

# Quality Resource Guide

## Contemporary Local Anesthetics in Dental Practice

### Author Acknowledgements

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### Educational Objectives

On completion of this unit, the learner should be able to:

1. Name the five injectable amide-local anesthetics currently available in North America.
2. Discuss the difference between the metabolism of ester- and amide-type local anesthetics.
3. Define “*target organ*” and name the target organs for local anesthetics.
4. Describe the initial signs and symptoms of local anesthetic systemic toxicity.
5. List the benefits associated with buffering local anesthetic solutions.
6. Discuss the efficacy of phentolamine mesylate in decreasing the duration of soft tissue anesthesia.
7. Discuss the clinical characteristics of articaine HCL compared to those of other amide local anesthetics.

MetLife designates this activity for **1.0 continuing education credits** for the review of this Quality Resource Guide and successful completion of the post test.

The following commentary highlights fundamental and commonly accepted practices on the subject matter. The information is intended as a general overview and is for educational purposes only. This information does not constitute legal advice, which can only be provided by an attorney.

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## Introduction

Local anesthetics (LAs) are the major drug group preventing a propagated nociceptive impulse from reaching the brain where it would be interpreted as pain. They form the backbone of pain control techniques in dentistry. Deposited close to a nerve they will – in virtually all situations – provide profound anesthesia, allowing dental procedures to be completed painlessly.

Within the category of ‘healthcare providers,’ dentists are the prime users of LAs. More than 300 million dental LA cartridges are administered annually in the United States;<sup>1</sup> in Canada between 30 and 40 million.<sup>2</sup> Worldwide, it is conservatively estimated that 1.96 billion dental cartridges are administered annually.<sup>3</sup> Additionally, in many countries (such as India and China) large volumes of LA injections are administered from multidose vials. Used properly, LAs represent the safest and most effective drugs for the prevention and management of peri- and post-operative pain.

This Quality Resource Guide reviews the evolution and clinical characteristics of the five LAs available for dental use in North America; discusses the prevention, recognition, and management of local anesthetic systemic toxicity (LAST); assesses several significant recent advancements in dental LAs, including: the LA ‘ON switch’ – buffering; the LA ‘OFF switch’ – phentolamine mesylate (PM); and reviews articaine, the most recent addition to the dental LA armamentarium.

## The Drugs

The history of anesthesia starts with Horace Wells, a Connecticut dentist, who, in 1844, introduced nitrous oxide anesthesia, followed in 1846 with the introduction of ether by William TG Morton (DDS, MD).<sup>4</sup> In 1860, the chemist Albert Niemann isolated cocaine – the active ingredient in coca leaves<sup>5</sup> but it wasn’t until 1884 that a Viennese ophthalmologist, Carl Koller, working with Sigmund Freud, performed the first medical operation using cocaine as a topical anesthetic on a patient with glaucoma.<sup>6</sup> Later that same year, the American surgeon William Stewart Halsted, MD was the first to inject a LA – cocaine. The injection was the inferior alveolar nerve block (IANB).<sup>7</sup>

### Amino-ester local anesthetics – the ‘esters’

Local anesthetics became quite popular within both medicine and dentistry, but it was dentistry where their use became commonplace. LAs began to be synthesized (cocaine is the only naturally occurring LA) including procaine (1906) and tetracaine (1933). These LAs and other similar compounds belong to the chemical classification of amino-esters (commonly called ‘esters’). (Figure 1)

It wasn’t until 1925 that the dental cartridge was introduced, under the trademarked name, Carpule®.<sup>8</sup> The trademark expired in 2006.<sup>9</sup> Carpules no longer exist.

### Amino-amide local anesthetics – the ‘amides’

Astra Pharmaceuticals (Sweden), in 1948, introduced the first amino-amide (‘amides’) LA – lidocaine (Xylocaine®). Demonstratively more effective than the esters, lidocaine quickly became the most used LA in dentistry, both in the USA and worldwide. Other amides (articaine, bupivacaine, mepivacaine, and prilocaine) were later introduced, providing dentistry with an armamentarium of safe and effective LAs in various formulations with a range of durations of action.

In the dental profession today – almost everywhere – amides have replaced esters as the drugs of choice for pain control during dental procedures. The only ester used to any degree is benzocaine, the most common active ingredient in topical anesthetics.

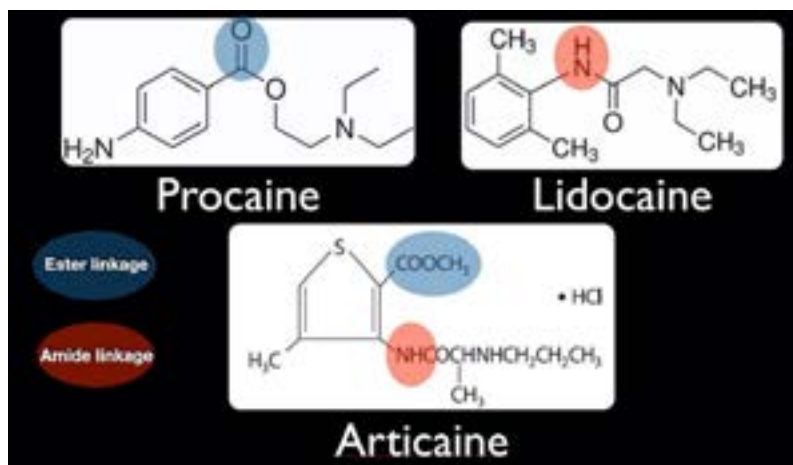
The addition of a vasoconstrictor to the LA solution increases both the depth and duration of anesthesia. Additionally, and perhaps most importantly, epinephrine decreases the plasma level of the LA, increasing the drug’s safety. With these benefits comes a significant increase in the duration of soft tissue anesthesia.

### Metabolism of local anesthetics

A significant difference between esters and amides is the pathway of their metabolic disposition (biotransformation, detoxification). It is important to understand that metabolism has no relevance to the clinical duration of a LA (nor any drug). The therapeutic action of a drug ends as it is redistributed from an area of high concentration at its site of action (a nerve for LAs) to other areas in the body where it does not exert a clinical effect.

The clinical action (anesthesia) of the LA is noted for as long as the drug remains within the affected nerve in a concentration high enough to block propagated nerve impulses. Just as a LA works by diffusing into a nerve from its site of deposition, a LA stops working by diffusing out of the nerve into the cardiovascular system (CVS). When the concentration of LA in the nerve falls below a threshold level, propagated pain impulses will again reach the brain where they are interpreted as pain. So, the process by which a drug stops working is termed ‘redistribution’ – it is redistributed from its target organ (e.g. nerve) to other places in the body where it has no clinical effect.

Figure 1 - Chemical formulas of ester (procaine); amide (lidocaine); and articaine



When a LA enters the CVS it is still pharmacologically active. As its blood level increases, it exerts clinical actions in its target organs (an area in the body where a drug exerts clinical actions). Target organs for LAs are (1) the brain (CNS); and (2) myocardium, both of which are depressed by LAs. The brain is appreciably more sensitive to elevated blood levels of LA than the myocardium.

### Local Anesthetic Systemic Toxicity (LAST)

Biotransformation of an ester LA into inactive chemicals occurs when it enters the CVS, being hydrolyzed by plasma esterases. What is known as elimination half-life is the time required for the blood concentration of a drug to decrease by 50%. At 6 half-lives, its blood concentration has decreased by 98.5% (assuming only one initial dose, ignoring any drug-drug interactions and assuming a healthy individual); a blood level well below the threshold for any clinical activity. For example, the elimination half-life of procaine (Novocain®) is 6 minutes. At 6 half-lives – 36 minutes – procaine has essentially been eliminated from the body.

Amide LA biotransformation is more complex, occurring primarily in the liver (by hepatic microsomal enzymes). Virtually the entire metabolic process for lidocaine, mepivacaine, prilocaine and bupivacaine occurs in the liver. The elimination half-life of lidocaine, mepivacaine, and prilocaine is approximately 90 minutes.<sup>10</sup> Articaine, though classified as an amide is, in actuality, a hybrid ester–amide molecule (Figure 1). About 90% to 95% of articaine’s metabolism occurs through plasma esterases (similar to the ester LAs).<sup>11</sup> Articaine’s half-life is 20 to 27 minutes in both adult and geriatric patients,<sup>11,12</sup> and 18.5 to 23.6 minutes in a pediatric patient.<sup>13</sup> Table 2 compares the elimination half-lives of ester and amide local anesthetics.

#### Local anesthetic systemic toxicity (LAST)

Used properly, LAs are extremely safe and effective drugs. However, all-too-many instances of serious adverse events associated with their

Table 1 - Local anesthetic formulations available in North America (February 2024)<sup>10</sup>

| Drug (formulations)                                   | Duration*                    | Mgs/cartridge+ | MRD# mg/kg (absolute maximum mg)                 |
|---|------------------------------|----------------|--|
| Articaine<br>4% + epi 1:100,000<br>4% + epi 1:200,000 | Intermediate<br>Intermediate | 72<br>72       | 7.0 (no absolute maximum listed in USA)          |
| Bupivacaine<br>0.5% + epi 1:200,000                   | Long                         | 9              | No mg/kg listed in USA (90);<br>Canada 2.0 (200) |
| Lidocaine<br>2% + epi 1: 50,000<br>2% + epi 1:100,000 | Intermediate<br>Intermediate | 36<br>36       | 7.0 (500)  |
| Mepivacaine^<br>3%                                    | Short                        | 54             | 6.6 (400)  |
| Prilocaine<br>4%<br>4% + epi 1:200,000                | Short<br>Intermediate        | 72<br>72       | 8.0 (600)  |

\* Short: pulpal anesthesia ~30 minutes; Intermediate: ~60 minutes; Long: >90 minutes  
 + Dental cartridges contain approximately 1.76 mL of local anesthetic solution,<sup>10</sup> though some are labeled as: “minimum content of each cartridge 1.7 mL” while others are labeled: “minimum content of each cartridge 1.8 mL”  
 # Maximum recommended dose, United States Food & Drug Administration.  
 epi: epinephrine  
 ^ Mepivacaine 2% with levonordefrin (Neo-Cobefrin®) is no longer marketed.

Table 2 - Elimination half-lives of local anesthetics

| Drug                       | Half-life (minutes) | 6x half-life (minutes) |
|----------------------------|---------------------|------------------------|
| Procaine<br>Chloroprocaine | 6                   | 36                     |
| Tetracaine                 | 20                  | 120                    |
| Articaine                  | 27                  | 162                    |
| Cocaine                    | 42                  | 252                    |
| Prilocaine                 | ~70                 | ~490                   |
| Lidocaine                  | ~90                 | ~540                   |
| Mepivacaine                | ~90                 | ~540                   |
| Bupivacaine                | ~210                | ~1,260                 |

Ester – blue, Amide – yellow, Articaine - green

administration are noted, both in professional literature<sup>14,15</sup> and the lay media.<sup>16</sup> Chicka *et al.*, in a review of 17 adverse anesthesia events, noted that 41% involved LAST. The average age of the affected patient was 3.6 years.<sup>14</sup> Gaiser, *et al.*,

observed that 36% of 14 dental office deaths in the United Kingdom involved LAST.<sup>15</sup> In Italy, Minoli *et al.*, reported on 36 fatal events in dental offices; 47% had a temporal relationship between injection of LA and the death of the patient.<sup>16</sup>

**LAST – Prevention**

The two most common etiologies of LAST are (1) rapid intravascular administration, and (2) administration of an excessive dose of LA. One cartridge of any LA formulation administered intravascularly in less than 15 seconds will produce a rapid and significant elevation in LA blood level, leading to the immediate onset of tonic-clonic seizure activity and/or cardiovascular collapse.

LAST from intravascular administration can almost always be prevented by:

- 1) performing two (2) aspiration tests before deposition of the LA, rotating the needle bevel ~45 degrees between the tests (if negative x2 the likelihood of intravascular injection is essentially zero);
- 2) slow administration of LA. The ideal rate of administration of any injectable drug is 1 mL/minute. As many dentists admit to injecting LA more rapidly,<sup>17</sup> it is recommended that a 1.8 mL cartridge be administered over at least one minute.<sup>18</sup>

However, the most common LAST scenario involves administering an excessive LA dose to a child weighing less than 30 kg.<sup>14,19,20</sup> (see Table 3) There exist almost no rational clinical scenarios for the administration of LA in all four quadrants at one time in lighter weight patients. Additionally, the volume of LA required for pain control in younger children is but a fraction of that in an adult.<sup>21</sup>

Considering that all injectable LAs are inherently vasodilators, it is recommended that whenever treating a patient weighing less than 30 kg in more than one quadrant, the LA should contain a vasoconstrictor. Vasoconstrictors increase the depth and duration of pain control, but more importantly, they produce a lower LA blood level, increasing the drug's safety.<sup>22</sup>

As de Jong stated in his classic textbook on local anesthesia: *“the brain responds to the concentration of local anesthetic delivered to it by the bloodstream and cares not at all how the drug got into the blood.”*<sup>23</sup>

**LAST – Recognition**

As LA blood level increases in the brain, clinical signs and symptoms (S&S) are noted. **Figure 2** illustrates the progression seen when an overly large dose of a ‘plain’ LA (3% mepivacaine or 4% prilocaine) has been administered ‘correctly’ – not intravascularly. In most instances of LAST, initial S&S involve the CNS and include a metallic taste, dizziness, tinnitus (‘ringing’ in the ears), and visual disturbances. Where an excessively large dose of a ‘plain’ LA has been administered, its seizure threshold will be exceeded approximately ten minutes following its administration. Tonic-clonic seizure activity is commonly observed with LAST.

Symptoms associated with myocardial depression usually appear after seizure activity has been

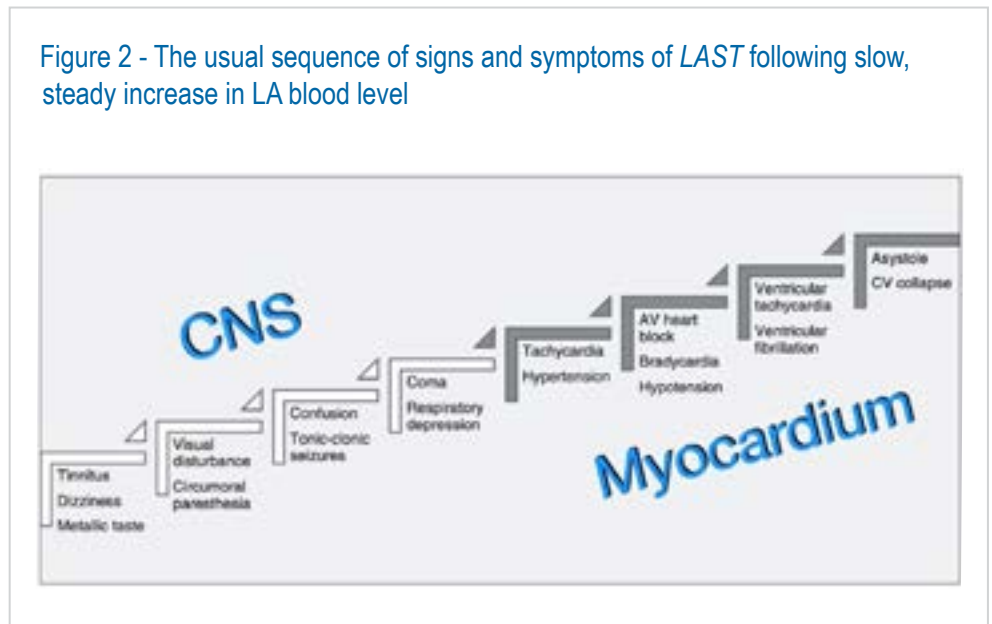
noted and most commonly when the LA has been administered directly into the CVS. S&S of LAST following intravascular administration appear within seconds; starting with seizure activity, oftentimes leading rapidly to ventricular dysrhythmias (ventricular fibrillation, cardiac arrest).

**LAST – Management**

Management of LAST follows the **P→C→A→B→D** protocol\* for all medical emergencies.<sup>24</sup> Emergency medical services (911) should be summoned immediately.

\* **P=Positioning; C=Circulation; A=Airway; B=Breathing; D=Definitive Care**

In the presence of seizure activity, preventing injury is paramount. The seizure will cease when



**Table 3 - Factors adding to increased risk of LAST in younger patients**

**The majority of local anesthetic overdose cases occur in general dentistry offices and involve the following:**

1. Well-behaved child weighing less than 30 kg
2. Treatment plan – all four quadrants treated with local anesthetic at one visit
3. Local anesthetic administered is “plain” (no vasoconstrictor)
4. Full cartridge (1.8 mL) administered with each injection
5. Local anesthetic administered to all four quadrants at one time
6. Exceeding the maximum dose based on the patient’s body weight

the LA has been redistributed and its blood level in the brain falls below its seizure threshold. In most instances – when a patent airway is maintained (e.g. head-tilt, chin-lift) – seizures last for about 1 minute.<sup>24</sup> The absolute importance of airway maintenance during and following the seizure is illustrated in **Figure 3**. Absent a patent airway the LA seizure threshold decreases significantly – 53% for lidocaine; 44% for mepivacaine – increasing both the duration and intensity of the seizure.

Data indicate that if LA-induced seizures are brief and well managed, no permanent neurological or behavioral sequelae will occur.<sup>25</sup>

### Recent Advances in Dental Local Anesthesia

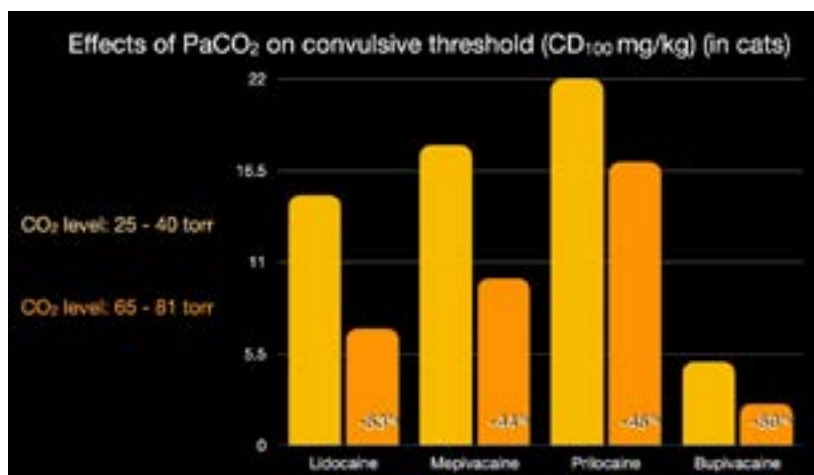
#### Buffering local anesthetic solutions – The local anesthetic ‘ON SWITCH’

LAs containing a vasoconstrictor are quite acidic – pH ranging from 3.0 to 4.0.<sup>26</sup> The pH decreases rapidly within the first 3 months of manufacture (original pH ~5.0), eventually plateauing at ~3.5 over the 24-month shelf life of the cartridge. Injection of this acidic solution is associated with a ‘stinging’ or ‘burning’ sensation. The addition of a defined volume of 8.4% sodium bicarbonate to a dental cartridge raises its pH to approximately 7.35 to 7.4, producing a more comfortable injection experience for the patient. Additional benefits of buffering include: (1) significantly more rapid onset of pulpal anesthesia – onset of pulpal anesthesia following IANB in 1 minute 51 seconds with buffered lidocaine versus 6 minutes 37 seconds with unbuffered lidocaine;<sup>27</sup> more profound anesthesia;<sup>28</sup> and decreased post-injection soreness.<sup>27</sup> Though not all assessments of buffering have demonstrated these benefits, the author recommends buffering for all LA injections.<sup>29,30</sup>

#### Phentolamine mesylate – The local anesthetic ‘OFF SWITCH’

The addition of a vasoconstrictor to the LA solution increases the depth of anesthesia as well as the duration. With these benefits comes a significant increase in the duration of soft tissue anesthesia. Self-inflicted soft tissue injury – biting

Figure 3 - Effects of hypercarbia (elevated CO<sub>2</sub>) on the convulsive threshold of local anesthetics



or chewing of the numb lip or tongue – is not uncommon in young patients,<sup>31</sup> as well as in developmentally disabled adults.

Phentolamine mesylate (PM), an alpha-adrenergic antagonist (e.g., vasodilator), injected at the end of a dental procedure into the site of previous LA administration, significantly decreases the duration of soft tissue anesthesia.<sup>32</sup> Following IANB, at 60 minutes 41% of subjects receiving PM had a complete loss of anesthesia of the lip compared to 7.4% of subjects receiving placebo.<sup>32</sup> At 90 minutes, the results were 70.5% versus 13.1%. (**Table 4**)

A ‘quality of life’ drug, PM is appropriate for any patient desiring a return to ‘normal’ sensation rapidly – including business people, those attending social gatherings, or lunch or dinner engagements, in addition to young children and developmentally disabled persons. Phentolamine mesylate is FDA-approved for patients 3 years of age and older.<sup>33</sup>

#### Articaine hydrochloride

In June of 2000, the FDA approved articaine HCl (4% with 1:100,000 epinephrine) for use in the USA. Articaine is the second most used dental LA, worldwide and along with lidocaine

Table 4 - Complete loss of anesthesia

| Time (minutes) | Upper lip    |         | Lower lip    |         |
|----------------|--------------|---------|--------------|---------|
|                | Phentolamine | Control | Phentolamine | Control |
| 30             | 26.7%        | 1.7%    | 17.2%        | 0.8%    |
| 60             | 59.2%        | 11.7%   | 41.0%        | 7.4%    |
| 90             | 75.0%        | 25.0%   | 70.5%        | 13.1%   |
| 120            | 88.4%        | 45.8%   | 81.1%        | 29.5%   |

is the most used in the United States (43% for each [4th quarter 2023]).<sup>34</sup> In 2005, articaine 4% with 1:200,000 epinephrine was FDA approved. Both formulations are categorized as intermediate duration. (Table 1)

A considerable body of research has demonstrated articaine's clinical superiority over other amide LAs.<sup>35,36</sup> There are two pharmacologic reasons for this: (1) a shorter elimination half-life, and (2) increased lipid-solubility.

**Shorter elimination half-life:** Articaine is a hybrid molecule – possessing both amide and ester linkages. (Figure 1) As discussed above, the half-life of articaine (~27 minutes) is shorter than that of other amide LAs (~90 minutes), conferring it with several advantages, including – in this authors opinion: decreased risk of LAST from the administration of higher doses of LA, thereby making it a preferred LA in lighter-weight patients,<sup>37</sup> pregnant and nursing patients,<sup>38</sup> as well as being more effective in achieving successful pain control in endodontically-involved teeth.<sup>28,39</sup>

**Greater lipid-solubility:** For a local anesthetic to diffuse through the lipid-rich nerve membrane it must be lipid soluble. Articaine – containing a thiophene ring is more lipid soluble than other amide local anesthetics (containing a benzene ring).<sup>40</sup> Suggested for mandibular molars: Following IANB

– regardless of the LA used for the block – infiltrate ½ to 2/3 of a cartridge of articaine into the buccal fold adjacent to the molar(s) being treated.<sup>41-43</sup> Kanaa *et al.*, demonstrated this protocol increased mandibular 1st molar anesthesia to 91.7% from 55.5%.<sup>43</sup> For extraction of maxillary permanent teeth without need for palatal injection: Gholami *et al.*, compared the ability of lidocaine and articaine to provide palatal soft tissue anesthesia adequate to painlessly extract a permanent tooth following buccal infiltration (BI).<sup>44</sup> At 6 minutes following BI of 1.8 mL, 1.3% of lidocaine patients had adequate palatal soft tissue anesthesia, while 82.7% of those receiving articaine BI had adequate palatal anesthesia. There was no difference in efficacy between anterior, premolar, and molar teeth.

**The Paresthesia 'Controversy':** Following articaine's introduction into Canada (1985) and later in the USA (2000), there was considerable discussion regarding a possible link between 4% LAs (articaine and prilocaine) and increased risk of paresthesia following IANB.<sup>46,47</sup> Paresthesia remains a topic of discussion, though recent laboratory research and clinical meta-analyses have concluded that articaine is as neurotoxic as other commonly used LAs, not more so.<sup>48-50</sup> Indeed, there exists no scientific evidence that articaine is more neurotoxic.

All LAs are potentially neurotoxic. Paresthesia (some degree of sensory dysfunction persisting more than 24 hours following injection), albeit extremely rare, can and does occur. Reported frequencies of permanent nerve injury (defined as symptoms remaining at nine months) following IANB vary considerably from 1:26,762 to 1:13.8 million injections.<sup>51</sup> Management of paresthesia is detailed in an article by Blanton.<sup>52</sup>

## Summary

Local anesthetics form the backbone of pain control techniques in dentistry. Used properly, local anesthetics are the safest and most effective drugs for the prevention and management of peri- and post-operative pain. Care must be taken whenever LAs are used to ensure their proper delivery and to avoid excessive dosing. The ability to prevent, recognize and effectively manage any adverse events associated with their administration is essential to their safe use. The availability of buffering (the LA 'on-switch') and phentolamine mesylate (the LA 'off-switch') greatly enhance patient comfort both during and after dental procedures, as well as increasing the likelihood of successful pain control being achieved. Advantage can be taken of articaine's greater lipid-solubility by BI following IANB for mandibular molars and for palatal soft tissue anesthesia when extracting maxillary teeth.

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## POST-TEST

Internet Users: This page is intended to assist you in fast and accurate testing when completing the “Online Exam.” We suggest reviewing the questions and then circling your answers on this page prior to completing the online exam.

(1.0 CE Credit Contact Hour) Please circle the correct answer. 70% equals passing grade.

1. Which of the following is/are target organs for local anesthetics?
  - A. Lungs
  - B. Myocardium
  - C. Liver
  - D. CNS
  - a. A only
  - b. D only
  - c. B and C only
  - d. A and B only
  - e. B and D only
2. Which of the following local anesthetics has the **LONGEST** duration of pulpal anesthesia?
  - a. Lidocaine HCl 2% with epinephrine.
  - b. Bupivacaine HCl 0.5% with epinephrine.
  - c. Mepivacaine HCl 3% via infiltration.
  - d. Prilocaine HCl 4% via nerve block.
3. Which of the following local anesthetics has the **SHORTEST** duration of pulpal anesthesia?
  - a. Lidocaine HCl 2% with epinephrine 1:50,000.
  - b. Bupivacaine HCl 0.5% with epinephrine 1:200,000.
  - c. Mepivacaine HCl 3% via infiltration.
  - d. Prilocaine HCl 4% via nerve block.
4. The process by which the clinical action of local anesthetics ceases is:
  - a. Biotransformation
  - b. Redistribution
  - c. Detoxification
  - d. Amniocentesis
  - e. Metabolism
5. A primary concern when administering local anesthetics to a 20 Kg child is:
  - a. Self-inflicted soft tissue trauma.
  - b. Allergy to the local anesthetic.
  - c. Allergy to the vasoconstrictor.
  - d. Local anesthetic systemic toxicity.
6. What is the absolute MRD for lidocaine?
  - a. 300 mg
  - b. 400 mg
  - c. 500 mg
  - d. 600 mg
  - e. No MRD is listed for lidocaine
7. Tonic-clonic seizures occur when the cerebral blood level of the local anesthetic is “too high”. Tonic-clonic seizures resulting from local anesthetics are the result of the CNS-stimulant actions of the local anesthetic.
  - a. Both statements are TRUE
  - b. Both statements are FALSE
  - c. 1st statement is TRUE; 2nd statement is FALSE
  - d. 1st statement is FALSE; 2nd statement is TRUE
8. What is the effect of increased CO<sub>2</sub> blood levels on the duration of a local anesthetic-induced generalized tonic-clonic seizure?
  - a. Changes in CO<sub>2</sub> levels have NO effect on local anesthetic-induced seizures.
  - b. Increased CO<sub>2</sub> levels will shorten the duration of a local anesthetic-induced seizure.
  - c. Increased CO<sub>2</sub> levels will prolong the duration of a local anesthetic-induced seizure.
9. Which of the following local anesthetics is a hybrid ester-amide molecule?
  - a. articaine HCl
  - b. bupivacaine HCl
  - c. lidocaine HCl
  - d. mepivacaine HCl
  - e. procaine HCl
10. Buccal infiltration (BI) of \_\_\_\_\_ by a mandibular molar, or BI in the maxilla, has been demonstrated to significantly improve the effectiveness of IANB and palatal anesthesia for maxillary extractions
  - a. articaine
  - b. bupivacaine
  - c. lidocaine
  - d. mepivacaine
  - e. prilocaine



