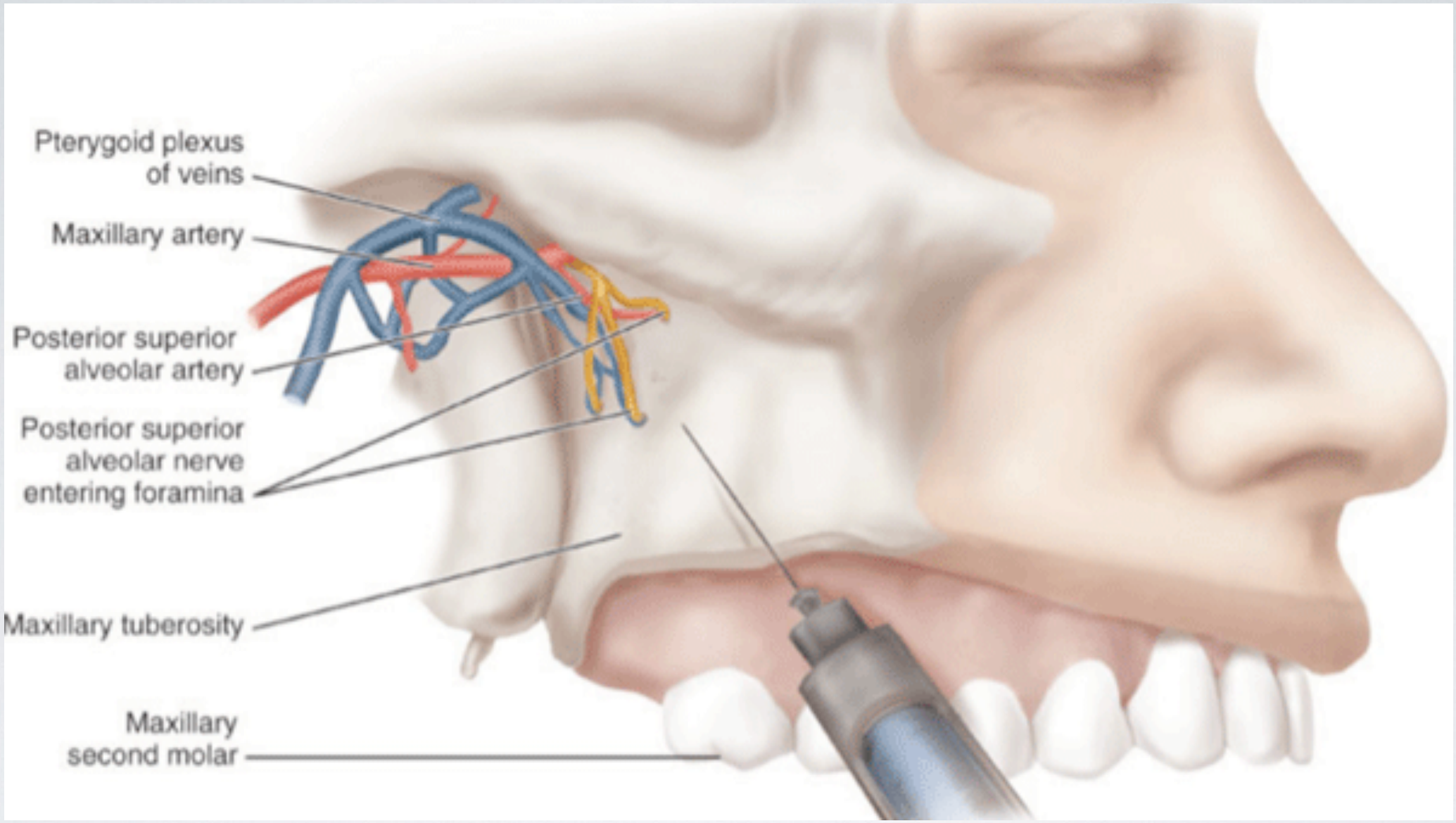

PHARMACOLOGY OF VASOCONSTRICTORS

Dental Local Anesthesia

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OUTLINE

- Introduction
- Chemical structure
- Modes of Action
- Dilutions of vasoconstrictors
- Pharmacology of specific agents

INTRODUCTION

- LA are vasodilators
- Injection of LA leads to:
  - ⬆️ absorption into CVS
  - ⬆️ plasma levels
  - ⬆️ bleeding
  - ⬇️ depth and duration of LA

INTRODUCTION

- Vasoconstrictors (VC's) added to LA have the following effects:
  - ⬇️ perfusion of site
  - ⬇️ absorption into CVS
  - ⬇️ plasma levels
  - ⬇️ bleeding
  - ⬆️ depth and duration of LA

INTRODUCTION

TABLE 3-1
Effects of Vasoconstrictor (Epinephrine 1:200,000) on Peak Local Anesthetic Levels in Blood

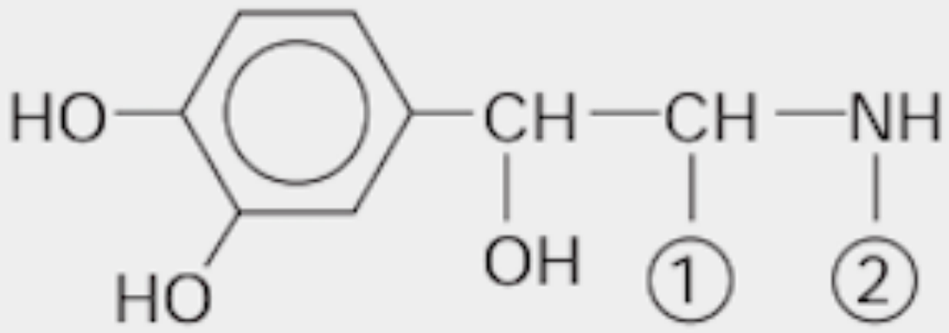
Local Anesthetic	Dose, mg	PEAK LEVEL, µg/mL	
		Without Vasoconstrictor	With Vasoconstrictor
Mepivacaine	500	4.7	3
Lidocaine	400	4.3	3
Prilocaine	400	2.8	2.6
Etidocaine	300	1.4	1.3

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

INTRODUCTION

- Most VC's used are sympathomimetic similar to epinephrine and norepinephrine

CHEMICAL STRUCTURE



	①	②
Epinephrine	H	CH_3
Levonordefrin	CH_3	H
Norepinephrine	H	H

CHEMICAL STRUCTURE

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

CHEMICAL STRUCTURE

Felypressin: analog of vasopressin, non sympathomimetic, vasoconstrictor

MODES OF ACTION

1. Direct action on adrenergic receptors

2. Indirect action by stimulating release of endogenous catecholamines.

3. Mixed action

MODES OF ACTION

BOX 3-1 Categories of Sympathomimetic Amines

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

MODES OF ACTION

TABLE 3-3
Systemic Effects of Sympathomimetic Amines

Effector Organ or Function	Epinephrine	Norepinephrine
Cardiovascular System		
Heart rate	+	−
Stroke volume	++	++
Cardiac output	+++	0, −
Arrhythmias	++++	++++
Coronary blood flow	++	++
Blood Pressure		
Systolic arterial	+++	+++
Mean arterial	+	++
Diastolic arterial	+, 0, −	++
Peripheral Circulation		
Total peripheral resistance	−	++
Cerebral blood flow	+	0, −
Cutaneous blood flow	−	−
Splanchnic blood flow	+++	0, +
Respiratory System		
Bronchodilation	+++	0
Genitourinary System		
Renal blood flow	−	−
Skeletal Muscle		
Muscle blood flow	+++	0, −
Metabolic Effects		
Oxygen consumption	++	0, +
Blood glucose	+++	0, +
Blood lactic acid	+++	0, +

Data from Goldenberg M, Aranow H Jr, Smith AA, Faber M: Pheochromocytoma and essential hypertensive vascular disease, Arch Intern Med 86:823–836, 1950.

+, Increase; −, decrease; *0,* no effect.

MODES OF ACTION

TABLE 3-2
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, 1995, WB Saunders.

DILUTIONS OF VC'S

- 1:1000 mean ===> 1 g per 1000 ml ===>

  1 mg/ml ===> 1000 µg/ml

- 1:100,000 means ===> ???

DILUTIONS OF VC'S

TABLE 3-4
Concentrations of Clinically Used Vasoconstrictors

Concentration (Dilution)	Milligrams per Milliliter (mg/mL)	Micrograms per Milliliter (µg/mL)	µg per Cartridge (1.8 mL)	Therapeutic Use
1:1000	1.0	1000		Epinephrine—Emergency medicine (IM/SC anaphylaxis)
1:2500	0.4	400		Phenylephrine
1:10,000	0.1	100		Epinephrine—Emergency medicine (IV/ET 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

CONCENTRATION OF VC'S

- Resting epinephrine plasma level = 39 pg/ml
- Doubled after one cartridge of LA with 1:100,000 Epinephrine VC
- Slow injection, aspiration, minimal amount

CONCENTRATION OF VC'S

- Epinephrine reaction: apprehension, tachycardia, sweating, palpitation.
- IV injection of 0.015 mg:
    - 25-70 bpm increase
    - 20-70 mm Hg increase in BP
    - Arrhythmias and PVC's

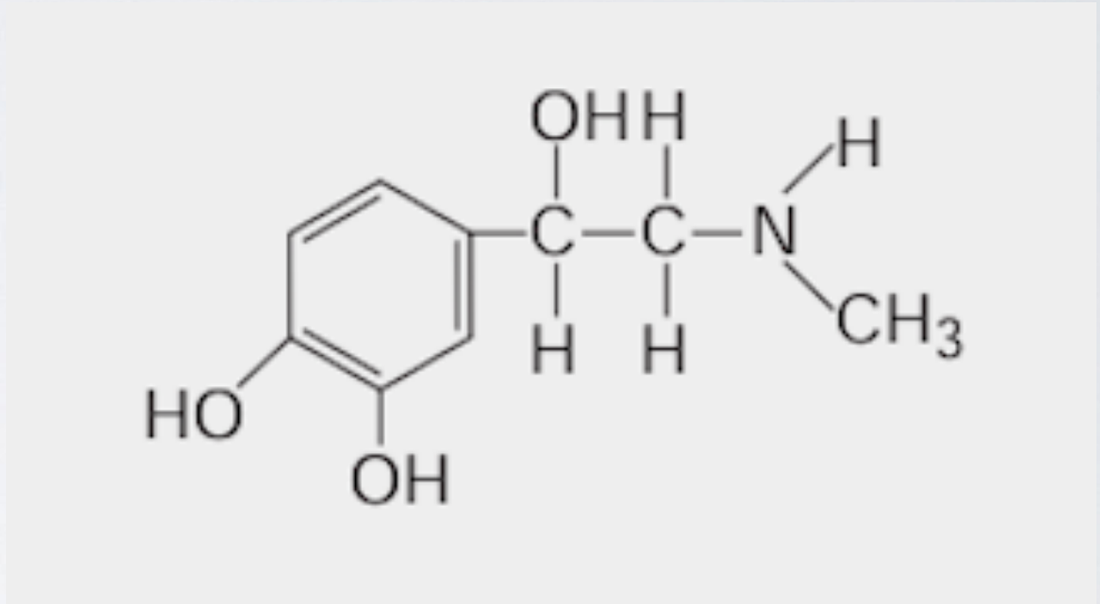
EPINEPHRINE

- <u>Chemical structure and source</u>

  - Deteriorates in air,

    heat and heavy metal

    ions ===> Na bisulfite



- Synthetic or natural

- Levo form 15 times more potent

EPINEPHRINE

- Mode of action
- Effects:
  - Myocardium: ⬆️ cardiac output & HR
  - Pacemaker cells: ⬆️ arrhythmias, VT and PVC's

EPINEPHRINE

- Effects:

- Coronary arteries: vasodilation, ⬆️ flow

- BP: initially ⬆️ diastolic and ⬇️ diastolic, higer concentrations ==> ⬆️ diastolic

EPINEPHRINE

- Effects:
  - CV dynamics: ⬇️ efficiency
  - Vasculature: mucous membranes, skin, kidney ==> vasoconstriction

    skeletal muscles ==> vasodilation „, later vasoconstriction

EPINEPHRINE

- Effects:
  - Hemostasis: vasoconstrictive followed by delayed vasodilation ===> bleeding 6 hours post op
  - Respiratory system: bronchodilation

EPINEPHRINE

- Effects:

- CNS: therapeutic doses ==> none

- Metabolism: ⬆️ glycogenolysis, ⬆️ plasma sugar

EPINEPHRINE

- <u>Termination of action:</u>
  - Primarily: re-uptake
  - MOA and COMT in plasma and liver
  - 1% excreted unchanged in liver

EPINEPHRINE

- <u>Termination of action and elimination:</u>
  - Primarily: re-uptake
  - MOA and COMT in plasma and liver
  - 1% excreted unchanged in liver

EPINEPHRINE

- Side effects and overdose

  - CNS: fear, anxiety, restlessness, throbbing headache, tremor, weakness, dizziness, pallor, respiratory difficulty, palpitation.

  - CV: arrhythmias, severe BP elevation ===> cerebral hemorrhage, angina

EPINEPHRINE

- **Clinical Applications**
  - Management of acute allergic reactions
  - Management of refractory bronchospasm (status asthmaticus)
  - Management of cardiac arrest
  - As a vasoconstrictor, for hemostasis
  - As a vasoconstrictor in local anesthetics, to decrease absorption into the cardiovascular system
  - As a vasoconstrictor in local anesthetics, to increase depth of anesthesia
  - As a vasoconstrictor in local anesthetics, to increase duration of anesthesia
  - To produce mydriasis

EPINEPHRINE

Epinephrine Dilution	Local Anesthetic (generic)
1:50,000	Lidocaine
1:80,000	Lidocaine (lignocaine) (United Kingdom)
1:100,000	Articaine Lidocaine
1:200,000	Articaine Bupivacaine Etidocaine† Lidocaine Mepivacaine* Prilocaine
1:300,000	Lidocaine*
1:400,000	Articaine*

*Not available in the United States (August 2011).
†No longer marketed in the United State (2002).

EPINEPHRINE

TABLE 3-5
Recommended Maximum Dosages of Epinephrine

	CARTRIDGES (ROUNDED OFF)	
Epinephrine Concentration (µg/Cartridge)	Normal, Healthy Patient (ASA I)*	Patient With Clinically Significant Cardiovascular Disease (ASA III or IV)†
1 : 50,000 (36)	5.5	1
1 : 100,000 (18)	11‡	2
1 : 200,000 (9)	22‡	4

*Maximum epinephrine dose of 0.2 mg or 200 µg per appointment.
†Maximum recommended dose of 0.04 or 40 µg per appointment.
‡Actual maximum volume of administration is limited by the dosage of local anesthetic drug.

EPINEPHRINE

TABLE 3-6
Means of Maximum Changes from Baseline for Blood Pressure and Heart Rate*

	max Δ SBP, mm	max Δ DBP, mm	max Δ HR, bpm
Hypertensives			
Anesthesia with epinephrine	15.3	2.3	9.3
Anesthesia without epinephrine	11.7	3.3	4.7
Normotensives			
Anesthesia with epinephrine	5.0	–0.7	6.3
Anesthesia without epinephrine*	5.0	4.0	0.7

Data from Cardiovascular effects of epinephrine in hypertensive dental patients: summary, evidence report/technology assessment number 48. AHRQ Publication Number 02-E005, Rockville, Md. March 2002, Agency for Healthcare Research and Quality. Available at: http://www.ahrq.gov/clinic/epcsums/ephypsum.htm

DBP, Diastolic blood pressure; *HR*, heart rate; *SBP*, systolic blood pressure.

EPINEPHRINE

- Patients with ASA 3 or 4 ??

NOREPINEPHRINE

- Almost not used anymore in dental LA
- 90% effect and Alpha receptors
- significant increase in BP and Arrhythmias
- ischemia and necrosis

LEVONORDEFRIN

- 75% action on alpha receptors and 25% on Beta receptors.
- actions very similar to Epinephrine but to a lesser extent (15% as potent as Epi.).
- Elimination via MOA and COMT
- Dosage usually 1:20,000
- Max dose: 1 mg per appointment

PHENYLEPHRINE

- 95% direct effect on alpha receptors
- Little or no effect on Beta receptors
- 5% as potent as Epi.
- Rarely causes dysrhythmias
- Dosage: 1:2500
- Max dose (healthy pt) 4 mg per appointment

FELYPRESSIN

- Non-sympathomimetic amine as vasoconstrictor.
- Direct stimulant of smooth muscles, mostly venous.
- no effect on heart
- contraindicated in pregnant females
- Wide margin of safety
- Dosage 0.03 IU/ml
- Max dose for ASA 3/4 = 0.27 IU ===> 9ml of 0.03 IU/ml

SELECTION OF VC

- Length of dental procedure
- Requirement for hemostasis
- Medical status of the patient

SELECTION OF VC

TABLE 3-7
Average Durations of Pulpal and Hard Tissue Anesthesia

Local Anesthetic	Infiltration, minutes	Nerve Block, minutes
Lidocaine HCL		
2% – no vasoconstrictor	5-10*	≈10-20*
2% + epinephrine 1 : 50,000	≈60	≥60
2% + epinephrine 1 : 100,000	≈60	≥60
2% + epinephrine 1 : 200,000	≈60	≥60
Mepivacaine HCL		
3% – no vasoconstrictor	5-10*	20-40*
2% + levonordefrin 1 : 20,000	≤60	≥60
2% + epinephrine 1 : 100,000	≤60	≥60
Prilocaine HCL		
4% – no vasoconstrictor	10-15*	40-60*
4% + epinephrine 1 : 200,000	≤60	60-90
Articaine HCL		
4% + epinephrine 1 : 100,000	≤60	≥60

*Indicates duration of pulpal anesthesia usually inadequate to provide pain control for a typical 48-minute procedure.

SELECTION OF VC

- Requirement for hemostasis
    - Epi. most used
    - Phenylephrine: less potent but no rebound vasodilation, long-term effect
    - Norepi.: not recommended.
    - Felypressin: mostly affects venous vessels.

SELECTION OF VC

- Medical status of the patient:
    - ASA 3/4
    - Allergy to Na Bisulfite, Thyroid disease, Diabetes.
    - MOA inhibitors, tricyclic anti-dep., phenothiazines

SELECTION OFVC

- Medical status of the patient:
    - norepinephrine and levonordefrin absolutely contraindicated in patients taking tricyclic anti depressants.
    - Felypressin best in patients at risk of arrhythmias.

REFERENCES

- Handbook of Local Anesthesia, 6th Edition. by S. Malamed - chapter 3