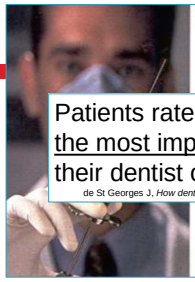
ARE YOUR PATIENTS GETTING COMFORTABLY NUMB?

LOCAL ANESTHESIA PHARMACOLOGY UPDATE

Alan W. Budenz, MS, DDS, MBA
Professor, Dept. of Biomedical Sciences and Interim Chair, Dept. of Diagnostic Sciences
University of the Pacific, Arthur A. Dugoni School of Dentistry
San Francisco, California
abudenz@pacific.edu



Patients rate *"painless injections"* as the most important criteria in evaluating their dentist or dental hygienist

de St Georges J, *How dentists are judged by patients*, Dentistry Today, Vol. 23, August 2004

90% of all patients report being anxious about going to the dentist or dental hygienist and receiving a shot.

Friedman & Krochak, *Using a precision-metered injection system to minimize dental injection anxiety*, Compend Contin Educ Dent, Vol. 19(2), Feb 1998

Patient anxiety

↳ Practitioner anxiety

The majority of dentists and dental hygienists report high personal stress levels when giving injections

Ask patients, "Do you feel that you are particularly sensitive to local anesthetics?"

Open a dialogue…

Simon et al, *Dentists troubled by the administration of anesthetic injections: Long-term stresses and effects*, Quintess Int, Vol. 25, 1994
Peltier B et al, *The injection procedure as a source of stress for dentists*, Gen Dent, Nov/Dec 1995

PHYSIOLOGIC FACTORS FOR DENTAL ANESTHESIA INJECTIONS

Success versus Failure

Physiology of Anesthetic Agents

- How do we assess anesthesia?
  - Question the patient
  - Probe the area
  - } Soft tissue only
  - Electric pulp tester
  - Cold test
  - } Pulpal tissue
- How is anesthetic success defined in studies?
  - Ideal: 2 consecutive 80/80 readings with EPT within 15 minutes of injection (and sustained for 60 mins)
- Cold Test:
  - Spray some Endo Ice (or use an ice stick) on to a cotton swab and place it on the dried buccal surface of the tooth/teeth you need to work on

Physiology of Anesthetic Agents

- Onset of anesthesia:
  1. Dependent upon anesthetic agent
     - Concentration
     - Diffusion to the site
     - Lipid solubility
     - Protein binding to receptor sites

Agent	Lipid Solubility	Protein Binding
Lidocaine	2.9	65%
Mepivacaine	1	75%
Prilocaine	1.5	55%
Articaine	49.5	95%

Physiology of Anesthetic Agents

- Onset of anesthesia:
  1. Dependent upon anesthetic agent
     - Concentration
     - Diffusion to the site
     - Lipid solubility
     - Protein binding to receptor sites
  2. Dependent upon technique, block versus infiltration
     - Infiltration has faster onset
     - Block has longer duration

Blocks versus Infiltrations

- Advantages of infiltrations
  1. Faster onset
  2. Simple
  3. Safe

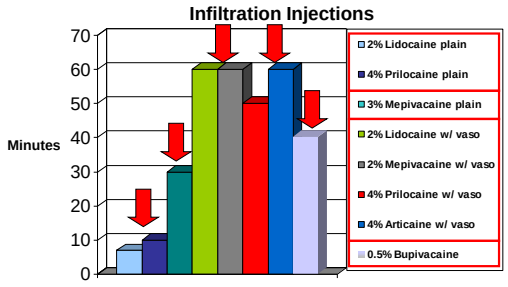
  Work well on children anywhere in the mouth because their cortical bone is not as dense as adults
  4. Good hemostasis (with vasoconstrictor)
- Disadvantages of infiltrations
  1. Multiple injections for multiple teeth
  2. Shorter duration of anesthesia, especially with children due to their higher metabolic rate

Blocks versus Infiltrations

- Dental anesthetic agents: all amides
  1. Lidocaine – (plain or) with vasoconstrictor
  2. Mepivacaine – plain or with vasoconstrictor
  3. Prilocaine – plain or with vasoconstrictor
  4. Articaine – with vasoconstrictor
  5. Bupivacaine – with vasoconstrictor
- Amide anesthetics have replaced ester anesthetics because of their very low risk of allergic reaction

Blocks versus Infiltrations

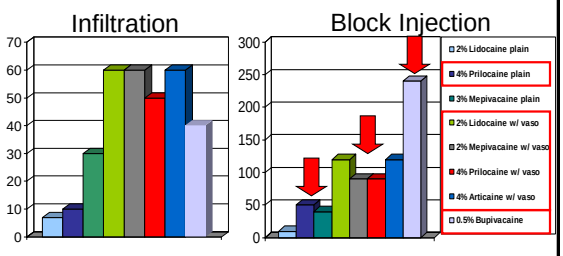
- Duration of pulpal anesthesia:



Manufacturer's Product Inserts; Malamed, Handbook of Local Anesthesia, 6th Ed, *Elsevier*, 2013; Jastak, Yagiela, Donaldson, Local Anesthesia of the Oral Cavity, *WB Saunders Co*, 1995

Blocks versus Infiltrations

- Duration of pulpal anesthesia:



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Blocks versus Infiltrations

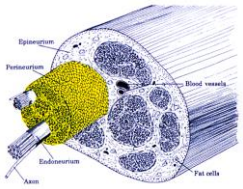
- Duration of anesthesia and onset:
  1. Dependent upon anesthetic agent
     - Concentration
     - Diffusion to/from the site
     - Lipid solubility
     - Protein binding to receptor sites
  2. Dependent upon technique, block versus infiltration
  3. Dependent upon vasoconstrictor presence, but NOT vasoconstrictor concentration*

*Malamed, Handbook of Local Anesthesia, 6th Ed, *Elsevier*, 2013

Physiology of Anesthetic Agents

1. Overall diameter (size) of the nerve bundle
2. Amount of myelin (lipid) sheath present
   - Time for entire nerve bundle to be penetrated
   - Central Core Theory:
   - Peripheral fibers anesthetized first
     - To most proximal structures (molars)
   - Central fibers anesthetized last
     - To most distal structures (incisors)

DeJong RH, Physiology and Pharmacology of Local Anesthesia, 1970

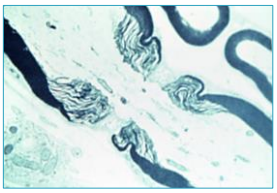


Jastak, Yagiela, Donaldson, Local Anesthesia of the Oral Cavity, *WB Saunders Co*, 1995

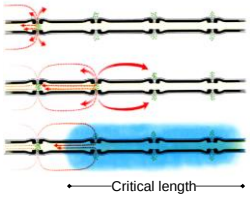
Physiology of Anesthetic Agents

- Critical length = 3 nodes minimum (5 – 8 mm)

  Tissue space & density → Anesthetic volume



Node of Ranvier



Evers & Haegerstam, Introduction to Dental Local Anesthesia, *Mediglobe*, 1990

Physiology of Anesthetic Agents

- The "right" volume depends on many variables
  - For infiltration injections, ½ to ¾ cartridge is generally ideal for adults; ⅓ for kids

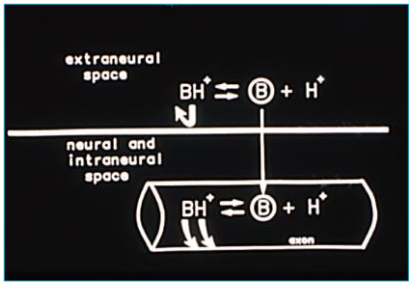
    Brunetto et al, *Anesthetic efficacy of 3 volumes of lidocaine with epinephrine in maxillary infiltration anesthesia*, Anesth Prog, Vol 55, 2008
  - For an inferior alveolar nerve block,
    - Less than ½ cartridge tends to be ineffective
    - ¾ – 1 cartridge is ideal for adults; ⅔ for kids
    - An additional cartridge may increase profundity & decrease onset time*

Nusstein et al, *Anesthetic efficacy of different volumes of lidocaine with epinephrine for inferior alveolar nerve blocks*, Gen Dent, Vol 50, 2002

*Kohler BR et al, *Gow-Gates technique: A pilot study for extraction procedures with clinical evaluation and review*, Anesth Prog, Vol. 55, 2008

Physiology of Anesthetic Agents

- How do local anesthetics work?



BH+ = acidic, ionized form:

Can't pass through nerve membrane (water soluble)

(B) = basic, unionized form:

Can pass through nerve membrane (lipid soluble)

Physiology of Anesthetic Agents

- How do we assess anesthesia?
  - Question the patient
  - Probe the area

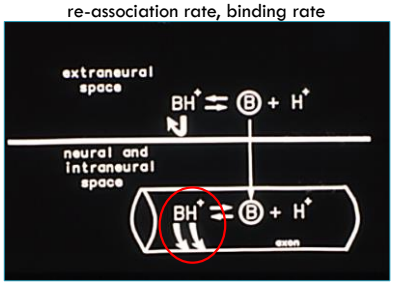
  } Soft tissue only
  - Electric pulp tester
  - Cold test

  } Pulpal tissue
- Delayed pulpal onset: occurs in the mandible of 19 – 27% of patients (even though soft tissue is numb)
  - Delayed over 30 minutes in 8%

Nusstein J et al. *The challenges of successful mandibular anesthesia*, Inside Dentistry, May 2008

Physiology of Anesthetic Agents

- Reasons for delayed or failed onset
  - Disassociation rate, transport/perfusion rate, re-association rate, binding rate



BH+ = acidic, ionized form:

Can't pass through nerve membrane (water soluble)

(B) = basic, unionized form:

Can pass through nerve membrane (lipid soluble)

Troubleshooting Local Anesthesia

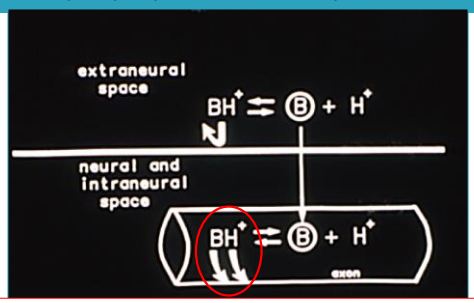
Is this failed anesthesia?

Frequency dependent conduction phenomenon

Wait!
I Still Feel That!

Physiology of Anesthetic Agents

- Frequency dependent conduction phenomenon



If we stimulate the nerve at sub-threshold levels, we can increase the number of open binding sites available to the anesthetic, increasing our anesthetic success

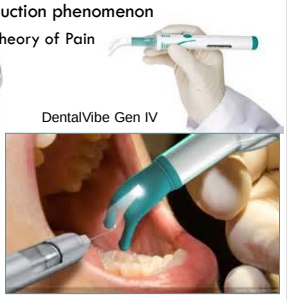
Use of Distraction Techniques

- Surface vibration
  - Creates a mucosal surface distraction
  - Ultrasonic surface vibration enhances mucosal penetration of topical anesthetics
- Devices that create deep tissue vibration via ultrasonics
  - Produce low-level sensory nerve stimulation, allowing greater anesthetic access to receptor sites to produce better anesthesia
    - By activating the Frequency Dependent Conduction phenomenon

Anesthesia Delivery Assistance Devices

- Devices that create ultrasonic vibration activate the Frequency Dependent Conduction phenomenon
  - Based on the Gate Control Theory of Pain

VibraJect



DentalVibe Gen IV

Anesthesia Delivery Assistance Devices

DentalVibe

- Place the device at the injection site and vibrate for **10 seconds before inserting the needle**.
- Continue vibrating while you deliver the anesthesia.
- After removing the needle, vibrate the injection site for 3 seconds

Anesthesia Delivery Assistance Devices

- The Gate Control Theory of Pain
  - Upon injection of anesthetic solution:
    - Nociceptors send most of the pain messaging to the brain via slow conducting, thin C nerve fibers
    - By contrast, **vibration** stimuli of the oral mucosa are transmitted by rapid conducting, large A-beta fibers
  - By applying the vibrations before starting the injection, the vibration sensations reach the brain first and cause release from inhibitory interneurons, blocking the C fiber pain stimulation by "closing the pain gate"

DiFelice MG et al, *Effects of a vibratory device on pain from anesthetic injections*, Compendium, Vol 35(4), April 2014

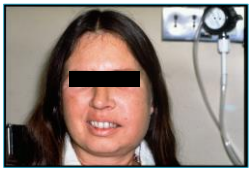
Reasons for Anesthetic Failures

1. Anatomical/physiological variations
2. Technical errors of administration
3. Patient anxiety
4. Inflammation and infection
5. Defective/expired solutions

Wong MKS & Jacobsen PL, *Reasons for local anesthesia failures*, J Am Dent Assoc, Vol 123, Jan 1992

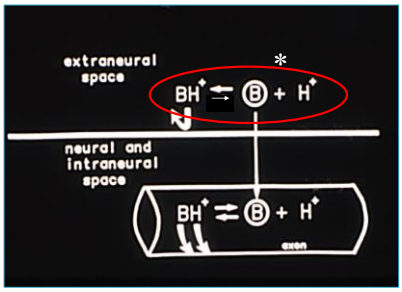
Reasons for Anesthetic Failures

4. Inflammation and infection
   - Causes increased tissue acidity (decreased pH)
   - Less anesthetic solution is available to enter into the nerve due to unfavorable dissociation equilibrium
   - Result is decreased anesthetic effect



Reasons for Anesthetic Failures

4. Inflammation and infection



Increased tissue acidity (decreased pH)

Decreased anesthetic disassociation

Decreased anesthetic effect

*Injecting too much anesthetic, or injecting it too fast, may decrease the tissue buffering capacity

Reasons for Anesthetic Failures

4. Inflammation and infection

Normal tissue	pH = 7.4	24% of injected anesthetic is unionized **B**
Intraneuronal	pH = 7.0	11.2 % to **B**
Inflammation or infection	pH = 5.0 to 3.0	pH 5.0 = 0.13% (1/20 of 7.4 pH) pH 4.0 = 0.013% (1/200 of 7.4 pH) pH 3.0 = 0.0013% (1/2000 of 7.4 pH)

Troubleshooting Anesthesia

- The "Hot" Tooth / "Hot" Gum
  - Includes:
    1. Infected teeth with irreversible pulpitis
    2. Severe periodontal infections
    3. Hypoplastic teeth with severe sensitivity
    4. Teeth with hypersensitivity due to recession, occlusal trauma/bruxing, etc.

All of these may be highly problematic to anesthetize

Troubleshooting Anesthesia

- The "Hot" Tooth / "Hot" Gum
- First, give a block injection
  - Well away from the site of any local inflammation or infection
    - The low pH will prevent the disassociation of the anesthetic agent
  - A needle should not be inserted into an area of active infection, such as a periodontal or periapical abcess
    - The volume of anesthetic is likely to increase pain
    - There is the potential for spreading the infection

Haas DA, *Localized complications from local anesthesia*, J Calif Dent Assoc, Vol 26 No 9, 1998

Troubleshooting Anesthesia

- The "Hot" Tooth / "Hot" Gum
- First, give a block injection
  - The Gow-Gates mandibular division block has a significantly higher success rate than all other techniques

Gow-Gates	52%
Vazirani-Akinosi	41%
Conventional IA	36%
Buccal-plus-lingual infiltration	27%

All with 4% articaine with 1:100,000 epinephrine

- No technique was fully acceptable by itself

Aggarwal V et al, *Comparative evaluation of anesthetic efficacy of Gow-Gates mandibular conduction anesthesia, Vazirani-Akinosi technique, buccal-plus-lingual infiltrations, and conventional inferior alveolar nerve anesthesia in patients with irreversible pulpitis*, J Oral Surg O Med O Path O Radio Endo, Vol. 109 No 2, Feb. 2010

Troubleshooting Anesthesia

- The "Hot" Tooth / "Hot" Gum
- First, give a block injection
  - The Gow-Gates mandibular division block has a significantly higher success rate than all other techniques

Patients who took 600mg of ibuprofen 1 hour before IANB for endodontic treatment of mandibular posterior teeth with irreversible pulpitis were 2x more likely to have "little or no pain during endodontic treatment."

Lapidus D et al, *Effect of premedication to provide analgesia as a supplement to inferior alveolar nerve block in patients with irreversible pulpitis*, J Amer Dent Assoc 147(6), June 2016

All with 4% articaine with 1:100,000 epinephrine

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Aggarwal V et al, *Comparative evaluation of anesthetic efficacy of Gow-Gates mandibular conduction anesthesia, Vazirani-Akinosi technique, buccal-plus-lingual infiltrations, and conventional inferior alveolar nerve anesthesia in patients with irreversible pulpitis*, J Oral Surg O Med O Path O Radio Endo, Vol. 109 No 2, Feb. 2010

Troubleshooting Anesthesia

- The "Hot" Tooth / "Hot" Gum
- First, give a block injection
  - Well away from the site of any local inflammation or infection
- Second, is topical/Oraqix around the tooth adequate?
- If not, give a periodontal ligament (PDL) or intraosseous injection
  - Periodontal ligament injections are quick and easy to give, but offer only short duration
  - Intraosseous injections are more reliable and have better duration

Troubleshooting Anesthesia

- The "Hot" Tooth / "Hot" Gum
- First, give a block injection
  - Well away from the site of any local inflammation or infection
- Second, is topical/Oraqix around the tooth adequate?
- If not, give a periodontal ligament (PDL) or intraosseous injection
- Or, give a buccal & /or lingual infiltration with articaine (or prilocaine)

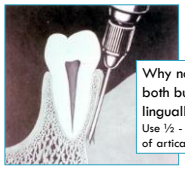
Hasse et al, *Comparing anesthetic efficacy of articaine versus lidocaine as a supplemental buccal infiltration of the mandibular first molar after an inferior alveolar nerve block*, J Am Dent Assoc, Vol 139 No 9, Sept 2008

Kanaa et al, *Articaine buccal infiltration enhances the effectiveness of lidocaine inferior alveolar nerve block*, Int Endo J, Vol 42, 2009

Infiltration Anesthesia

- Works well for the maxilla, but for the mandible…
  - Works fairly well for anteriors and bicuspids
  - More variable predictability for molars
  - Greater success using articaine & faster onset
    - Lidocaine 45 – 67%; articaine 75 – 92%
    - Lidocaine 6.1 – 11.1 minutes; articaine 4.2 – 4.7 minutes

Facial



Why not infiltrate both buccally and lingually?
Use ½ - 1 cartridge of articaine for each

Robertson et al, *The anesthetic efficacy of articaine in buccal infiltration of mandibular posterior teeth*, JADA, Vol 138 No 8, 2007

Meechan, Practical Dental Local Anesthesia, *Quintessence*, 2002

Pharmacology of Anesthetic Agents

- A Practical Armamentarium:
  - From a meta-analysis of 13 clinical trials:
    - Evidence strongly supported articaine's superiority over lidocaine for infiltration anesthesia
    - Evidence was weak for any significant difference between lidocaine and articaine for block anesthesia

Brandt RG et al, *The pulpal anesthetic efficacy of articaine versus lidocaine in dentistry: A meta-analysis, J Am Dent Assoc, Vol 142(5), May 2011*

    - Articaine was 4 times more effective, with greater duration, than lidocaine as an infiltration injection when used for teeth diagnosed with irreversible pulpitis

Ashraf H et al, *Efficacy of articaine versus lidocaine in block and infiltration anesthesia administered in teeth with irreversible pulpitis: A prospective, randomized, double-blind study*, JOE, Vol 39(1), Jan 2013

Troubleshooting Anesthesia

- The "Hot" Tooth / "Hot" Gum
- Why is the "hot" tooth so hard to anesthetize?
  - Inflammation may cause an increase in anesthetic-resistant sodium channels that exist in pain neurons.
  - Inflammation may cause an increase in the number and in the receptive field of pain neurons.
  - The barrage of pain impulses to the CNS produces "central sensitization": an exaggerated CNS response to even gentle peripheral stimuli.
  - Apprehensive patients have a reduced pain threshold.

Hot teeth are tough to treat!

Hargreaves & Keiser, *Local anesthetic failure in endodontics: Mechanisms and management*, Endodontic Topics, 2002

Troubleshooting Anesthesia

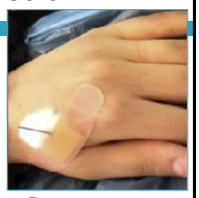
- There is no contraindication for combining any of the amide anesthetic agents
  - Plain anesthetics have better dissociation in a site of infection (but will wash out faster!)
  - Using an anesthetic with a vasoconstrictor is advantageous for better duration
    - Articaine tends to work well in an infected, low pH environment
    - But proper disassociation of any anesthetic solution may be a problem

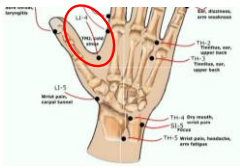
Troubleshooting Anesthesia

- There is no contraindication for combining any of the amide anesthetic agents
  - Using plain anesthetic for "pre-injection", then using anesthetic with vasoconstrictor
    - Anesthetic with vasoconstrictor: pH ~3.5, highly acidic
    - Plain anesthetic: pH ~6.5, significantly less acidic
    - Therefore, plain anesthetics have less "burning" sensation
  - Using a plain anesthetic first may be more comfortable for the patient,
  - But it may also mildly increase the cardiovascular side-effects of vasoconstrictor in the second injection

Troubleshooting Anesthesia

- The "Hot" Tooth/ "Hot" Gum
  - Ongoing research: Acupuncture
  - For teeth with irreversible pulpitis:
    IA block alone: 20% success
    IA block + LI4 Hegu acupoint:
    60% success





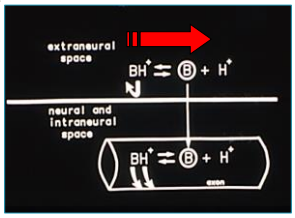
Jalali S et al, *The effect of acupuntcure on the success of inferior alveolar nerve block for teeth with symptomatic irreversible pulpitis: A triple-blind randomized clinical trial*, J Endod 41, Sept 2015

WHAT'S NEW IN DENTAL LOCAL ANESTHESIA?

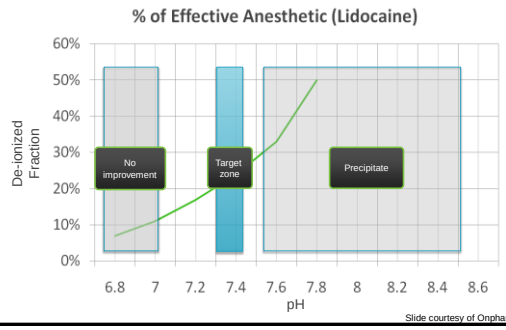
Buffered Anesthetics
Inhalation Local Anesthesia
Iontophoretic Anesthesia
Anesthetic Reversal Agent

Buffering of Local Anesthetics

- Buffer with sodium bicarbonate immediately before delivery
  - Increases dissociation of anesthetic agent for rapid uptake into the nerve
    - Potentially faster onset
    - Potentially more comfortable
    - Potentially more profound
    - Potentially higher success rate

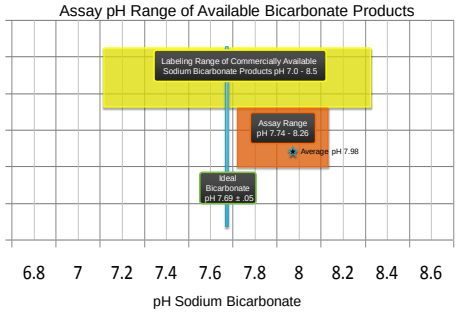


Buffering of Local Anesthetics



Slide courtesy of Onpharma

Buffering of Local Anesthetics



Slide courtesy of Onpharma

Buffering of Local Anesthetics

OnSet sodium bicarbonate cartridges remain pH stable in the pen for up to 5 days

Falkel M & Goetz J, *Buffering, it's not just for lidocaine anymore,* Dentistry Today, Nov. 2015

OnSet mixing pen: insert anesthetic cartridge, mix, load in syringe, and inject – for best results, inject within 30 seconds of mixing

Slide courtesy of Onpharma

Buffering of Local Anesthetics

- Mixing Pen settings:

Falkel M & Goetz J, *Buffering, it's not just for lidocaine anymore,* Dentistry Today, Nov. 2015

Buffering of Local Anesthetics

- An anesthetic buffering device and a multi-dose delivery syringe
  - All constituents remain stable for 7 days
  - Syringe allows delivery of up to 6cc of anesthetic solution with a single penetration
    - Both audible & haptic feedback

Buffering of Local Anesthetics

- An anesthetic buffering device and a multi-dose delivery syringe
  - Uses medical multi-dose anesthetic vials
  - Contain preservative methylparaben: increased potential for allergic reaction (but is this significant?)

Larson CE, *Methylparaben – an overlooked cause of local anesthetic hypersensitivity,* Anesth Prog 1977
Cashman AL & Warshaw EM, *Parabens: a review of epidemiology, Structure, allergenicity, and hormonal properties,* Dermatitis 2005

New Technology: Buffering

- Improve patient satisfaction
  - More comfortable injections
  - More predictable anesthesia
  - More profound anesthesia
- Decrease appointment times
  - Less waiting for anesthetic onset (1 – 2 minutes)
  - See more patients
    - Emergency patients
    - Hygiene patients

New Product: Kovanaze

- Intranasal spray delivery
  - Utilizing the BD ACCUSPRAY® technology currently used in the Flumist® nasal product
- 3% tetracaine HCl plus 0.05% oxymetazoline vasoconstrictor
- Produces a regional block enabling invasive quadrant dentistry on maxillary teeth #4 – 13 and A – J in children ≥ 40 kg/88 lb.

New Product: Kovanaze

- "Sniff" administration
  - No needle
  - Non-invasive, painless
  - Easy to administer
- Anesthetic enters the trigeminal neural pathway within the nasal cavity
  - Adult dosage: 2 sprays; 1st spray, wait 4 minutes; 2nd spray, wait 10 minutes
  - Start work: about 15 minutes from 1st spray

New Product: Kovanaze

- Safety profile
  - Tetracaine is an ester anesthetic; metabolism begins as soon as it enters the bloodstream
    - Less burden on the liver
  - No lip/face anesthesia
  - Shorter duration of post-operative anesthesia
    - Safer for children?
    - More comfortable for adults?
  - Minor side effects: stuffy nose, sneezing, runny nose
    - Side effects same as for common OTC nasal decongestant products

New Product: Kovanaze

- Phase 3 clinical trial results:
  1. 88% success for restorative procedures for 1st premolar, canine, and incisors (compared to 93% success with infiltration injection of 2% lidocaine with 1:100,000 epi)
  2. 60 – 66% success for 2nd premolar
  3. Side effects:
     a. Runny nose 57%
     b. Nasal congestion 26%
- FDA approved June 2016

Hersh EV et al, *Double-masked, randomized, placebo-controlled study to evaluate the efficacy and tolerability of intranasal K305 (3% tetracaine plus 0.05% oxymetazoline) in anesthetizing maxillary teeth,* J Am Dent Assoc 147(4), April 2016

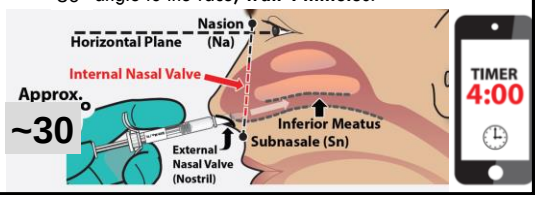
Ciancio SG et al, *Comparison of 3 intranasal mists for anesthetizing maxillary teeth in adults: A randomized, double-masked, multicenter phase 3 clinical trial,* J Am Dent Assoc 147(5), May 2016

New Product: Kovanaze

- Instructions for use:

The sprays must be administered into the nasal cavity on the same side (ipsilateral) as the planned dental procedure.

3. The first spray must be horizontal at approximately a 30º angle to the face; **wait 4 minutes**.

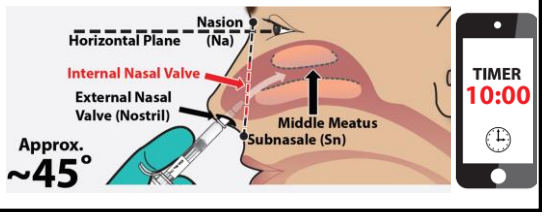


New Product: Kovanaze

- Instructions for use:

  After 4 minutes:

  4. The second spray must be at approximately a 45° angle up; **wait 10 minutes.**



New Product: Kovanaze

5. Before starting the dental procedure **wait 10 minutes**

WAIT 10 Minutes

Then Do Test Drill

IMPORTANT:
To ensure efficacy, please wait the ENTIRE 10 minute period before doing the test drill.

Maybe doing the Cold Test would be better?!

New Product: Kovanaze

6. Optional 3rd spray (adults only)
   - **For adults ≥ 18 years:** If the anesthesia is insufficient, you will need to administer a third spray (repeat Step 5). Wait an additional 10 minutes after the third spray.

   - **DO NOT ADMINISTER A THIRD SPRAY TO CHILDREN UNDER 18 YEARS OLD.**

New Product: Kovanaze

- Important Notes and Frequently Asked Questions:

What will the patient feel during the spray?
The solution has no smell and will feel like a light mist of water.

How can I tell if the spray was not properly administered?
If the sprayer is not actuated quickly enough, liquid could drip from the nostril, stream onto the back of the patient's throat, or stay in the device.

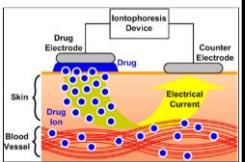
Note: A small drop from the nostril sometimes occurs with proper technique.

QUESTIONS? Call 1-800-865-4925
St. Renatus, LLC
1000 Centre Avenue
Fort Collins, CO 80526

KOVANAZE

New Research: Iontophoresis

- Uses a low-density electric current to introduce ionic drugs into the body through the skin or mucosa
  - Over 100 years of research in medical settings
  - In early stages of dental efficacy research
- Needle-free anesthetic delivery
- Faster onset and prolonged duration likely



Cubayachi C et al, *Needle-free buccal anesthesia using iontophoresis and amino amide salts combined in a mucoadhesive formulation*, Colloids Surf B Biointerfaces 1(136), Dec 2015

New Research: Light-Reactive Anesthetics

- Anesthetic is clinically inactive when injected
- Activated by exposure to a particular wavelength of violet light
- At end of the procedure, anesthetic is inactivated by exposure to a particular wavelength of green light

The ultimate on-off switch!

Electronic Anesthesia

- The ultimate on/off switch?
  - TENS units
    - H – wave machine
    - 3M machine
  - Cedeta

    Cell **D**emodulated
    Electronic **T**argeted
    Anesthesia

None of these devices are currently being marketed

OraVerse Reversal Agent

- Indicated for reversal of soft-tissue anesthesia,
  - i.e., anesthesia of the lip and tongue, and the associated functional deficits resulting from an intraoral submucosal injection of local anesthetics containing a vasoconstrictor
- Restores normal sensation *twice as fast**
- *Accelerates* the return to normal function so patients can speak, smile and drink normally

* Versus control group in clinical trials

OraVerse Reversal Agent

- Pulpal anesthesia wears off in 45-60 minutes
- Soft tissue numbness can last 3-5 hours

Local Anesthetics with Vasoconstrictors	Expected Duration (minutes)	
	Pulpal Anesthesia	Soft Tissue Anesthesia
Articaine 4% + epinephrine 1:100,000	45-60	180-300
Lidocaine 2% + epinephrine 1:100,000	60	180-300
Mepivacaine 2% + levonordefrin 1:20,000	60	180-300
Prilocaine 4% + epinephrine 1:200,000	60-90	180-480

Malamed SF, Handbook of Local Anesthesia, 5th Ed, *C.V. Mosby, St. Louis, MO*, 2004

OraVerse Reversal Agent

- Loss of Function can result in
  - Difficulty with speaking
  - Difficulty in smiling
  - Difficulty with eating
  - Difficulty with drinking
  - Uncontrolled drooling
  - Biting of lip or cheek
  - Patient's perceived sense of altered appearance

OraVerse (Phentolamine Mesylate)

- Phentolamine mesylate (alpha adrenergic antagonist) is a vasodilator originally developed in 1952 to treat hypertension
- Administered by injection
  - With standard dental syringe, same injection site, and identical technique used for delivery of the original local anesthetic agent(s)
- Dilates blood vessels at the anesthetic site, speeding up vascular removal of the anesthetic
  - Reverses the effect of vasoconstrictors

OraVerse Reversal Agent

- Recovery time:
  - Median time to recovery of normal lip sensation
  - Lower lip:
    - 70 minutes for OraVerse group vs. 155 minutes for control group (121% faster)
    - Reduced median time to normal sensation by 85 minutes
      - After 1 hour: 41% OraVerse patients normal vs. 7% of controls
  - Upper lip:
    - 50 minutes for OraVerse group vs. 133 minutes for control group (166% faster)
    - Reduced median time to normal sensation by 83 minutes
      - After 1 hour: 59% OraVerse patients normal vs. 12% of controls

Hersh EV, Moore PA, Papas AS, et al. *Reversal of soft-tissue local anesthesia with phentolamine mesylate in adolescents and adults*, J Am Dent Assoc, Vol. 139 No. 8, Aug 2008

OraVerse Reversal Agent

- Recovery time:
  - Median time to recovery of normal sensation
    - 110 minutes for OraVerse group vs. 180 minutes for control group
    - Reduced median time to normal sensation by 70 minutes
      - At any point, the OraVerse patients had a 2.77-fold higher chance of recovery to normal sensation versus control patients
  - Median time to recovery of normal function
    - 111 minutes for OraVerse group vs. 190 minutes for control group
    - Reduced median time to normal function by 79 minutes
      - At any point, the OraVerse patients had a 2.94-fold higher chance of recovery to normal function versus control patients

Daubländer M, Liebaug F, et al. *Effectiveness and safety of phentolamine mesylate in routine dental care*, J Am Dent Assoc, Vol. 148 No. 3, March 2017

OraVerse Reversal Agent

- Safety Profile
  Across all studies:
  - No contraindications
  - No evident toxicity
  - No known drug interactions with OraVerse
  - No difference in adverse events versus control
    - Only 1% difference in transient injection site pain for OraVerse group (5%) versus the Control group (4%)
    - All adverse events were mild and resolved within 48 hours

Hersh EV, Moore PA, Papas AS, et al. *Reversal of soft-tissue local anesthesia with phentolamine mesylate in adolescents and adults*, J Am Dent Assoc, Vol. 139 No. 8, Aug 2008
Daubländer M, Liebaug F, et al. *Effectiveness and safety of phentolamine mesylate in routine dental care*, J Am Dent Assoc, Vol. 148 No. 3, March 2017

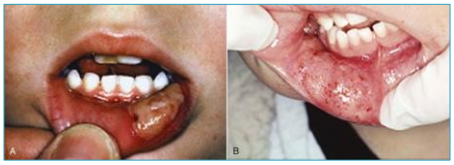
OraVerse Reversal Agent

- When to use:
  - Patients who have received anesthetic with a vasoconstrictor
  - Procedures where post-procedural pain is not anticipated:
    - Cavity preparations
    - Crown preparations
    - Crown placements
    - Inlays
    - Onlays
    - Veneers
    - Non-surgical periodontal scaling and root planning

  - Patients who may not be able to control post-op tendency to bite themselves

OraVerse Reversal Agent

- When to use:
  - Patients who may not be able to control post-op tendency to bite themselves



Malamed, Handbook of Local Anesthesia, 6th Ed, *Elsevier*, 2013

OraVerse Reversal Agent

- Case Selection:
  - Special needs patients
  - Children going back to school or to after-school activities
  - People that want to get back to work, to their day
    - "As a busy executive, not allowing me the option to pay for this product is a complete disservice... In this economy I can't afford to lose work; not giving me the option to purchase this product is just wrong !!" Patient blog
  - People who dislike being numb

OraVerse Reversal Agent

- A patient service that may distinguish your practice from others
- This is a service, an option, to be able to offer your patients

It's the thought that counts!

PHARMACOLOGY OF ANESTHETIC AGENTS

Pharmacologic Factors for Success and Safety

Pharmacology of Anesthetic Agents

- Dental anesthetic agents: all amides
  1. Esters: high incidence of allergic reaction
     - Frequent cross-reactivity
     - No longer available in U.S. in dental cartridges
     - Available in multidose bottles
  2. Amides: <1% incidence of allergic reaction
     - True allergy very rare
     - Sensitive patients usually not reactive to other amide agents
     - Recommend patch testing by allergist
       - Note: This is not entirely reliable

Baluga JC et al. *Allergy to local anesthetics in dentistry: Myth or reality?*, Allergol Imunopathol, 30(1), 2002

Pharmacology of Anesthetic Agents

- Dental anesthetic agents: all amides
  1. Lidocaine – (plain or) with vasoconstrictor
     Xylocaine, Octocaine, Lignospan, etc.
  2. Mepivacaine – plain or with vasoconstrictor
     Carbocaine, Polocaine, Isocaine, Scandonest, etc.
  3. Prilocaine – plain or with vasoconstrictor
     Citanest and Citanest forte
  4. Articaine – with vasoconstrictor
     Septocaine, Zorcaine, Articadent, Orabloc
  5. Bupivacaine – with vasoconstrictor
     Marcaine, Vivacaine

Pharmacology of Anesthetic Agents

- Common usage:
  (Expected duration of pulpal anesthesia)
  - Short procedures: less than 1 hour
    1. Mepivacaine 3% plain (as infiltrate or block)
    2. Prilocaine 4% plain (as block)
  - Routine procedures: 1 to 2 hours
    1. Lidocaine 2% with vasoconstrictor
    2. Mepivacaine 2% with vasoconstrictor
    3. Articaine 4% with vasoconstrictor
    4. Prilocaine 4% with vasoconstrictor

Pharmacology of Anesthetic Agents

- Common usage:
  - Long procedures: more than 2 hours or for post-operative analgesia
    1. Bupivacaine 0.5% with vasoconstrictor (as block)
  - Difficult to anesthetize patients:
    1. Prilocaine 4% with vasoconstrictor
    2. Articaine 4% with vasoconstrictor

Clinical Research Associates Newsletter, June 2001

Anesthetic Agents

- A Practical Armamentarium:
  - 2% Lidocaine with 1:100,000 epinephrine
    - For one to two hour procedures and most block injections
  - 3% Mepivacaine plain
    - For short duration procedures or the rare "no vasoconstrictor" patient
  - 4% Articaine with 1:200,000 epinephrine
    - For infiltrations and "hard to anesthetize" patients
  - 0.5% Bupivacaine with 1:200,000 epinephrine
    - For prolonged pain control and long duration procedures
  - And some buffering agent and OraVerse anesthetic reversal agent

Pharmacology of Anesthetic Agents

- Adverse reactions to anesthetic agents:
  1. Psychogenic reactions
     - Syncope the most common reaction
  2. Allergic reactions - uncommon
  3. Toxic reactions - uncommon
  4. Idiosyncratic reactions
     - Emotional factors may play a key role in producing unusual symptoms that cannot be related to pharmacology or anatomy

Pharmacology of Anesthetic Agents

- Adverse reactions to anesthetic agents:
  1. Psychogenic reactions
     - Syncope the most common reaction
       - 76% of medical emergencies in the dental office are related to stress and anxiety
       - Low blood sugar, lack of sleep, and/or dehydration may also cause syncope
     - To avoid syncope:
       - Give injections with the patient lying supine, then slowly sit the patient upright

Pharmacology of Anesthetic Agents

- Adverse reactions to anesthetic agents:
  1. Psychogenic reactions
     - Management of syncope:
       - Lay patient supine with legs above head
       - Maintain airway; may administer O_2
       - Monitor pulse, blood pressure & breathing
       - Loosen tight collar; keep patient warm
       - Calmly reassure the patient

Pharmacology of Anesthetic Agents

- Adverse reactions to anesthetic agents:
  2. Allergic reactions
     - Question the patient carefully
     - Get a full history of the incident
     - Was it really an allergic reaction?
     - Allergy to an amide anesthetic is very rare

Pharmacology of Anesthetic Agents

- Adverse reactions to anesthetic agents:
  2. Allergic reactions
     - Mild
       - Rash, skin itches, runny nose and eyes (leaky capillaries)
       - Majority of allergic responses are contact dermatitis
     - Moderate
       - Swelling of tongue or throat
       - Asthmatic wheezing (respiratory constriction)
     - Severe
       - Anaphylaxis: may develop within minutes!
       - CV system relaxes, BP drops, shock, failure

Most adverse drug reactions develop during the injection or within 5 to 10 minutes post-injection

Malamed, Handbook of Local Anesthesia, 6th Ed, *Elsevier*, 2013

Pharmacology of Anesthetic Agents

- Adverse reactions to anesthetic agents:
  2. Allergic reactions
     - Anaphylaxis
       - Initial signs and symptoms:
         warm moist skin, apprehension, diffuse erythema/hives, itching, angioedema
       - Subsequent signs:
         abdominal cramps, vomiting, wheezing, dyspnea, difficulty talking

Progressive signs and symptoms develop very quickly!

Most adverse drug reactions develop during the injection or within 5 to 10 minutes post-injection

Malamed, Handbook of Local Anesthesia, 6th Ed, *Elsevier*, 2013

Pharmacology of Anesthetic Agents

- Adverse reactions to anesthetic agents:
  2. Allergic reactions: mild to moderate

Reactions	Treatment
Uticaria Angioneurotic edema Mucous membrane congestion	- Diphenhydramine (Benadryl) 25 to 50 mg orally if no respiratory or circulatory compromise - Continue every 6 hours for 2 to 3 days - Bronchodilator: Albuterol or Alupent inhaler

Pharmacology of Anesthetic Agents

- Adverse reactions to anesthetic agents:
  2. Allergic reactions: severe

Reactions	Treatment
Anaphylaxis	- Have front desk call 911
Airway restriction	- Give positive pressure O_2
Hypotension "something wrong" "sick feeling"	- Epinephrine 1:1000 (Epi pen) 0.3 – 0.5 cc subcutaneously, repeat every 10 – 15 mins. if needed - Diphenhydramine 2 mg/kg IV or IM

Pharmacology of Anesthetic Agents

- Adverse reactions to anesthetic agents:
  2. Allergic reactions
     - Primary reasons for allergic reactions to dental local anesthetics:
       - X The preservative for the anesthetic: Methyl paraben
         FDA ordered removed from all U.S. dental cartridges in 1984
       - X Ester anesthetics: high allergic incidence; cross-reactive
         Replaced with amide anesthetics in mid 1990's
       - X Latex in cartridge stopper and diaphragm: molecules leached into the anesthetic solution
         Replaced with silicone in early 2000's
       4. The antioxidant for the vasoconstrictor:
          Sodium or potassium metabisulfite (0.50 mg/ml)

Pharmacology of Anesthetic Agents

- Adverse reactions to anesthetic agents:
  2. Allergic reactions
     - The antioxidant for the vasoconstrictor:
       Sodium or potassium metabisulfite (0.50 mg/ml)
     - Possible sulfite sensitivity, especially for corticosteroid-dependent asthmatics (10 – 20%)
       - Ask about food sensitivities:
         Dried fruits, beer and wine, salami and pepperoni-type meats: all have sulfites
       - Also sprayed on many foods in markets to give foods a "fresher" appearance

Bush RK et al, *Prevalence of sensitivity to sulfiting agents in asthmatic patients*, Am J Med, Vol 81, 1986
Canfield DW & Gage TW, *A guideline to local anesthetic allergy testing*, Anesth Prog, Vol 34, 1987
Manufacturer package insert information, 2014

Pharmacology of Anesthetic Agents

- Adverse reactions to anesthetic agents:
  2. Allergic reactions
     - What are the contents of a cartridge of 2% lidocaine with 1:100,000 epinephrine?
       1. Lidocaine HCl 2% concentration
       2. Epinephrine (as the bitartrate dilution)
       3. Distilled water
       4. Sodium chloride 10.2 mg
       5. (Citric acid 0.34 mg)
       6. Sodium or potassium metabisulfite 0.85 mg

Manufacturer package insert information 2014

Pharmacology of Anesthetic Agents

- Adverse reactions to anesthetic agents:
  2. Allergic reactions
     - If an allergy to an amide anesthetic is suspected:
       1. Have patient patch tested (skin "prick" test followed by intradermal injection) for all amides and for at least one ester anesthetic (send dental cartridges with patient)
       2. A challenge test to duplicate symptoms can be used if there is no response to skin testing; this is more reliable
       3. May use 1% diphenhydramine (Benadryl) with 1:100,000 epinephrine as an alternative anesthetic
          Short duration (infiltrant), may require multiple injections

Canfield DW & Gage TW, *A guideline to local anesthetic allergy testing*, Anesth Prog, Vol 34, 1987
Tomoyasu et al, *Allergic reactions to local anesthetics in dental patients: Analyisis of intracutaneous and challenge tests*, Open Dent J, Vol. 5, 2011

Pharmacology of Anesthetic Agents

- Adverse reactions to anesthetic agents:
  3. Toxic reactions: Uncommon

     Signs:
     - Low: sedation, analgesia
     - Intermediate: lightheadedness, slurred speech, drowsiness, euphoria/dysphoria, diplopia, muscle twitching
     - High: disorientation, tremors, respiratory depression, tonic/clonic seizures
     - Lethal: coma, respiratory arrest, cardiovascular collapse

     Progression may be very rapid with local anesthetics

Pharmacology of Anesthetic Agents

- Adverse reactions to anesthetic agents:
  3. Toxic reactions: Contributing factors
     - Type of anesthetic
       - Plain anesthetics have rapid systemic absorption
     - Dosage of anesthetic
     - Route of administration
     - Rate of administration
     - Patient's physical condition and health
       - Includes previous exposure
       - Drug interactions
       - Psychological response

Pharmacology of Anesthetic Agents

- Adverse reactions to anesthetic agents:
  3. Toxic reactions: Contributing factors
     - Drugs that alter the functioning of the CNS or CVS may lower the toxicity threshold for local anesthetics
     - This is especially true for drugs that decrease liver or cardiac functions or that stimulate the CNS
     - **Limiting the total dose and using anesthetics with vasoconstrictors are the two common means of avoiding local anesthetic toxicity reactions.**

Chen AH, *Toxicity and allergy to local anesthesia,* J Calif Dent Assoc, Vol 26 No 9, 1998

Pharmacology of Anesthetic Agents

- Local anesthetic dosage
  - Calculating dosage:

    In dental cartridges,

    ~18 mg anesthetic/% concentration
  - 2% lidocaine 36 mg/cartridge
  - 3% mepivacaine 54 mg/cartridge
  - 4% prilocaine or 4% articaine 72 mg/cartridge

Cartridge volume officially 1.78 to 1.82 ml; all labeled as 1.7 ml.

Pharmacology of Anesthetic Agents

- Local anesthetic dosage (FDA approved max. dosage)*
  1. 2% lidocaine w/epi 3.2 mg/lb
     4% articaine w/epi
     (500 mg max. for any patient)
  3. 3% mepivacaine plain 3.0 mg/lb
     2% mepivacaine w/levo
     (400 mg max. for any patient)
  4. 4% prilocaine plain or w/epi 4.0 mg/lb
     (600 mg max. for any patient)
  5. 0.5% bupivacaine w/epi 0.6 mg/lb
     (90 mg max. for any patient)

*Within a 24 hour timeframe

Pharmacology of Anesthetic Agents

- Local anesthetic dosage (FDA approved max. dosage)
  - Calculating dosage: 150 lb. adult

2% lidocaine with epinephrine

150 lb. x 3.2 mg/lb. = 480 mg

500 mg is the maximum for any patient

$$\frac{480 \text{ mg}}{36 \text{ mg/cartridge}} = 13.33 \text{ cartridges}$$

14 cartridges is the maximum for any patient ≥ 156 lb.

(Exceeds the maximum safe dosage of epinephrine = 11 cartridges)

Pharmacology of Anesthetic Agents

- Local anesthetic dosage (FDA approved max. dosage)
  - Calculating dosage: 70 lb. child

2% lidocaine with epinephrine
70 lb. x 3.2 mg/lb. = 224 mg

224 mg / 36 mg/cartridge = 6.22 cartridges

Pharmacology of Anesthetic Agents

- Local anesthetic dosage (FDA approved max. dosage)
  - Calculating dosage: For children
    - Maximum recommended dosage is 2.0 mg/lb. for all anesthetics*, and use of a vasoconstrictor is strongly recommended
    - Note: Children have a higher metabolic rate, which means that more anesthetic enters their bloodstream in a shorter time.
    - Hence the reduction of maximum dosage to 2.0 mg/lb. for children for all anesthetics

*Systemic absorption of topical anesthetics must also be considered when calculating total anesthetic dosage

Malamed, Handbook of Local Anesthesia, 6th Ed, *Elsevier*, 2013

Pharmacology of Anesthetic Agents

- Local anesthetic dosage (FDA approved max. dosage)
  - Calculating dosage: 70 lb. child

2% lidocaine with epinephrine
70 lb. x 2.0 mg/lb. = 140 mg

140 mg / 36 mg/cartridge = 3.88 cartridges

For 50 lb. child = 2.77 cartridges

Pharmacology

- Local anesthetic dosage (FDA approved max. dosage)
  - Calculating dosage: For children Based on *weight!*

Guidelines on the Use of Local Anesthesia for Pediatric Dental Patients, American Academy of Pediatric Dentistry, 2009

Age	Average weight in lbs.	Cartridges of 2% lidocaine
2	32	1.7
3	37	2.0
4	45	2.5
5	49	2.7
6	54	3.0
7	60	3.3
8	70	3.8
9	82	4.5
10	94	5.2
11	105	5.8
12	122	6.7
13	136	7.5

Pharmacology of Anesthetic Agents

- Local anesthetic dosage (FDA approved max. dosage)
  - Calculating dosage: 150 lb. adult

3% mepivacaine plain
150 lb. x 3.0 mg/lb. = 450 mg
But…400 mg is maximum for <u>any</u> patient!

400 mg / 54 mg/cartridge = 7.40 cartridges

7 cartridges is the maximum for any patient ≥ 135 lb.

Pharmacology of Anesthetic Agents

- Local anesthetic dosage (FDA approved max. dosage)
  - Calculating dosage: 70 lb. child

3% mepivacaine plain
70 lb. x 2.0 mg/lb. = 140 mg

140 mg / 54 mg/cartridge = 2.59 cartridges

Pharmacology of Anesthetic Agents

- Local anesthetic dosage (FDA approved max. dosage)
  - Calculating dosage: 150 lb. adult

2% mepivacaine with levonordefrin
150 lb. x 3.0 mg/lb. = 450 mg
But…400 mg is maximum for <u>any</u> patient!

$$\frac{400\ \text{mg}}{36\ \text{mg/cartridge}} = 11.11\ \text{cartridges}$$

11 cartridges is the maximum for any patient ≥ 135 lb.

Pharmacology of Anesthetic Agents

- Local anesthetic dosage (FDA approved max. dosage)
  - Calculating dosage: 70 lb. child

2% mepivacaine with levonordefrin
70 lb. x 2.0 mg/lb. = 140 mg

$$\frac{140\ \text{mg}}{36\ \text{mg/cartridge}} = 3.88\ \text{cartridges}$$

Pharmacology of Anesthetic Agents

- Local anesthetic dosage (FDA approved max. dosage)
  - Calculating dosage: 150 lb. adult

4% prilocaine plain or with epinephrine
150 lb. x 4.0 mg/lb. = 600 mg
600 mg is maximum for <u>any</u> patient!

$$\frac{600\ \text{mg}}{72\ \text{mg/cartridge}} = 8.33\ \text{cartridges}$$

8 cartridges is the maximum for any patient ≥ 150 lb.

Pharmacology of Anesthetic Agents

- Local anesthetic dosage (FDA approved max. dosage)
  - Calculating dosage: 150 lb. adult

4% articaine with epinephrine
150 lb. x 3.2 mg/lb. = 480 mg
500 mg is the maximum for <u>any</u> patient

$$\frac{480\ \text{mg}}{72\ \text{mg/cartridge}} = 6.66\ \text{cartridges}$$

7 cartridges is the maximum for any patient ≥156 lb.

Pharmacology of Anesthetic Agents

- Local anesthetic dosage (FDA approved max. dosage)
  - Calculating dosage: 70 lb. child

4% prilocaine plain or with epinephrine or articaine with epinephrine
70 lb. x 2.0 mg/lb. = 140 mg

$$\frac{140\ \text{mg}}{72\ \text{mg/cartridge}} = 1.94\ \text{cartridges}$$

Pharmacology of Anesthetic Agents

- Local anesthetic dosage (FDA approved max. dosage)
  - Calculating dosage: 150 lb. adult

0.5% bupivacaine with epinephrine
150 lb. x 0.6 mg/lb. = 90 mg
90 mg is the maximum for <u>any</u> patient

I do not recommend using this anesthetic in children

$$\frac{90\ \text{mg}}{9\ \text{mg/cartridge}} = 10\ \text{cartridges}$$

10 cartridges is the maximum for any patient ≥150 lb.

Pharmacology of Anesthetic Agents

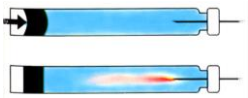
- Local anesthetic dosage
  - Factors to keep in mind:
    1. The time interval of injections is important
       - The half-life of lidocaine in the bloodstream is 90 minutes; for articaine the half-life is <30 minutes
       - Half-life is a serum phenomenon related to potential toxicity; it is not related to anesthetic duration
       - Ultimately, the total dosage given is the important toxicity factor, but the timeframe of administration affects duration
         - **Small amounts given over time provide better duration and are safer than large amounts given quickly**

Pharmacology of Anesthetic Agents

- Vasoconstrictors in local anesthetics
  - All anesthetic agents are vasodilators
  - Vasoconstrictors
    1. Slow the rate of uptake into the bloodstream
       - Lidocaine plain reaches a maximum blood level at 10 minutes after injection
       - Lidocaine with epinephrine reaches maximum blood level at 60 minutes and at a lower concentration
       - Therefore, vasoconstrictors reduce the risk of toxicity
    2. Increase the duration of anesthesia
    3. Induce localized hemostasis

Pharmacology of Anesthetic Agents

- Vasoconstrictors in local anesthetics
  - Are they safe to use?
    1. Review patient's health history
    2. Is the patient medically stable?
    3. OK to use unless physician consult says "No!"
    4. Always aspirate
    5. Inject slowly
    6. Minimize volume injected



Evers & Haegerstam, Introduction to Dental Local Anaesthesia, *Medilobe*, 1990

Pharmacology of Anesthetic Agents

- Vasoconstrictors in local anesthetics
  - Local anesthetics, with or without vasoconstrictors, are remarkably safe at therapeutic doses.
  - Two basic concerns when treating medically complex patients
    1. Existing systemic diseases that may be exacerbated by the agent, and
    2. Medications that may have an adverse interaction with the agent

Pharmacology of Anesthetic Agents

- Vasoconstrictors in local anesthetics
  - Absolute contraindications:
    - Unstable angina
    - Myocardial infarction within 6 months*
    - Coronary artery bypass surgery within 3 months*
    - Refractory arrhythmias
    - Untreated or uncontrolled hypertension
    - Untreated of uncontrolled congestive heart disease
    - Uncontrolled diabetes or other endocrine diseases

    *The timeframe is variable; a physician consult is recommended

Pérusse, Goulet, Turcotte, *Contraindications to vasoconstrictors in dentistry: Part I*, O Surg O Med O Pathol, Vol 74 No 5, Nov 1992
ADA/PDR Guide to Dental Therapeutics, 5th Ed, 2009

Pharmacology of Anesthetic Agents

- Vasoconstrictors in local anesthetics
  - Patients with stabilized hypertension or other cardiovascular diseases
    - The results of a number of studies indicate that the use of 1 or 2 cartridges of vasoconstrictor-containing anesthetic is of little clinical significance for most patients with stabilized hypertension or other CV diseases.
    - **The benefits of maintaining adequate anesthesia for the duration of the procedure should not be underestimated.**
    - The important issue: the patient's tolerance of stress.

Pharmacology of Anesthetic Agents

- Vasoconstrictors in local anesthetics
  - Patients with stabilized hypertension or other cardiovascular diseases
    - Maximum dosage of epinephrine
      Healthy patients: up to 0.2 mg
      equals 11 cartridges
      Cardiac patients: up to 0.04 mg
      equals 2.2 cartridges (1:100,000)

      American Heart Association and American Dental Association, 1964
    - 1:100,000 epinephrine = 0.018 mg/cartridge
      1:200,000 epinephrine = 0.009 mg/cartridge

      Management of dental problems in patients with cardiovascular disease, JADA Vol 68 No 3, 1964
      American Dental Society of Anesthesiology, The Pulse Vol 41 No 1, 2008

Pharmacology of Anesthetic Agents

- Vasoconstrictors in local anesthetics
  - Epinephrine has its primary effect on the alpha 1 receptors
    - Produces localized vasoconstriction
    - Increases peripheral blood pressure as enters the blood stream (minimal if over time)
    - Caution to prevent intravascular injection
    - **Requires caution with hypertensive patients**
      - **Check blood pressure before injecting**
      - **Are they controlled?**

Pharmacology of Anesthetic Agents

- Vasoconstrictors in local anesthetics
  - Epinephrine has its primary effect on the alpha 1 receptors
    - In patient's with controlled hypertension, use of local anesthetics with vasoconstrictor is OK.
      - Can initially give up to a maximum of 2 cartridges of anesthetic with 1:100,000 epinephrine, then wait at least 10 minutes.
      - If no problems arise in that time, additional cartridges may be used judiciously,
      - Or switch to a plain anesthetic for additional doses.

      Brown RS & Rhodus NL, *Epinephrine and local anesthesia revisited*, O Surg O Med O Pathol, Vol 100 No 4, Oct 2005

Pharmacology of Anesthetic Agents

- Vasoconstrictors in local anesthetics
  - Epinephrine has its primary effect on the alpha 1 receptors
    - Patients on alpha 1 blockers (vasodilators like *minipress*) have decreased anesthetic duration
    - Patients on beta 1 blockers have an increased alpha 1 response
      - Increased anesthetic duration
      - Increased peripheral blood pressure
      - Risk greatest with nonselective beta blockers (*propanolol & timolol*); fewer problems with *atenolol & Lopressor*

Pharmacology of Anesthetic Agents

- Vasoconstrictors in local anesthetics
  - Levonordefrin (Neo-Cobefrin)
    - Similar to epinephrine, but a little less beta effect on heart rate
    - Has a moderate effect on blood pressure
    - 1/5 the potency, therefore in 5x the concentration: 1:20,000
    - **Contraindicated in the same patients as epinephrine**

Pharmacology of Anesthetic Agents

- Vasoconstrictors in local anesthetics
  - Relative contraindications:
    - Patients taking tricyclic antidepressants (*Elavil, Triptil, Aventyl*)
      - No interactions with serotonin re-uptake inhibitors (*Paxil, Zoloft, Prozac*)
    - Patients taking phenothiazine antipsychotics (*Thorazine, Compazine, Haldol*)
    - Patients taking nonselective beta blockers (*propanolol [Inderal], timolol*)
    - Patients taking recreational drugs (cocaine, methamphetamines, etc.) or ADD/ADHD medications*

    Brown RS & Rhodus NL, *Epinephrine and local anesthesia revisited*, O Surg O Med O Pathol, Vol 100 No 4, Oct 2005
    *ADA/PDR Guide to Dental Therapeutics, 5th Ed, 2009

Pharmacology of Anesthetic Agents

- Vasoconstrictors in local anesthetics
  - Patients taking tricyclic antidepressants (*Elavil, Triptil, Aventyl*)
    - Uses: treatment of depression, neuropathic pain, chronic pain, obsessive compulsive disorder, anxiety, and panic disorder. Other possible uses may include migraine prophylaxis, treatment of attention-deficit/hyperactivity disorder (ADHD), and nocturnal enuresis, and as adjunctive therapy for smoking cessation.
    - Can carefully use epinephrine, but monitor for possible sympathomimetic side-effects, i.e. increased blood pressure and heart rate
    - **Use of levonordefrin is NOT recommended due to greater tendency to produce sympathomimetic side-effects than seen with epinephrine**

Lexi-Comp Tricyclic Antidepressant update, Feb. 2012
Boakes AJ et al, *Interactions between sympathomimetic amines and antidepressant agents in man*, Brit Med Jour, Vol 1, 1973

Pharmacology of Anesthetic Agents

- Vasoconstrictors in local anesthetics

1. Slow the rate of uptake into the bloodstream, reducing the risk of toxicity
2. Increase the duration of anesthesia
3. Induce localized hemostasis

Vasoconstrictors increase safety

Pharmacology of Anesthetic Agents

- Metabolism of local anesthetics
  - Amide agents primarily biotransformed in the liver by P-450 cytochrome enzymes
  - Due to decreased liver function
    - Plasma levels of anesthetic stay elevated longer
    - Additional doses are additive: possible toxicity
  - Reduce maximum safe dosage figures for patients
    1. With liver impairment due to cirrhosis, hepatitis, etc., or
    2. Taking medications metabolized by the P-450 liver enzymes, which includes many, many medications

Pharmacology of Anesthetic Agents

- Metabolism of local anesthetics
  - Articaine begins rapid biotransformation in the bloodstream due to its ester moiety, then completed in the liver
    - 90 – 95% metabolized in the blood stream; 5 – 10% metabolized in the liver
    - Articaine may be a better local anesthetic agent for patients with impaired liver function

Oertel R et al, *Clinical pharmacokinetics of articaine*, Clin Pharmacokinet, Vol. 33(6), 1997

Pharmacology of Anesthetic Agents

- Other local anesthetic complications
  - Excessive doses have been associated with drug-induced methemoglobinemia
    - Small amounts are normal in everyone
    - Systemic methemoglobinemia a rare disease
    - Risk factors for anesthetic-induced disease:
      1. Extremes of age
      2. Anemia
      3. Respiratory disease
      4. Certain hereditary enzyme deficiencies

Moore PA, *Adverse drug interactions in dental practice: Interactions associated with local anesthetics, sedatives, and anxiolytics*, J Am Dent Assoc, Vol 130, 1999

Pharmacology of Anesthetic Agents

- Other local anesthetic complications
  - Excessive doses (injectable or topical) have been associated with drug-induced methemoglobinemia
    - Risk may be increased in presence of oxidizing drugs such as acetaminophen, nitroglycerin, or sulfonamides.
    - Particular caution recommended with use of prilocaine (Citanest) in patients at risk
      - Respiratory obstruction: COPD, emphysema
      - Anemia
      - Pregnancy

Moore PA, *Adverse drug interactions in dental practice: Interactions associated with local anesthetics, sedatives, and anxiolytics*, J Am Dent Assoc, Vol 130, 1999

Pharmacology of Anesthetic Agents

- Safest local anesthetics during pregnancy and breast-feeding:
  - Lidocaine and prilocaine are FDA Category B
  - All others are Category C

Donaldson M & Goodchild JH, *Pregnancy, breast-feeding and drugs used in dentistry,* J Am Dent Assoc, 143(8), August 2012

Pharmacology of Anesthetic Agents

U.S. Food and Drug Administration pregnancy risk factor definitions.*

CATEGORY	DEFINITION
A	The results of controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of risk in later trimesters), and the possibility of fetal harm appears remote
B	Either the results of animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women OR the results of animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester and there is no evidence of risk in later trimesters
C	Either the results of studies in animals have revealed adverse effects (teratogenic, embryocidal or other) on the fetus and there are no controlled studies in women OR results of studies in women and animals are not available; drug should be given only if the potential benefit justifies the potential risk to the fetus
D	There is positive evidence of human fetal risk, but the benefits of use in pregnant women may be acceptable despite the risk (for example, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective)
X	Results of studies in animals or humans have demonstrated fetal abnormalities or evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit; use of the drug is contraindicated in women who are or may become pregnant

* Sources: U.S. Food and Drug Administration.[4,20,22]

Pharmacology of Anesthetic Agents

- Safest local anesthetics during pregnancy and breast-feeding:
  - Lidocaine ~~and prilocaine~~ are FDA Category B
  - All others are Category C
  - Risk of methemoglobinemia with topicals (especially esters: benzocaine, tetracaine) and injectable prilocaine
  - Epinephrine is OK!
- 2% lidocaine with 1:100,000 epinephrine is the safest anesthetic to use during pregnancy
  - Always use only as much as is truly necessary

Donaldson M & Goodchild JH, *Pregnancy, breast-feeding and drugs used in dentistry,* J Am Dent Assoc, 143(8), August 2012

Pharmacology of Anesthetic Agents

- Treating medically complex patients
  - Local anesthetics, with or without vasoconstrictors, may be safely used in most medically complex patients.
  - Observance of simple safety guidelines for administration of local anesthetics should be universally applied to all patients.

Pharmacology of Anesthetic Agents

- Safety Guidelines for local anesthesia
  1. Aspirate carefully before injecting to reduce the risk of unintentional intravascular injection.
  2. Inject slowly! A maximum rate of 1 minute per cartridge.
     - For safety, efficacy, and comfort!
  3. Monitor the patient for unusual reactions both during and after the injection.

Kanaa MD et al, *Speed of injection influences efficacy of inferior alveolar nerve blocks: A double-blind randomized controlled trial in volunteers,* J of Endodont, Vol 32 No 10, Oct 2006

Pharmacology of Anesthetic Agents

- Safety Guidelines for local anesthesia (contd.)
  4. Select the anesthetic agent and whether to use it with or without a vasoconstrictor based upon the duration of anesthesia needed for the planned procedure.
  5. Use the minimum amount of anesthetic solution that is needed to achieve adequate anesthesia to keep the patient comfortable throughout the procedure.

Pharmacology of Anesthetic Agents

- Safety Guidelines for local anesthesia (contd.)
  6. An additional guideline useful for the majority of medically complex patients is to reduce the amount of vasoconstrictor containing anesthetic to no more than 2 cartridges if possible.
     - If additional volume of anesthetic solution is required, consider switching to a plain, non-vasoconstrictor containing agent.

Troubleshooting Anesthesia

- The tooth is only <u>partially</u> numb!
- Or the tooth is numb, but duration is short and/or anesthesia is not profound
- Solution: give a second injection in the same site <u>with a different anesthetic agent</u>
  - Increases the volume at a correct site
  - Addresses patient sensitivity variations to anesthetic agents
  - There is no contraindication for combining any of the amide anesthetic agents
  - If a different anesthetic, or combination of anesthetics, is found to work better for a patient, <u>record that fact</u> and start with that anesthetic at the next appointment

Troubleshooting Anesthesia

- There is no contraindication for combining any of the amide anesthetic agents
  - However, all of the amide anesthetics are additive in dosage,
  - Therefore, you should not exceed the maximum safe dosage for the agent with the highest concentration.

Jong RH & Bonin JD, *Mixtures of local anesthetics are no more toxic than the parent drugs*, Anesthes, Vol 54 No 3, 1981

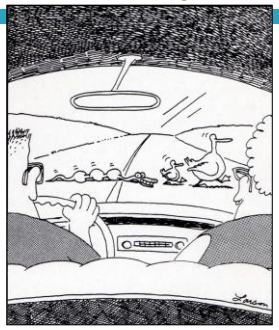
Pharmacology of Anesthetic Agents

- Local anesthetic dosage
  - Calculating dosage: For adults
  - 150 lb. adult (FDA approved max. dosage):
    - 2% lidocaine w/epi = 13 cartridges maximum
    - 4% prilocaine = 8 cartridges maximum
    - **Lidocaine & prilocaine together = 8 cartridges maximum**
    - 4% articaine = 7 cartridges maximum
    - **Lidocaine & articaine together = 7 cartridges maximum**
    - **For 70 lb. child, lidocaine & articaine together = 1.94 max**

Use of nitrous oxide/oxygen analgesia/anxiolysis does <u>not</u> require reduction of local anesthesia dosage

Pharmacology of Anesthetic Agents

- Troubleshooting
  - Summation of the amide anesthetics increases the risk of toxicity
  - Keep count!



Pharmacology of Anesthetic Agents

- Treating local anesthetic complications
  - One more suggestion:

In severely immunocompromised patients, an antiseptic rinse such as chlorhexidine prior to injection can reduce the risk of infection from the injection – a risk that is normally very low.

It's the thought that counts!

ARE 4% ANESTHETIC SOLUTIONS SAFE?

The Controversy Surrounding Articaine and Prilocaine

4% Dental Anesthetic Agents

Articaine (Septocaine, Zorcaine, Articadent)

- Released in the U.S. in 2000
  - Released in Europe in 1975 (Germany), and in Canada in 1983

Prilocaine (Citanest & Citanest forte)

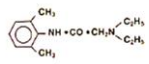
- Released in the U.S. in 1965
  - Released in Europe in 1960, Canada shortly thereafter

4% Dental Anesthetic Agents

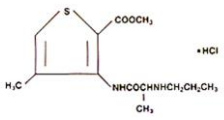
- Articaine is a unique "hybrid" amide anesthetic:
  - Contains a thiophene ring rather than a benzene ring – increases lipid solubility
  - Contains <u>both</u> ester and amide chemical groups

PROCAINE

LIDOCAINE



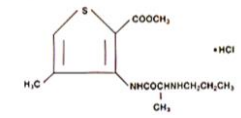
ARTICAINE



4% Dental Anesthetic Agents

- Articaine is a unique "hybrid" amide anesthetic:
  - Classified as an amide agent because it has the low allergenicity rate of other amides
  - Ester group means it is metabolized in both the bloodstream and the liver
  - Shorter plasma half-life potentially reduces risk of toxicity

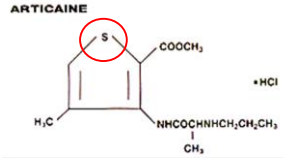
ARTICAINE



4% Dental Anesthetic Agents

- Articaine anesthetic:
  - One reason for the delay in releasing articaine in the U.S. was the presence of **sulfur** in the thiophene ring
  - There have been no adverse reactions reported

ARTICAINE



Attributes of Articaine

1. Fast onset
   - 1 to 6 minutes
2. Greater diffusion/penetration
   - Often obtain adequate anesthesia with infiltrations alone
3. More profound anesthesia
4. Greater success
   - With hard to anesthetize patients
   - Fewer missed blocks

   Clinical Research Associates, June 2001
5. Low allergenicity
   - Amide characteristic
6. Rapid metabolism → reduced risk of toxicity
   - Ester characteristic
   - Half-life in bloodstream 27 minutes (lidocaine 90 minutes)

Potential for Nerve Injury

In 1995, Haas DA & Lennon D published:

A 21 year retrospective study of reports of paresthesia following local anesthetic administration, J Can Dent Assoc, Vol 61 No 4

Articaine (Septocaine) and prilocaine (Citanest) were more likely to be associated with paresthesia injuries compared with other anesthetics,

and this was statistically significant when compared to the distribution of use.

Potential for Nerve Injury

- Focused only on reports of paresthesia
  - "All forms of altered nerve sensation"
- All cases involving surgery were excluded (304)
  - 143 paresthesias "from injection alone"
  - Average = 6.8 paresthesias per year
    - High = 20 (1990); low = 0 (1973 & 1979)

Haas DA & Lennon D, *A 21 year retrospective study of reports of paresthesia following local anesthetic administration*, J Can Dent Assoc Vol 61 No 4, 1995

Potential for Nerve Injury

- All 143 paresthesias in mandibular arch
  - 92 involved tongue; 42 lower lip; 9 both
- Number of reported cases low until 1984, then gradually increased
  - Articaine introduced in Canada in 1983
- 102 cases where anesthetic(s) used were known

Articaine	49.0%	Lidocaine	4.9%
Prilocaine	42.2%	Mepivacine	3.9%

Haas DA & Lennon D, *A 21 year retrospective study of reports of paresthesia following local anesthetic administration*, J Can Dent Assoc Vol 61 No 4, 1995

Potential for Nerve Injury

- In 1993, 14 paresthesias occurred from an estimated 11,000,000 injections
  - Incidence of 1 paresthesia/785,000 injections
- Of the 14 paresthesias

  10 were with articaine, 4 with prilocaine
  - Probability of paresthesia using articaine = 2.27/million injections
  - Probability of paresthesia using prilocaine = 1.7/million injections

Haas DA & Lennon D, *A 21 year retrospective study of reports of paresthesia following local anesthetic administration*, J Can Dent Assoc Vol 61 No 4, 1995

Potential for Nerve Injury

- Conclusions:
  - Articaine (Septocaine) and prilocaine (Citanest) were more likely to be associated with paresthesia injuries compared with other anesthetics
  - This was statistically significant when compared to the distribution of use
  - **Although it can occur, the risk of paresthesia from injection itself is <u>extremely low</u>**
  - **This extremely low risk does not warrant advising every patient prior to injection**

Haas DA & Lennon D, *A 21 year retrospective study of reports of paresthesia following local anesthetic administration*, J Can Dent Assoc Vol 61 No 4, 1995

Potential for Nerve Injury

Clinical Research Associates, in a study of 13,000 patient treatments by 94 dentists using articaine, reported 2 paresthesias.

- Both were associated with "mandibular" blocks
- Both resolved: Incidence = 0.03%

Clinical Research Associates Newsletter, June 2001

CRA follow-up 2005: 73% of articaine paresthesias were with "mandibular" regional nerve block injections

Clinical Research Associates Newsletter, June 2005

Potential for Nerve Injury

In a second publication by Haas and Gaffen using the same source:

- 182 paresthesias from 1999 to 2008
  - 180 associated with the inferior alveolar nerve block
    - 172 inferior alveolar block alone
    - 8 inferior alveolar block combined with 1 or more other injections
  - Incidence of 1/609,000 injections

Gaffen AS & Haas DA, *Retrospective review of voluntary reports of nonsurgical paresthesia in dentistry,* J Can Dent Assoc, Vol 75 No 8, October 2009

Potential for Nerve Injury

From the U.S. FDA Adverse Event Reporting System data:

- 248 paresthesias from 1997 to 2008
  - 94.5% associated with the inferior alveolar nerve block
    - Articaine associated injuries 3.6 times greater than expected
    - Prilocaine associated injuries 7.3 times greater than expected

Garisto et al, *Occurrence of paresthesia after dental local anesthetic administration in the United States,* J Am Dent Assoc, Vol 141, July 2010

If Injury Does Occur

- Anesthesia-induced nerve injuries are VERY rare (Temporary 0.15 – 0.54%; permanent 0.0001-0.01%)

Hillerup S, Jensen R, *Nerve injury caused by mandibular block analgesia,* Int J Oral Maxillofac Surg Vol 35, 2006

- Most paresthesias are reversible, resolving within 2 to 8 weeks
- Mandibular nerve injuries are far more common than maxillary
  - The vast majority of nerve injuries are associated with the conventional IA block injection technique

Nerve Paresthesia Injury

- Theories of causes:
  1. Injury due to direct contact of the needle with the nerve (traumatic injury)
  2. Injury due to direct contact of the anesthetic solution with the nerve (toxicity injury)
  3. Injury due to hematoma within the nerve sheath or in close proximity to the nerve (compression injury)
  4. Injury due to stretching of the nerve (morphology injury)*

Pogrel MA et al, *Nerve damage associated with inferior alveolar nerve blocks,* J Am Dent Assoc, Vol 126, 1995

* Mason DA, *Lingual nerve damage following lower third molar surgery,* Int J Oral Maxillofac Surg, Vol 17, 1988

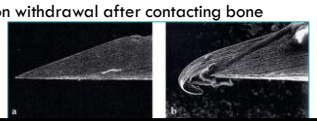
Nerve Paresthesia Injury

- Theories of causes:
  1. Injury due to direct contact of the needle with the nerve (traumatic injury)
- Incidence of "electric shock" injection:
  - Occurs once every one to two weeks in "average" practices
  - Approximately 8% of these result in some form of paresthesia
  - Incidence of permanent paresthesia is very low from these injections

Pogrel MA et al, *Nerve damage associated with inferior alveolar nerve blocks,* J Am Dent Assoc, Vol 126, 1995

Nerve Paresthesia Injury

- Theories of causes:
  1. Injury due to direct contact of the needle with the nerve (traumatic injury)
     - Experiments have shown that the needle will usually pass between nerve fasicles
     - Blunt injury may occur if the nerve is pinned against bone
     - A blunted, barbed needle tip may injure the nerve upon withdrawal after contacting bone



Meechan, Practical Dental Local Anesthesia, *Quintessence,* 2002

Nerve Paresthesia Injury

- Theories of causes:
  2. Injury due to direct contact of the anesthetic solution with the nerve (toxicity injury)
     - All agents are neurotoxic, however, the higher the concentration, the higher the risk of causing neurotoxicity
     - Injury correlation with anesthetic agent

	Lido	Mepiv	Prilo
US usage	62%	23%	13%
Injuries	48%	5%	47%

Pogrel MA & Thamby S, *Permanent nerve involvement resulting from inferior alveolar nerve blocks*, J Am Dent Assoc, Vol 131, 2000

Nerve Paresthesia Injury

- Theories of causes:
  2. Injury due to direct contact of the anesthetic solution with the nerve (toxicity injury)
     - All agents are neurotoxic, however, the higher the concentration, the higher the risk of causing neurotoxicity
     - Injury correlation with anesthetic agent

	Lido	Mepiv	Prilo	Arti
US usage	54%	15%	6%	25%
Injuries	35%	0%	30%	30%

Articaine + lidocaine, prilocaine + lidocaine, bupivacaine: <2% each

Conclusion: Prilocaine appears to have the highest incidence of injury; articaine less risk than prilo.

Pogrel MA, *Permanent nerve damage from inferior alveolar nerve blocks – an update to include articaine*, J Calif Dent Assoc, Vol 36 No 4, April 2007

Nerve Paresthesia Injury

- Theories of causes:
  2. Injury due to direct contact of the anesthetic solution with the nerve (toxicity injury)

It is noteworthy that in Denmark, where prilocaine is marketed as a 3% solution, 2 studies have linked paresthesia to 4% articaine use, but not to prilocaine use.

Gaffen AS & Haas DA, *Retrospective review of voluntary reports of nonsurgical paresthesia in dentistry*, J Canadian Dent Assoc, Vol 75 No 8, October 2009

Nerve Paresthesia Injury

- The rapid breakdown of articaine and the apparent inactivity of its metabolites imply that articaine is a safer local anesthetic agent than other available agents.
- Two very important points must be emphasized:
  1. Articaine, like lidocaine, has a maximum dose of 3.2 mg/lb for healthy adults
  2. Articaine, like prilocaine, is a 4% solution; patients will tolerate fewer cartridges as compared with a 2% solution*

Isen DA, *Articaine: Pharmacology and clinical use of a recently approved local anesthetic*, Dentistry Today, Vol 19 No 11, Nov 2000

*Articaine has 72 mg of anesthetic/cartridge; lidocaine has 36 mg of anesthetic/cartridge

Nerve Paresthesia Injury

- Local anesthetic dosage
  - FDA approved max. dosage for 150 lb. adult:
    - 2% lidocaine w/ epi = 13 cartridges
    - 4% prilocaine = 8 cartridges
    - 4% articaine = 7 cartridges
- To reduce the risk of nerve injury when using prilocaine (Citanest) or articaine (Septocaine):
  1. Inject less, usually about half the dosage, than for lidocaine or mepivacaine

Wynn RL et al, *Paresthesia associated with local anesthetics: A perspective on articaine*, General Dentistry (Journal AGD), Nov/Dec 2003

Nerve Paresthesia Injury

- To reduce the risk of nerve injury when using prilocaine (Citanest) or articaine (Septocaine):
  1. Inject less, usually about half the dosage, than for lidocaine or mepivacaine

Wynn RL et al, *Paresthesia associated with local anesthetics: A perspective on articaine*, General Dentistry (Journal AGD), Nov/Dec 2003

  2. Inject that reduced volume more slowly – about twice as long as the rate with lidocaine or mepivacaine – particularly with the inferior alveolar nerve block technique

Potential for Nerve Injury

What is the most likely cause of injury?

- One single cause is unlikely
- It appears that it may be the higher dose of drug (neurotoxicity) combined with a mechanical insult that predisposes the nerve to injury.

Gaffen AS & Haas DA, *Retrospective review of voluntary reports of nonsurgical paresthesia in dentistry*, J Canadian Dent Assoc, Vol 75 No 8, October 2009

- Use of higher concentration anesthetic solutions may be a factor, but is clearly ***not*** the exclusive cause of nerve injury.

Renton T et al, *Trigeminal nerve injuries in relation to the local anaesthesia in mandibular injections*, Brit Dent J, Vol 209 No 9, 2010

Nerve Paresthesia Injury

- To reduce the risk of nerve injury when using prilocaine (Citanest) or articaine (Septocaine):
  - 75 – 95% of all paresthesia injuries from injections are with the inferior alveolar block injection

3. Due to apparent potential neurotoxicity injury, **prudent clinicians** may consider avoiding use of high-concentration (4 percent) anesthetic formulations for inferior alveolar nerve blocks in cases where there are viable alternatives.

Hillerup S et al, *Trigeminal nerve injury associated with injection of local anesthetics: Needle lesion or neurotoxicity*, J Am Dent Assoc, Vol 142(5), May 2011

Nerve Paresthesia Injury

- Theories of causes:

3. Injury due to hematoma within the nerve sheath or in close proximity to the nerve (compression injury)
   - Intraneuronal bleeding (hematoma) is neurotoxic
   - Compression may cause temporary loss of blood supply (ischemia) to part or all of the nerve distal to the injury site
   - May heal with fibrotic scar tissue producing permanent compression injury to the nerve distal to the injury site

Pogrel MA & Thamby S, *Permanent nerve involvement resulting from inferior alveolar nerve blocks*, J Am Dent Assoc, Vol 131, 2000

Nerve Paresthesia Injury

- Theories of causes:

4. Injury due to stretching of the nerve (morphology injury)

Mason DA, *Lingual nerve damage following lower third molar surgery*, Int J Oral Maxillofac Surg, Vol 17, 1988

   - Physical tearing of the nerve unlikely
   - Ischemic incident of stretched nerve possibility supported by studies of
     - General anesthesia vs. local anesthesia extraction cases – 5 fold greater injury rate

Brann CR et al, *Factors influencing nerve damage during lower third molar surgery*, Brit Dent Jour, Vol 186 No 10, May 1999

   - Histologic studies of structure of lingual vs. inferior alveolar nerve: fewer fascicles, more easily injured

Pogrel MA et al, *Lingual nerve damage due to inferior alveolar nerve blocks: A possible explanation*, J Am Dent Assoc, Vol 134, Feb 2003

Nerve Paresthesia Injury

- Prevention:

There is no guaranteed method to prevent nerve injuries due to injections.

Such injuries are not de facto indications of improper technique; they are a risk of carrying out intraoral injections.

Haas DA, *Localized complications from local anesthesia*, J Calif Dent Assoc, Vol 26 No 9, 1998

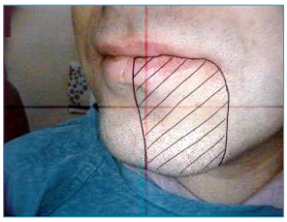
What is the influence of technique?

- Is a 4% anesthetic a wise choice with a conventional inferior alveolar nerve block?

Nerve Paresthesia Injury

- Management of nerve injuries:

1. See the patient immediately and document the injury carefully
   - Mark the area of abnormal sensation on a photograph
   - Use to compare area of affect at follow-up visits



Nerve Paresthesia Injury

- Management of nerve injuries:
  1. See the patient immediately and document the injury carefully
  2. Advise the patient that the symptoms may continue for an indefinite time
     - 85% (to 94%)* of injuries caused by injections recover spontaneously within 2 to 12 weeks
     - ~5% will recover within 9 months
     - Up to 10% of remaining injuries will likely never recover completely

Krafft TC & Hickel R, *Clinical investigation into the incidence of direct damage to the lingual nerve caused by local anesthesia,* J Craniomaxillofac Surg, Vol 22 No 5, 1994

*Smith MH & Lung KE, *Nerve injuries after dental injection: A review of the literature,* J Can Dent Assoc , Vol 72 No 6, 2006

Nerve Paresthesia Injury

- Management of nerve injuries:
  3. Contact the patient after 24 hours
     - If symptoms have improved, GREAT!
     - If no improvement, use careful judgment to set up intervals for follow-up visits

  Most injection-type injuries will show some sign of improvement within 2 – 4 weeks
  4. If no improvement after 2 – 4 weeks, consider referral to a nerve injury specialist.

Bagheri SC & Meyer RA, *When to refer a patient with a nerve injury to a specialist,* J Am Dent Assoc, Vol. 145(8), August 2014

Nerve Paresthesia Injury

- The No Fault Theory

  It is important to note that complications with oral injections are not always preventable, and their occurrence does not necessarily imply poor technique by the dentist or dental hygienist.

  Haas DA, *Localized complications from local anesthesia,* J Calif Dent Assoc, Vol 26 No 9, 1998

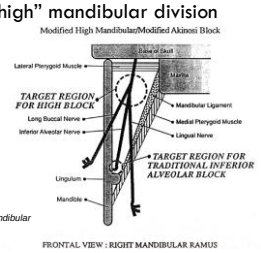
  Dentists and dental hygienists must carefully weigh the risks and benefits of the agent and the technique preferred for each clinical situation.

Anesthetic Agents

- A Practical Armamentarium:
  - 2% Lidocaine with 1:100,000 epinephrine
    - For one to two hour procedures and most block injections
  - 3% Mepivacaine plain
    - For short duration procedures or the rare "no vasoconstrictor" patient
  - 4% Articaine with 1:200,000 epinephrine
    - For infiltrations and "hard to anesthetize" patients
  - 0.5% Bupivacaine with 1:200,000 epinephrine
    - For prolonged pain control and long duration procedures
  - And some buffering agent and OraVerse anesthetic reversal agent

Mandibular Anesthesia

- The risk of nerve injury with administration of prilocaine (Citanest) or articaine (Septocaine) may be reduced by using "high" mandibular division block techniques
  - Gow-Gates technique
  - Vazirani – Akinosi technique



Wolfe SH, *The Wolfe nerve block: A modified high mandibular nerve block,* Dentistry Today, June/July 1992

WHAT ALTERNATIVES DO WE HAVE TO INJECTIONS?

Topical Anesthetics

Topical Anesthetics

- Penetrate 2 – 3 mm
- Adequate anesthesia for minor/superficial procedures
- Pre-injection anesthesia for all techniques

Jeske AH & Blanton PL, *Misconceptions involving dental local anesthesia, Part 2: Pharmacology*, Texas Dent J, 119(4), 2002

Meechan, Practical Dental Local Anesthesia, *Quintessence*, 2002

Topical Anesthetics

- Lidocaine 2 – 5% (amide)

Note: esters have better absorption through mucosa*

- Benzocaine ≤ 20% (ester)
- Tetracaine 0.2 – 2% (ester)
- Cetacaine (benzocaine 14%, butamben 2%, tetracaine HCl 2% - esters)
- Anbesol (benzocaine 10%, phenol 0.5%, alcohol 70% - ester)
- Compounded topicals: combine amide and ester
  (Profound, Profound PET (Profpet), TAC 20 percent Alternate, TheBestTopicalEver)

*Therefore, a decreased safety margin, especially with children

Topical Anesthetics

- Compounded formulas:
  - Profound – 10% lidocaine, 10% prilocaine, 4% tetracaine
  - Profound PET (Profpet) – same as above plus 2% phenylephrine, more viscous
  - TAC 20 percent Alternate – 20% lidocaine, 4% tetracaine, 2% phenylephrine
  - TheBestTopicalEver – 12.5% lidocaine, 12.5% tetracaine, 3% prilocaine, 3% phenylephrine

Are neither FDA regulated nor unregulated:

"Unapproved drug products whose benefits may not outweigh their risks"

Kravitz ND, *The use of compound topical anesthetics*, J Am Dent Assoc, Vol 138, October 2007

Topical Anesthetics

- Compounded formulas:
  - Maximum recommended dose is unknown
  - Narrow difference between optimal therapeutic dose and toxic dose level
  - Vary in composition, quality, and strength
  - Recommendation to avoid tissue sloughing:
    - Use only a small amount
    - Apply for maximum of 60 – 90 seconds
    - Rinse area thoroughly after application

Kravitz ND, *The use of compound topical anesthetics*, J Am Dent Assoc, Vol 138, October 2007

Topical Anesthetics

- Refrigerant application: Pain Ease (Gebauer, Cleveland)

  1,1,1,3,3-pentafluoropropane/1,1,1,2-tetrafluoroethane
  - 5 second application
  - FDA approved for oral tissues
    - Nonirritant to oral mucosa
    - Nontoxic if inhaled
  - Significant reduction in posterior palatal injection pain
    - Good evidence from medical studies
    - Limited dental anecdotal reports

Kosaraju A & Vandewalle KS, *A comparison of a refrigerant and a topical anesthetic gel as preinjection anesthetics: A clinical evaluation*, J Am Dent Assoc, Vol 140, Jan 2009

Topical Anesthetics

- EMLA = Eutectic Mixture of Local Anesthetics
  2.5% lidocaine, 2.5% prilocaine
  - EMLA cream/topical never approved for intraoral use in the U.S.
  - However, we do have…

Meechan, Practical Dental Local Anesthesia, *Quintessence*, 2002

Topical Anesthetics

- Oraqix
  2.5% lidocaine, 2.5% prilocaine periodontal gel
  - Approved for intraoral use
  - 30 second onset
  - 20 minute duration (range 14 – 31 min.)

Topical Anesthetics

- Oraqix
  2.5% lidocaine, 2.5% prilocaine periodontal gel
  - 30 second onset
  - 20 minute duration (range 14 – 31 min.)
  - Typically, 1 cartridge/quadrant
  - 5 cartridges maximum

Topical Anesthetics

- Dyclone (Dyclonine HCl)
  - Currently commercially unavailable
    - Available from compounding pharmacies
  - 0.5%, or 1.0% DS
  - Apply with swab or as a diluted rinse
    - ~45ml for 1 minute (swish & spit)
  - Slow onset, 5 – 10 minutes
  - Duration ~30 minutes

WHAT OTHER TOOLS DO WE HAVE?

Alternative Devices

Computer-Controlled Delivery Systems

- The "Wand": Single Tooth Anesthesia (STA) system
  - Milestone Scientific
- The Comfort Control Syringe
  - Dentsply, Inc. (This device is no longer marketed)
- Objective is to deliver the anesthetic at a rate and pressure that is below the threshold of pain
  - Potentially pain-free injections
  - Reduced volumes of anesthetic injected

Slow Injection of Anesthetic Solutions

- Safety Guidelines for local anesthesia
  - Inject slowly! A maximum rate of 1 minute per cartridge
  - Computer-controlled anesthetic delivery systems:
    - The "Wand": Single Tooth Anesthesia (STA) system
      - Milestone Scientific
    - The Comfort Control Syringe (no longer marketed)
    - New: Calaject – just now being introduced
      - Aseptico
  - Objective is to deliver the anesthetic at a rate and pressure that is below the threshold of pain
    - Potentially pain-free injections
    - Reduced volumes of anesthetic injected

Computer-Controlled Delivery Systems

- The "Wand": STA
  - Can give all traditional injections
  - Safer PDL injections
  - Painless palatal injections

Can use for primary or secondary anesthetic injections
- Foot pedal controlled
- Aspiration enabled

Computer-Controlled Delivery Systems

- Calaject
  - Three injection modes
    - Intraligamentary/palatal
    - Infiltrations
    - Regional nerve blocks
  - Cartridge in handpiece
  - Standard needles
  - No disposables
    - Foot pedal controlled
    - Aspiration enabled
  - Handpiece cannot be sterilized

Computer-Controlled Delivery Systems

- The Wand STA system
- The Comfort Control Syringe

TABLE 1: PREPROGRAMMED INJECTION RATES

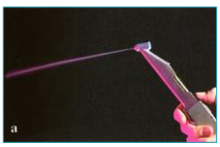
Injection Technique Selection	Injection Rate (cc/sec)	Typical	Typical
Block	0.020		
Infiltration	0.017		
Palatal	0.008	Full cartridge	3 min
PDL	0.007	.2cc per root	30 sec per root
Intraosseous	0.020	.9cc	45 sec

NO! YES!

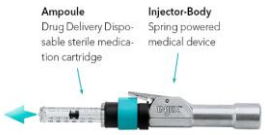
(Total Injection Volume and Time are not preset and depend on the clinician manually stopping the injection. The "Injection Technique" selections named on the [redacted] are intended only to be a convenient guide to selecting an injection rate. Your clinical judgement should always prevail in making that selection.)

Needleless Injectors

- Pressure injectors
  - 2 – 4+ mm depth of penetration
  - Good for infiltrations only
  - Higher incidence of intravascular injection?



Meechan, Practical Dental Local Anesthesia, *Quintessence*, 2002



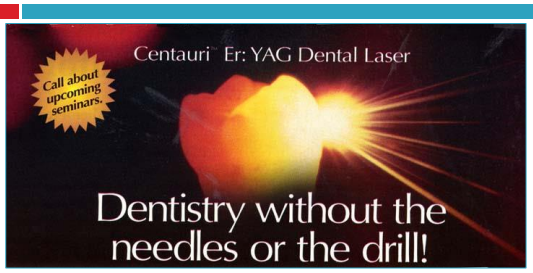
INJEX needleless injector system

Needleless Injectors

- New Product:
  NumBee needleless infiltration tip

1. No PDL tissue penetration; anesthetic solution is dripped into the sulcus
2. Tip is designed to be angled from 0° to 90°
3. Risk of post-operative discomfort greatly reduced
4. Risk of injury to bone, developing teeth, etc. eliminated
5. 60 second onset; about 35 – 40 minutes duration with less anesthetic solution

This was the promise…



We are closer…

Laser Analgesia

- Erbium (Er,Cr:YSGG) lasers may be used for rapid tooth preparation of small lesions using low to high power settings (3 to 8 watts)
  - Direct analgesia: 3 to 4 watts, defocused with quick movements over the occlusal surface for 60 to 90 sec.
  - If inadequate patient comfort, 0.25 to 0.5 watts, defocused on the buccal surface with slow movements 6 mm from the surface for 90 seconds
- Low energy light results in generation of fewer nerve impulses per second, and a greater stimulus is required to initiate an action potential

Hendy J, *Understanding laser analgesia of tooth preparations with erbium lasers*, J Laser-Assisted Dent , Spring 2015

Laser Analgesia

- A similar technique with deciduous teeth achieves greater analgesia at lower power in less time
  - Probably due to thinner enamel and dentin layers
- Will have residual analgesia for about 20 to 30 seconds post-preparation of a small lesion
  - Use handpiece and bur or spoon excavator to complete decay removal
  - Always complete the prep with the laser to remove the smear layer
- Erbium lasers may also be used for soft tissue applications using 3 watts defocused for 90 seconds with constant small movements

Hendy J, *Understanding laser analgesia of tooth preparations with erbium lasers*, J Laser-Assisted Dent , Spring 2015

Reasons for Anesthetic Failures

1. Anatomical/physiological variations
2. Technical errors of administration
3. Patient anxiety
4. Inflammation and infection
5. Defective/expired solutions

"It'll take you a couple of days to get used to them."

What defines success?

"Adequate anesthesia to insure patient comfort for the duration of the procedure"

- Different for each procedure
- Different for each patient

"I'm your anesthetist and he's my 'back-up man'."

Keys to Success

- Anesthetic failures happen
- The "Three Strikes Rule"
  - 3 attempts at anesthesia, then stop
- It's not about "fault"
  - It's not the patient's fault
  - It's not your fault
  - Failures happen

Reschedule the patient!

Reasons for Anesthetic Failures

3. Patient anxiety

Anxiety lowers the threshold of pain.

Therefore, even non-painful stimuli are likely to be perceived as painful.

"Try to relax."

Keys to Success

3. Patient anxiety

   When patients sense that the dentist or dental hygienist is sincere in doing everything possible to insure the patient's comfort,

   they will relax!

Keys to Success

The No Fault Theory

It is important to note that complications with oral injections are not always preventable, and their occurrence does not necessarily imply poor technique by the dentist or dental hygienist.

"Hold still! I dropped my little mirror."

Haas DA, *Localized complications from local anesthesia*, J Calif Dent Assoc, Vol 26 No 9, Sept 1998

In Conclusion

It's the thought that counts