Local Anesthetics: An Overview

A Companion to the Required Textbook Chapter:
"Local Anesthetics"
CONTEMPORARY DENTAL PHARMACOLOGY
Evidence-Based Considerations
(A.H. Jeske, Ed., 2019)

PHC 721

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Neuroscience Background

Nerve Fiber Types, Nociceptors

Neuronal Fiber Classification:

- Aα/Aγ - Heavy Myelination/Large Diameter/Fast/High Frequency - Somatic Motor Neurons
- Aβ - Heavy Myelination/Large Diameter/Fast/High Frequency - Tactile and Proprioceptors
- **Aδ - Light Myelination/Smaller Diameter/Slower /Lower Frequency - Pain**, Thermal, Pressure
- B - Light Myelination - Autonomic Preganglionic (Sympathetic & Parasympathetic)
- **C - Unmyelinated/Smallest Diameter/Slow - Pain**, Thermal, **Postganglionic Sympathetic**

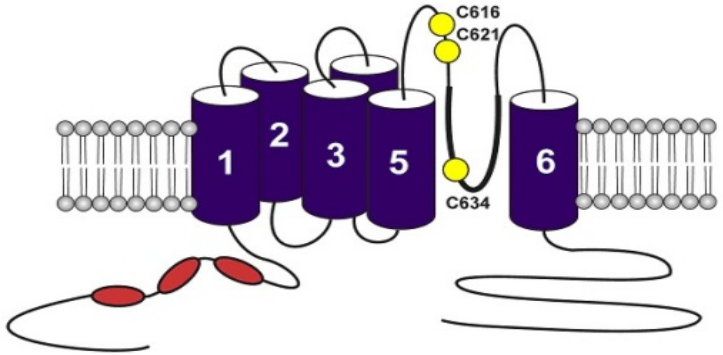
Nociceptors (Latin: *Nocere*, 'to hurt'): Endings that initiate the sensation of pain
Nociception: the perception of pain

Three Classes of Somatic Nociceptors:

- **Aδ Mechanosensitive & Aδ MechanoThermal Nociceptors** - First Pain (sharper, shorter lasting)
- **C Polymodal Nociceptors** - Second Pain (duller/burning, longer lasting)

TRPV1:

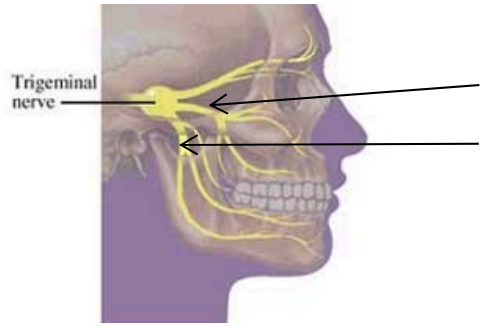
Transient Receptor Potential (TRP) family
Voltage-sensitive, permeable to Na^+ & Ca^{2+},
ligand-gated: capsaicin (hot peppers),
acid, anandamide (cannabinoid); 45°C



TRPV1

Neuroscience Background

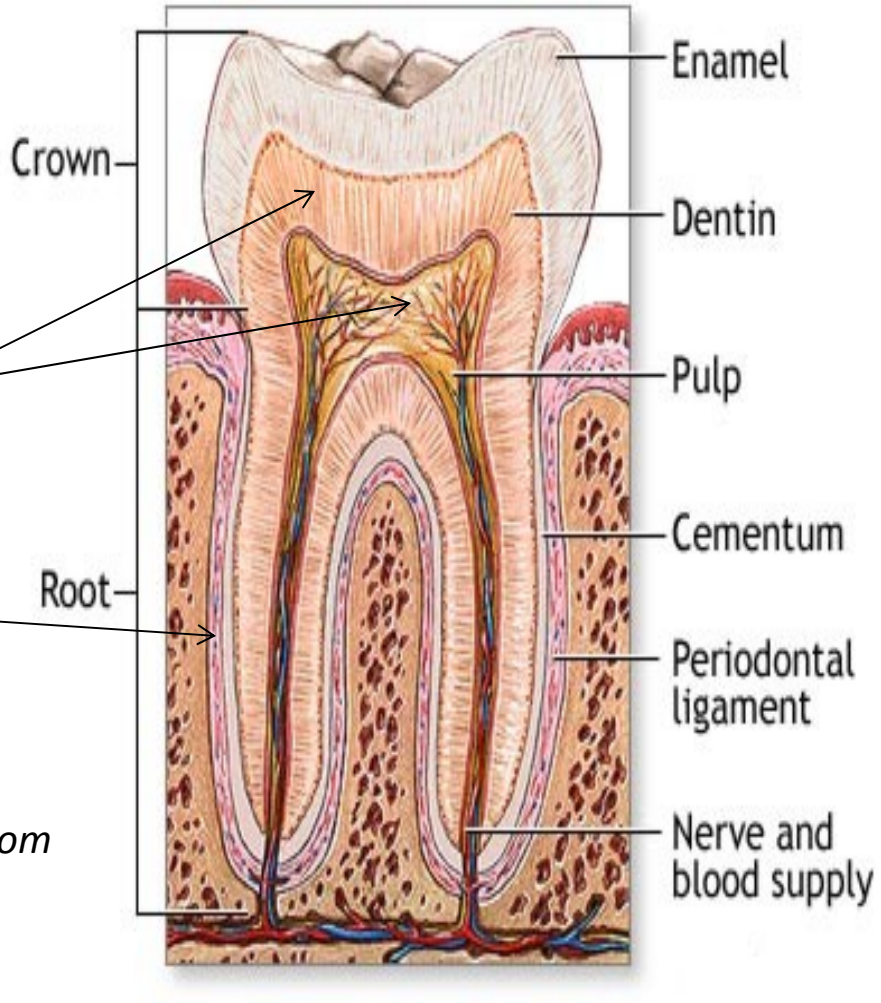
Tooth Innervation



Trigeminal Nerve (V):
Maxillary Nerve (V2)
Mandibular Nerve (V3)

Tooth:
A β-, Aδ- (minority) & C- (majority) fibers
200-1000 neuronal axons per tooth
A few penetrate into dentinal tubules (Nociceptors)
Most terminate in the pulp (Nociceptors and some mechanoreceptors-tactile information)
A few (10%) innervate blood vessels (sympathetics)

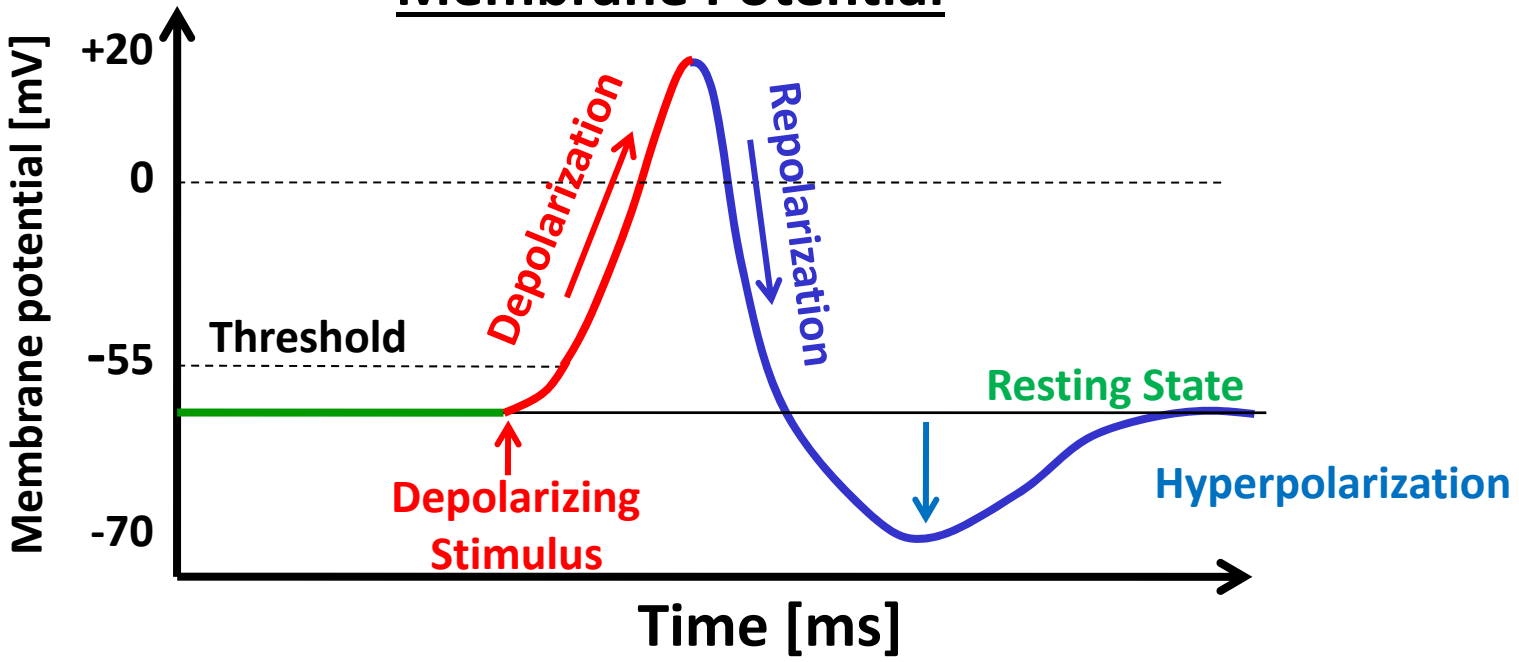
Periodontal Ligament:
Aβ-fibers (Mechanoreceptors)
normal tooth tactile sensation (very sensitive)
Aδ- & C- fibers (Nociceptors)

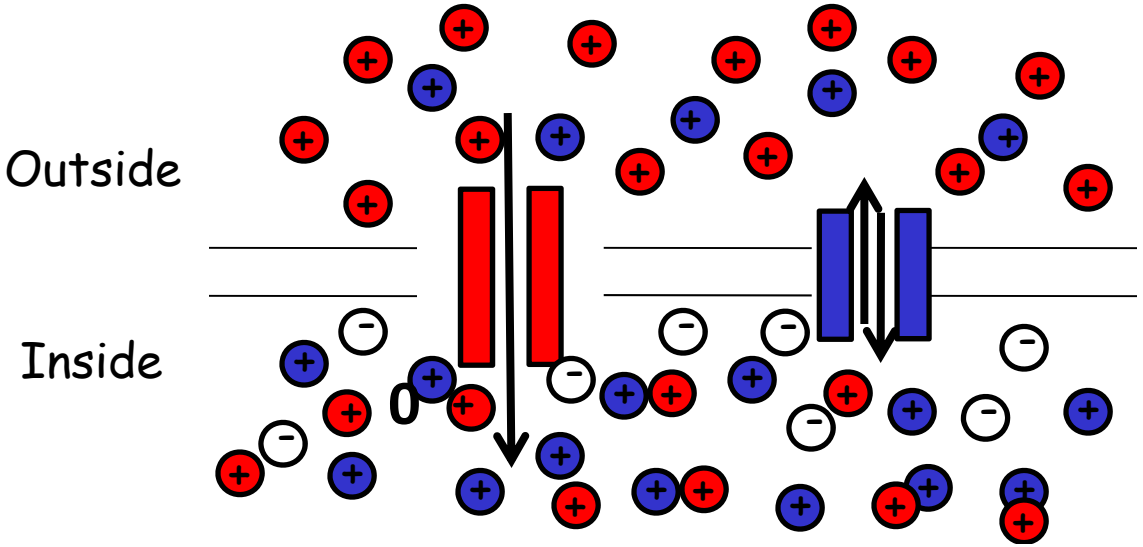


Pain is the predominant modality that can be elicited from the tooth pulp or dentin tubules (directly), or through physical transmission of stimuli to the pulp and through odontoblastic processes as transducers.

Neuroscience Background

Membrane Potential





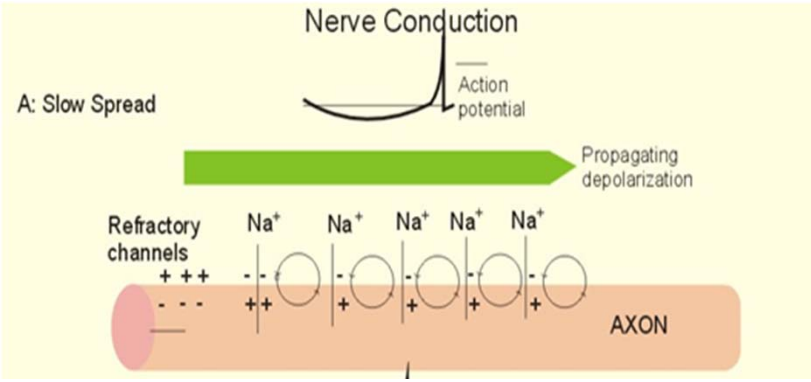
Na^+

Voltage-dependent channels open upon depolarization…
…and Na^+ rushes in (down its concentration gradient)– further depolarization-

K^+ *action potential!*

Neuroscience Background

Action Potential Propagation – Nerve Conduction



Unmyelinated fibers:

- A low density of evenly distributed sodium channels
- 'Continuous' **action potential (AP)** propagation

Myelinated fibers:

- High density of Sodium Channels in Nodes of Ranvier;
- Saltatory ("jumping") action potential propagation;
- APs can propagate despite missing (i.e., 'jump-over') two Nodes (a safety feature) ⇒ at least 3 consecutive blocked Nodes required to interrupt transmission (the critical length);
- ↑ Fiber diameter ⇒ ↑ Distance between Nodes;
- Partial blockade (with >70% Na^+ channels blocked) ⇒ ↓ AP amplitude ⇒ conduction failure if a sufficient nerve length is affected by the blockade;

Nerve Conduction Readily Disrupted

(highly susceptible to block; blocked faster & taking longer to recover):

Small Fibers (Aδ & C; Pain, Sympathetic)

but not

Large Fibers (Aα & Aβ; Motor, Proprioception, Touch, Pressure

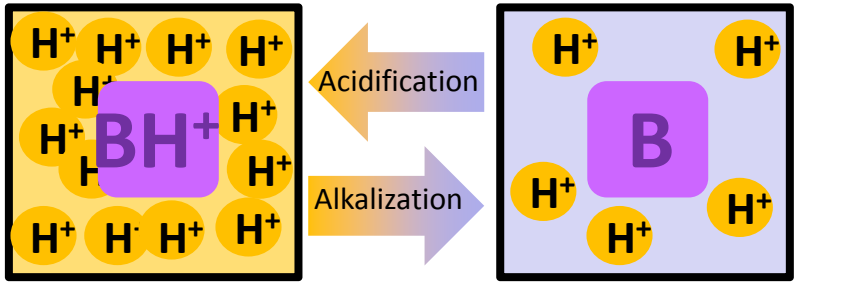
Passage Across Biological Membranes

Passive Diffusion – Influence of pH

Weakly basic drugs:

$$pH - pK_a = \log \frac{[Unionized]}{[Ionized]}$$

pH<pKa ⇒ log<0 ⇒ Unionized<Ionized



Acidic Conditions:
Drug (Conjugate Acid)
holds onto H^+ ⇒ Ionized
⇓
Membrane Impermeable

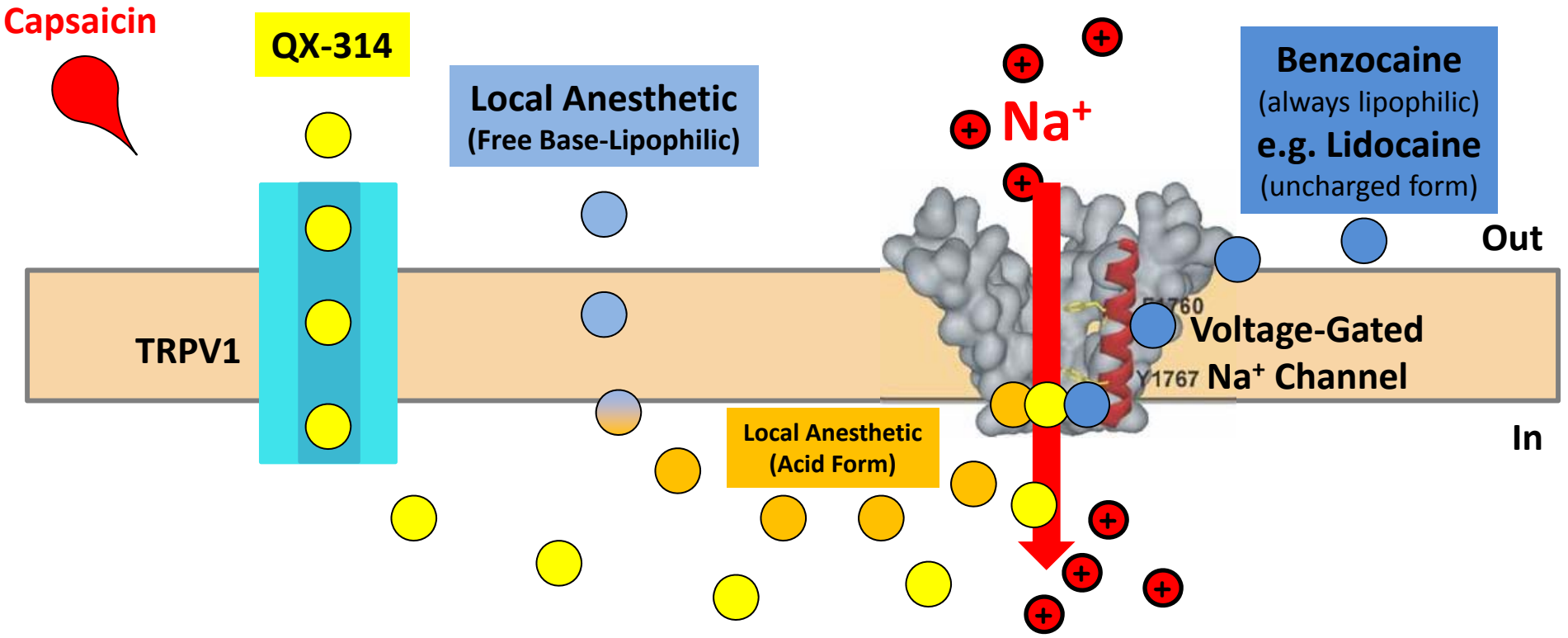
Alkaline Conditions:
Drug (Free Base)
after losing H^+ ⇒ Unionized
⇓
Membrane Permeable

Tip of the Day:
A drug will become
less ionized (more lipid-soluble)
at a **pH similar to its own pH**

Pharmacodynamics of Local Anesthetics

Mechanism of Action

Local Anesthetics bind reversibly to a specific receptor site within the pore of Voltage-Gated Na^+ Channels and block ion movement, thus inhibiting the generation and conduction of action potentials .



Local Anesthetics gain access to their receptor by traveling up an aqueous route within the Na^+ channel, which must be open to permit their entry from the cytoplasm.

Use (Frequency) Dependence: Rapid firing increases exposure of the receptor site $\Rightarrow\uparrow$ Drug Action.

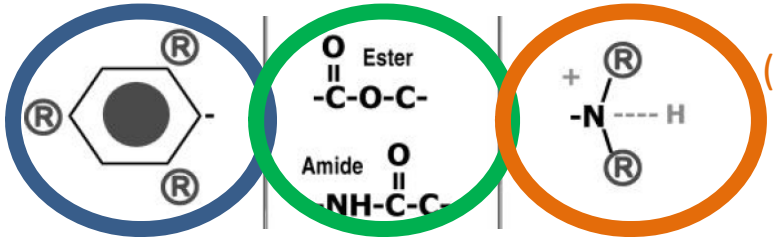
Lipophilic molecules (e.g., Benzocaine, uncharged form of Lidocaine) can reach the receptor site by traversing the cell membrane lipid and hydrophobic portions of the Na^+ channel (hydrophobic path).

Charged anesthetics (investigational) enter through TRPV1 receptor channels (hydrophilic path).

Local Anesthetics

Structure-Activity Relationship:

Performance-Defining Properties



Aromatic Ring

Lipophilic

Determines Lipid Solubility

⇓

Diffusion through Nerve Sheaths & Neuronal Membranes of Axons

⇓

Proportion of administered dose entering neurons

⇓

POTENCY

e.g.,
Bupivacaine (0.5%, 5 mg/ml dose)
is more lipid-soluble
& more potent than:
Lidocaine (2%, 20 mg/ml dose)
Articaine (4%, 40 mg/ml dose)

All have similar
EFFICACY

Intermediate Ester or Amide Chain/Linkage

Determines METABOLISM:

- Esters hydrolyzed by plasma pseudocholinesterase (short half-life; not in dental cartridges)

- Amides metabolized by the liver CYP3A4, CYP1A2

Articaine *(Amide & Ester side chain)*
⇒ both types of metabolism

Active metabolites ⇒ Toxicity

Kidney excretes metabolites

Terminal Amine

'On-Off' switch:

- Tertiary
(3 bonds, Base, B)
lipid soluble
(extracellular fluid, diffusion through membranes) **vs.**

- Quaternary Salt
(4 bonds, Acid, BH^+)
water soluble
(before injection, in the axoplasm - responsible for Na^+ channel block)

⇓

TIME FOR ONSET

determined by
pKa of drug & pH of tissue
(proportion of molecules that convert to lipid soluble form)
e.g., in acidic environment (inflammation)
fewer lipid soluble molecules
Bupivacaine (pKa 8.1)
least effective
Mepivacaine (pKa 7.6)
most likely to anesthetize & faster onset

DURATION OF ACTION determined by:

Absorption into the bloodstream/Distribution away from the site of injection.
Plasma protein binding (α-1-acid glycoprotein) correlates with affinity for protein within Na^+ channels ⇒ ↑ protein binding increases duration of action.
E.g., longest-acting available in dental cartridges is Bupivacaine – 95% binding.

Local Anesthetics

Pharmacodynamic and Pharmacokinetic Properties of Anesthetics Available in Dental Cartridges

Local Anesthetic	Intermediate Linkage	Concentration (Potency)	pKa (Onset of Action)	Protein Binding (Duration of Action)
Bupivacaine	Amide	0.5 % (High)	8.1 (Moderate; 6-10 min)	95% (Long)
Lidocaine	Amide	2% (Moderate)	7.8 (Fast; 2-3 min)	70% (Moderate)
Mepivacaine	Amide	2% and 3% (Moderate)	7.6 (Fast; 1.5-2 min)	55% (Moderate)
Articaine	Amide (Ester)	4% (Moderate)	7.8 (Fast; 2-3 min)	66% (Moderate)
Prilocaine	Amide	4% (Moderate)	7.8 (Fast; 2-4 min)	55% (Moderate)

Vasoconstrictors in Local Anesthetics

Local Anesthetics reduce vascular tone (↓ sympathetic neuron and smooth muscle activity).
Toxic blood concentrations of Anesthetic ⇒ Arteriolar Dilation and Hypotension.
In decreasing order of Vasodilatory Potential:

Procaine, **Bupivacaine, Lidocaine, Articaine, Prilocaine, Mepivacaine**, Cocaine

Vasoconstrictors inhibit systemic absorption of anesthetics by decreasing blood flow.

Benefits of impeding systemic absorption of anesthetics (1,2,3) and decreasing blood flow (4):

1) Prolongs the duration of local anesthesia several times;
2) Improves the success rate and intensity of nerve block;
3) Minimizes systemic toxicity of the local anesthetic by reducing its peak blood concentration:
A. Less drug may be needed; **B.** Metabolism is more likely to keep pace with drug absorption
4) With infiltration, tend to reduce blood loss associated with surgical procedures (hemostasis)

EPINEPHRINE:
5 µg/mL – 20 µg/ml (1:200,000 – 1:50,000)
For cardiac patients,
current evidence indicates that
minimizing Epi to a level of less than 40 µg
with vital sign monitoring is appropriate.
At doses approaching 200 µg, Epi titers
can surpass titers associated with
heavy exercise, surgery, pheochromocytoma
⇒ ↑risk of myocardial ischemia and arrhythmias

LEVONORDEFRIN:
1:20,000 solution
(clinical efficacy ~ 1:100, 000 Epi)
Indicated for cardiac patients
because of fewer/less pronounced
cardiac effects compared with Epi
(predominantly
alpha-adrenergic agonist)

Systemic Toxicity of Local Anesthetics

Local anesthetics can act on any part of the nervous system and every excitable cell: life-threatening depression of excitability concerns the Central Nervous System and the Heart.

Mild → Moderate Overdose:

I. Selective depression of inhibitory neuronal pathways ⇒ Excitatory Phase (may be brief or non-existent):
Talkativeness, Slurred Speech, Nystagmus, Tinnitus, Disorientation, ↑ BP/HR/RR, Twitching/Stuttering

Loss of Consciousness

First Sign May Be DROWSINESS and RESPIRATORY ARREST

Cardiovascular effects develop long after Neurological

Moderate → Severe Overdose:

Tonic-Clonic seizure (Lidocaine ~ 8 μg/mL), General CNS Depression, ↓ BP/HR/RR, Myocardial Depression

Cardiac Arrest

Other Life-Threatening Effects of Overdose:

1) Vasodilation ⇒ Hypotension with large doses
2) Potentiation of Respiratory Depression caused by Sedatives / Opioids (also ↑ risk of seizures)
3) Hypercarbia ⇒ ↓ seizure threshold (lower plasma levels of anesthetic can evoke seizures)
4) Methemoglobinemia caused by Prilocaine metabolite (metHb > 10% ⇒ cyanosis)