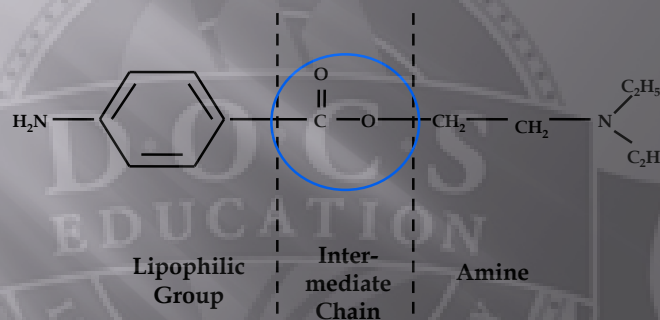
The pharmacological qualities of local anesthetics can be traced to their chemical structure. There are two major chemical variants, the aminoamide and the aminoester.

Chemical Structure - Aminoamide



Lidocaine

Chemical Structure - Aminoester



Procaine

The aminoamide, of which lidocaine is a prime example contains a lipophilic group connected to an amine by an amide intermediate chain. In the case of the aminoester such as procaine, the intermediate chain is an ester. This ester portion is readily metabolized by plasma esterases, making its duration of action much shorter than the aminoamides.

Common Local Anesthetics & Their Characteristics

Lidocaine

Xylocaine[®], Octocaine[®]

First aminoamide local anesthetic

Available in 1 & 2% concentrations

1 and 2% with 1:100,000 epinephrine

2% with 1:200,000 epinephrine

2% with 1:50,000 epinephrine

Prilocaine

Citanest®

Less pain upon injection than other local anesthetics, possibly due to higher pH

Used in combination with lidocaine in the topical anesthetic EMLA

Rare side effect of methemoglobinemia

Available in 3 & 4% concentrations

4% without epinephrine (plain)

4% with 1:200,000 epinephrine (Citanest Forte®)

Metabolism is hepatic and renal

Half life of 10-150 minutes

Mepivacaine

Carbocaine®, Polocaine®

Available in 1, 1.5, 2, & 3% concentrations

3% without epinephrine

Surgical anesthesia of Mepivacaine without vasoconstrictor is 20-25 minutes

2% with 1:20,000 levonordephrin

Chemically related to bupivacaine

Pharmacologically related to lidocaine

Relatively low toxicity

Less pronounced vasodilator activity than lidocaine

Bupivacaine

Marcaine®, Senorcaine®, Vivacaine®

Available in 0.25, 0.5, & 0.75% concentrations

0.25, 0.5, 0.75% with 1:200,000 epinephrine

Metabolism Hepatic, Elimination Renal

Long duration of action

Half-Life 3.5 hours

Greater lipid solubility and protein binding than lidocaine

Period of analgesia that persists after return of sensation, during which time the need for strong analgesics is reduced

Greater cardiotoxicity

Articaine

Septocaine®

Contains both ester and amide groups

Acts like an aminoamide with hepatic metabolism

Ester group allows plasma metabolism via pseudocholinesterase, increasing rate of breakdown and reducing its toxicity

30 minutes half life

Available in 4% concentrations with 1:100,000 epinephrine

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Higher relative lipid solubility
Reported superior clinical properties
Long-term or transient paresthesia occurs more frequently than with lidocaine

PHARMACODYNAMICS OF LOCAL ANESTHETICS

Mechanism of Action

Local anesthetics are weak bases that exist in one of two forms, as a charged cation (RNH^+), or an uncharged base (RN). The relative percentage of these two forms affects both onset of action and efficacy, and is described by the pK_a of the agent. The pK_a of most local anesthetics is in the range of 8.0 – 9.0, meaning that at neutral pH, most of the local anesthetic exists as the charged cation form.

Many excitable membranes in the body, including nerve axons are influenced through gated sodium channels which open and close, allowing influx of sodium ions (Na^+). The resulting depolarization allows an electrical impulse to be propagated down the length of the nerve membrane. As a result of depolarization, the Na^+ channels close and the Potassium ion (K^+) channels open. Outward flow of K^+ repolarizes the membrane and returns the Na^+ channels to the rested state.

Local anesthetic agents work by binding to and inactivating sodium channels in the nerve membrane, thus blocking conduction in peripheral nerves.

Onset of Action

Being knowledgeable of the factors that determine the characteristics of the action of local anesthetics allows the practitioner to better control the outcome of local anesthesia. The onset of action is a prime example. It is determined by:

Diffusion to the site of action – Generally speaking, the closer to the nerve being anesthetized, the faster the action. This partly explains why infiltration often works faster than a block.

Nerve Morphology – The smaller in diameter the nerve, the faster anesthesia occurs. Pain fibers are relatively thin compared to motor fibers.

More specifically, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers.

Clinically, the order of loss of nerve function is as follows:

1. Pain
2. Temperature
3. Touch
4. Proprioception
5. Skeletal Muscle Tone

Lipid Solubility – Since the nerve membrane is lipid in nature, the more lipophilic (lipid loving) the agent, the more readily it penetrates the nerve sheath. This is the major determinant of potency of local anesthetics. Therefore, agents with lower solubility are generally marketed at higher concentrations.

Local Anesthetic	Lipid Solubility	Concentration (%)
Articaine	40	4
Mepivacaine	42	2-3
Prilocaine	55	4
Lidocaine	110	2
<u>Bupivacaine</u>	1,853	0.5

pK_a of the agent – The lower the pK_a, the higher the portion of the agent that is uncharged, which is the portion capable of penetrating the nerve membrane.

In the body, local anesthetics exist as the uncharged base or as a cation:

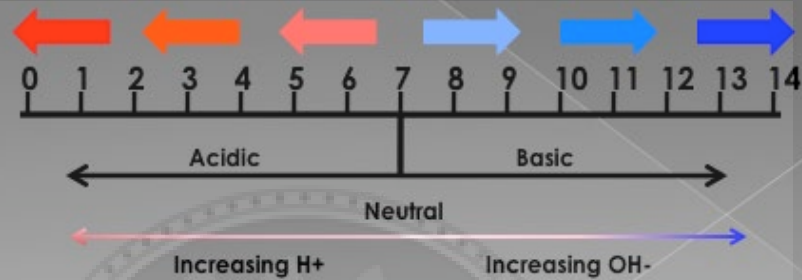


The relative proportions of these two forms are governed by their pK_a and the pH of the body fluids.

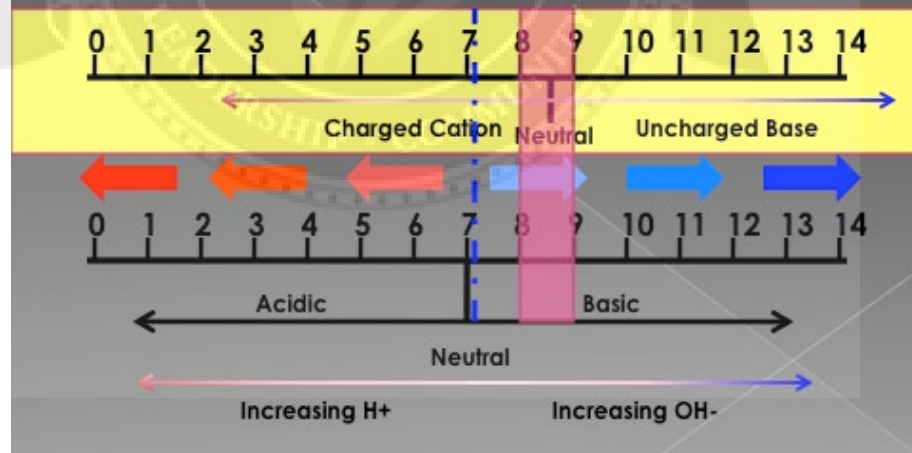
pKa of the Agent

The pK_a of a LA is the hydrogen conc. where the uncharged base equals the charged cation

A neutral solution has a pKa of 7.0

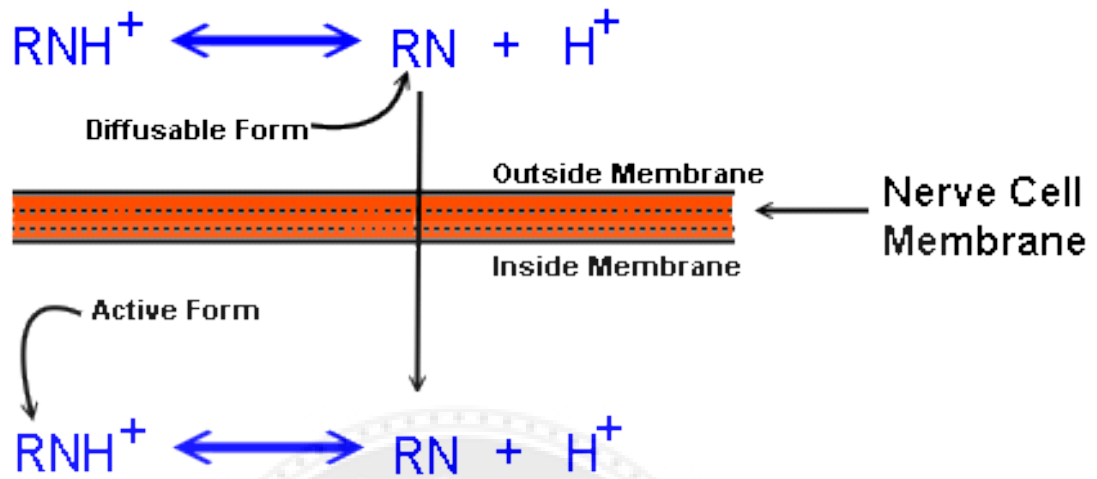


Because the pK_a of most local anesthetics is in the range of 8.0-9.0, the larger percentage in body fluids at physiological pH will be the charged, cationic form.



The uncharged form is more lipid soluble, therefore more readily crosses the cell membrane. This is important to producing a clinical effect, since the local anesthetic receptor is not accessible from the external side of the cell.

Once inside the nerve cell, equilibrium is re-established with the ionized form:



It is this ionized form that is most active at the receptor site because it is less lipid soluble and cannot exit from closed channels.

A lower pK_a means a greater fraction of the local anesthetic exists in the unionized (base) form, which more easily crosses nerve membranes leading to faster onset of action. Therefore, the onset of action of commonly used local anesthetics reflects their pK_a .

Agent	pK_a	% RN at pH 7.4	Onset in Minutes
Mepivacaine	7.6	40	2 to 4
Etidocaine	7.7	33	2 to 4
Articaine	7.8	29	2 to 4
Lidocaine	7.9	25	2 to 4
Prilocaine	7.9	25	2 to 4
Bupivacaine	8.1	18	5 to 8
Procaine	9.1	2	14 to 18

pH of the tissue – The lower the pH, the higher the portion of the agent that is charged, which is the portion least able to penetrate the nerve membrane. Inflamed tissue is more acidic, which explains why local anesthesia action in the presence of inflammation results in a slower onset of action.

Duration of Action

The duration of action is determined by:

Volume – Doubling the dose increases duration by ~ 1 half-life.

Lipid Solubility – Cell membranes are made up of a lipid bilayer. If the local anesthetic agent dissolves easier into this bilayer, then there is less agent available to diffuse away from the cell.

Protein Binding – Higher plasma protein binding means higher binding to the receptor site in the ion channel. Therefore, increased protein binding = longer duration of action.

Agent	Approximate Protein Binding
Prilocaine	55
Lidocaine	65
Mepivacaine	75
Bupivacaine	95
Articaine	95

Diffusion away from the site – This is potentiated by vasodilation and reduced by the addition of a vasoconstrictor in the local anesthetic solution.

Other factors affecting duration of action – The type of injection (block, infiltration), and the tissue anesthetized have an effect on the duration of action of local anesthetics.

Soft tissue anesthesia outlasts pulpal anesthesia, while block anesthesia lasts longer than that obtained through infiltration alone.

Duration of Action of Local Anesthetics (minutes)				
	Maxillary Infiltration		Inferior Alveolar Block	
Formulation	Pulp	Soft Tissue	Pulp	Soft Tissue
Articaine 4% with epi 1:100,000 or 1:200,000	60	190	90	230
Bupivacaine 0.5% with epi 1:200,000	40	340	240	440
Lidocaine 2% with epi 1:50,000 or 1:100,000	60	170	85	190
Mepivacaine 2% with 1:20,000 levonordephrin	50	130	75	185
Mepivacaine 3% plain	25	90	40	165
Prilocaine 4% with epi 1:200,000	40	140	60	220
Prilocaine 4% plain	20	105	55	190

While the duration of action is more relevant to the quality of the anesthesia, the agent's half-life describes the length of time the agent is in the patient's system, capable of causing adverse reactions including interactions with other drugs. Despite the differences between duration of action and half-life, the longer acting local anesthetics also have longer elimination half-lives.

Elimination Half-Lives of Local Anesthetics	
Local Anesthetic	Elimination Half-Life (hrs.)
Lidocaine	1.6
Mepivacaine	1.9
Prilocaine	1.6
Bupivacaine	3.5
Articaine	1.8

CALCULATING LOCAL ANESTHETIC DOSAGE ADMINISTERED

When calculating the amount (mg) of local anesthetic administered, the first step is to determine the mg/ml given the concentration of the

agent. This is accomplished by moving the decimal point of the concentration one (1) place to the right.

For example:

Bupivacaine 0.5% - Moving the decimal point one place to the right = 5. Therefore, Bupivacaine 0.5% contains 5 mg/ml.

Other examples:

Lidocaine 2% = 20 mg/ml

Prilocaine 4% = 40 mg/ml

Articaine 4% = 40 mg/ml

Once the amount of mg/ml is determined then this amount is multiplied by the number of ml (cc) administered. For example:

If one 1.8 ml cartridge of 2% lidocaine is administered then,
1.8 ml X 20 mg/ml = 36 mg of lidocaine administered

CALCULATING VASOCONSTRICTOR DOSAGE ADMINISTERED

As when calculating the amount (mg) of local anesthetic administered, the first step in calculating the amount (mg) of vasoconstrictor administered is to determine the mg/ml given the concentration of the agent. This is accomplished by moving the decimal point of the concentration one (1) place to the right.

From the dilution:

1:1000 = 0.1% or 1mg/ml

1:10,000 = 0.01% or .1mg/ml

1:20,000 = 0.005% or .05mg/ml

1:50,000 = 0.002% or .02mg/ml

1:100,000 = 0.001% or .01mg/ml

1:200,000 = 0.0005% or .005 mg/ml

If administering 1.8 ml of solution containing 1:100,000 epinephrine, then multiply 1.8 X 0.01 = 0.018mg

LOCAL ANESTHETIC ADVERSE REACTIONS

Local anesthetics, like any drugs carry with them the potential for adverse reactions. These include the following:

- Psychogenic
- Allergy
- Toxicity
- Local Reaction
- Methemoglobinemia
- Paresthesia
- Drug Interaction with Vasoconstrictors in the Local Anesthetic

Of these, the adverse reactions of most significance to the sedation dentists are local anesthesia toxicity, paresthesia, and vasoconstrictor toxicity and drug interactions.

Toxicity – Local anesthetics can block conduction in other tissues (eg. Heart, Brain) in addition to its action on peripheral nerves. However, this is unusual during our applications because it requires larger amounts of circulating local anesthetic atypical in a dental setting. Still, these larger than normal amounts can occur if excessive amounts of local anesthetic are administered, local anesthetic is injected directly into a blood vessel, or local anesthetic is administered in large amounts in the absence of a vasoconstrictor.

Signs of Local Anesthetic Overdose include:

Low/Moderate Overdose Levels

- Confusion
- Apprehension
- Restlessness
- Slurred Speech
- Muscular twitching/tremor of the face
- Elevated heart rate, blood pressure, respiratory rate

Moderate/Severe Overdose Levels

- Seizures
- Generalized CNS Depression
- Depressed heart rate, blood pressure, respiratory rate

Treatment of Local Anesthetic Overdose:

- Stop dental treatment

- Oxygen via a controlled airway
- Monitor vital signs
- Reassure patient, allow time for drug to distribute and be metabolized
- If patient becomes unstable, activate EMS and emphasize PABCDs

Prevention of Local Anesthetic Overdose*:

Use good technique

- Use judiciously
- When appropriate, use vasoconstrictor
- Avoid intravascular injections

*Local Anesthetic overdose can occur more easily in children, the elderly, and medically complex patients

Remember the maximum recommended doses:

Drug	Maximum Dose	Max. # of Cartridges
Articaine 4% with epi	7 mg/kg in adults (up to 500mg) 5mg/kg in children	7
Bupivacaine 0.5% with epi	2 mg/kg (up to 200mg)	10
Lidocaine 2% with epi	7 mg/kg (up to 500mg)	13
Mepivacaine 2% with levonordephrin	6.6mg/kg (up to 400mg)	11
Mepivacaine 3% plain	6.6mg/kg (up to 400mg)	7
Prilocaine 4% plain or with epi	8mg/kg (up to 500mg)	8

Paresthesia – Most likely to occur with the inferior alveolar or lingual nerves, and rarely lasts longer than eight weeks. Some literature

supports the conclusion that it is most likely to occur with certain local anesthetics (prilocaine and articaine).

Articaine Controversies

Efficacy

- In a 2000 report, a majority of 94 dentists stated that articaine anesthesia was more profound than “routinely used anesthetics”.
- In addition, the onset of effects was faster and the anesthesia achieved greater success among difficult-to-anesthetize patients.
- According to Dudkiewicz et al., articaine was able to diffuse through bone onto the lingual side of teeth.
- Kanaa et al. found mandibular buccal infiltration to be more effective with septocaine than with lidocaine Vree and Gielen found that articaine diffuses better through the soft tissue and bone than other local anesthetics.
- Mounting body of evidence that says articaine does not outperform the old standard lidocaine.
- Prospective, randomized, double-blind study by Mikesell et al.,. It was concluded that for pulpal anesthesia, articaine was similar to lidocaine.
- Studies by Berlin et al., as well as Claffey et al., resulting in similar conclusions

Toxicity

- Haas and Lennon, in a 21 year retrospective study, reported that paresthesia occurred most often following the injection of articaine and prilocaine.
- Hillerup and Jensen examined 54 injection injuries in 52 patients caused by mandibular block analgesia affecting the lingual and/or inferior alveolar nerve. The results indicated neurotoxicity as a central etiological factor.

Recommendations

- Use good technique
- If you use articaine for block anesthesia, use it judiciously.
- For maximum risk elimination of dental injection paresthesia, avoid articaine during block anesthesia.

The Mandibular Cocktail Block Technique

- A technique for profound anesthesia, maximum comfort, and minimum risk of local anesthesia and vasoconstrictor toxicity for the sedation patient with full mouth dentistry in one appointment.
- The purpose is to provide profound pulpal anesthesia in the lower arch for the duration of the sedation appointment, preventing discomfort later in the appointment and the need for re-administration of local anesthetic.
- Utilizes four different local anesthetics to exploit the advantages that each has to offer:
 1. Prilocaine's higher pH – more comfortable injection
 2. Articaine's efficacy and diffusion qualities
 3. Lidocaine's efficacy and safety – reduces the amount of articaine needed
 4. Bupivacaine's extended anesthesia with block anesthesia
- Technique:
 1. Topical anesthesia on dry tissue for one minute
 2. ¼ Cartridge of 4% Prilocaine Plain
 3. ½ Cartridge of 2% Lidocaine with 1:100,000 epinephrine
 4. ½ Cartridge of 4% Articaine with 1:100,000 epinephrine
 5. 1 Cartridge of 0.5% Bupivacaine with 1:200,000

Vasoconstrictor Toxicity related to medical conditions – The addition of vasoconstrictors to local anesthetics serves four functions:

1. Prolong duration of action of the local anesthetic
2. Enhance the depth of anesthesia
3. Enhance hemostasis
4. Reduce systemic local anesthetic toxicity

In many randomized studies, pain control is significantly impaired in those patients receiving local anesthetics without vasoconstrictors. Inadequate pain control increases endogenous production of norepinephrine, which increases heart rate, cardiac workload and cardiac stress.

Most of the adverse reactions associated with vasoconstrictor toxicity have to do with its affect on the cardiovascular system, and should be avoided in the following situations:

Cardiovascular Diseases

- Resting blood pressure >200mm Hg systolic or >115mm Hg diastolic
- Myocardial infarction within the past six months
- Cerebrovascular accident (stroke) within the past six months
- Unstable angina (angina at rest or not well controlled with medication)
- Coronary artery bypass graft within the past six months
- Uncontrolled arrhythmias
- Uncontrolled congestive heart failure

The maximum recommended dose of vasoconstrictor in cardiovascular patients is 0.04mg.

- 1 cartridge of 2% lidocaine with 1:50,000 epinephrine
- 2 cartridges of 2% lidocaine with 1:100,000 epinephrine
- 4 cartridges of 2% lidocaine with 1:200,000 epinephrine
- 2 cartridges of local anesthetic with 1:20,000 levonordephrin (1/5 potency of epinephrine)

Treatment modifications for patients at risk with vasoconstrictors:

Monitor blood pressure and heart rate preoperatively

Consider limiting epinephrine to 0.04mg or levonordephrin to 0.02mg

Monitor blood pressure and heart rate 5 minutes post-injection

May re-administer epinephrine or levonordephrin if blood pressure and heart rate are stable

Avoid 1:50,000 epinephrine

Never use epinephrine-impregnated retraction cord

Other medical conditions also warrant caution when considering the use of a vasoconstrictor with a local anesthetic:

- Uncontrolled hyperthyroidism
- Pheochromocytoma
- Sulfite-sensitive asthma
- True sulfite allergy

Vasoconstrictor Toxicity related to drug interactions – In order to better understand the interaction between some drugs and vasoconstrictors, it is helpful to review the different receptors affected by vasoconstrictors and the resulting action.

Alpha 1 receptors exist in blood vessels and when affected by vasoconstrictors, result in vasoconstriction. With regard to the use of vasoconstrictors in dentistry, this is a desired effect.

Beta 1 receptors exist in the heart and activation of these receptors results in tachycardia and hypertension, clearly undesirable side effects. Norepinephrine actually has higher beta-1 activity than either epinephrine or levonordephrin and would cause increase in heart rate and increase in cardiac work-load. This has actually led to cessation of use of norepinephrine as a vasoconstrictor in local anesthetics.

There are also beta-2 receptors in the vessel walls, causing slight vasodilation, balancing somewhat the alpha 1 effect. This effect is not desirable. Under normal circumstances, the alpha 1 effect of vasoconstrictors dominates over the beta effects. The net result is increased blood pressure and increased heart rate.

In the choice of vasoconstrictors, one would like to optimize the alpha effect and minimize the beta-1 and beta-2 effects.

Anti-hypertensive drugs that fall in the class of **alpha blockers** reduce blood pressure by blocking the alpha 1 vasoconstriction activity, allowing the beta 2 effect to go unchecked. Examples of alpha blockers are:

Blood Pressure Medications

- Aldomet
- Labetolol
- Pentolamine
- Hytrin
- Cardura

Antipsychotics

- Phenothiazines

The significance to dentistry is that in the presences of an alpha blocking agent, epinephrine actually causes vasodilation, shorter durations of anesthesia and more bleeding. This phenomenon is called **Epinephrine Reversal**.

To avoid epinephrine reversal, use levonordephrin in place of epinephrine:

Vasoconstrictor	Beta 1 Selectivity %	Beta 2 Selectivity %	Relative Alpha Potency%
Epinephrine	50	50	100
Levonordephrin	75	25	15

Interestingly, this alpha adrenergic blocking effect is the proposed mechanism of the soon to be released “local anesthetic reversal agent” **Phentolamine Mesylate** (formerly known as NV-101). This drug will be sold under the brand name, **Oraverse[®]**, and has been shown to effectively reduce the time from soft tissue local anesthesia to normal sensation by 56%. Although its exact mechanism is unknown, it is thought to result from a predominance of beta-2 vasodilation in the area of local anesthesia administration, therefore resulting in more of the local anesthetic being absorbed into the blood vessels.

Non-Selective beta blocking agents act by blocking both the beta 1 effect (resulting in decreased heart rate) and the beta 2 effect (resulting in less vasodilation of peripheral blood vessels). Non-selective beta blockers are widely used in patients with hypertension, angina, congestive heart failure and arrhythmia. Examples of non-selective beta blockers are:

Nadolol (Corgard)
 Propranolol (Inderal)

Selective beta blocking agents block only the beta 1 effect (resulting in decreased heart rate), and not the vasodilation which somewhat counteracts the alpha 1 effect. Examples of selective beta blockers are:

Atenolol (Tenormin)
 Bisoprolol (Zebeta)

Metoprolol (Lopressor, Toprol XL)

When administered a vasoconstrictor, patients on cardio-selective beta blockers exhibit the “typical” increase in blood pressure without the “typical” increase in heart rate.

However, when administered a vasoconstrictor, patients on non-selective beta blockers often notice a marked increase in blood pressure. The goal with these patients is to dose local anesthetics with vasoconstrictors “low and slow”.

Patients taking **tricyclic antidepressants** (TCAs) have been shown to have an increased pressor response in combination with epinephrine and levornordephrin. Examples of the TCAs include:

- Imipramine (Tofranil)
- Amitriptyline (Elavil)
- Desipramine (Norpramin)
- Nortriptyline (Aventyl)
- Doxepin (Sinequan)
- Protriptyline (Vivactil)

