Pharmacology of Local Anesthetics: Clinical Implications

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Introduction
Participants in this course will be introduced to evidence-based information related to basic mechanisms of pain, the pharmacology of local anesthetic agents, and factors to consider in selecting the most effective and least toxic local anesthetic agent for perioperative pain management.

Conflict of Interest Disclosure Statement
• Dr. Taifour reports no conflict of interest with this course.
• Dr. Terézhalmy has done consulting work for Procter & Gamble and has served on the dentalcare.com Advisory Board.

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**Overview**
Participants in this course will be introduced to evidence-based information related to the basic mechanisms of nociception; the pharmacology of local anesthetic agents (LAs); issues related to potency, onset and duration of action of LAs as factors to be considered in selecting a LA for perioperative pain management; reducing needle-insertion pain; reversing soft-tissue anesthesia; and precautions to consider before administering local anesthetic agents.

**Learning Objectives**
Upon completion of this course, the dental professional should be able to:
- Discuss the mechanism of nociception.
- Discuss the pharmacology of local anesthetic agents.
- Select the most effective and least toxic local anesthetic agent for perioperative pain management.
- Discuss technical issues, sterilization, and storage of local anesthetic agents.
- Discuss factors affecting needle-insertion pain and take preemptive action.
- Discuss and implement reversal of soft-tissue anesthesia.
- Discuss precautions related to the administration of local anesthetic agents.

**Introduction**
The most common complaint causing a person to seek the services of an oral healthcare provider is pain. Consequently, the primary obligation and ultimate responsibility of every clinician is to relieve pain. This requires an understanding of the complexity of pain, an appreciation for the factors that determine its expression in the clinical setting, the initiation of disease-modifying procedures (i.e., primary dental care), and the implementation of appropriate perioperative pharmacological strategies.

**Mechanism of Nociception**
Nociception or pain perception is the result of sensory detection, transduction, and neural transmission of noxious events to the central nervous system (CNS). The initial stimulus affects “high-threshold” primary afferent sensory neurons, i.e., free nerve endings called nociceptors located in superficial soma (skin, mucosa), deep soma (muscles, bone) and viscera (organs). Intense mechanical stimuli activate mechanoreceptors, while intense heat or cold activate thermal nociceptors.

However, chemical activators (e.g., protons, ATP, bradykinin), which directly excite primary afferent sensory neurons, are the most important stimuli. Other chemicals, known as sensitizing agents (e.g., prostaglandin E2), increase the sensitivity of nociceptors to chemical activators. Protons, from low extracellular pH associated with ischemia and inflammation, activate acid sensitive ion channels (ASICs) and transient receptor potential vanilloid ion channels (TRPV1, TRPV3).

High extracellular ATP levels associated with cell injury activate P2X ligand-gated channels and P2Y G-protein-coupled receptors. Bradykinins, associated with tissue damage and inflammation, activate G1-protein-coupled bradykinin B1 and...
B₁ receptors. B₁ receptors are expressed in response to bacterial lipopolysaccharides and inflammatory cytokines. Activation of B₁ receptors, which are expressed constitutionally in neurons, promotes the synthesis of prostaglandin E₂ (PGE₂). Activation of peripheral sensory terminals by noxious stimuli leads to intracellular sodium and calcium ion influx and neuronal depolarization (Figure 1). If the threshold for activation of voltage-sensitive sodium channels is reached, neuronal depolarization leads to action potential generation. There are six types of voltage-gated sodium channels, four of which are expressed uniquely in primary afferent sensory fibers and two of these only respond to high-threshold peripheral stimuli.

Incoming action potentials in the trigeminal/dorsal root complex activate pre-synaptic voltage-sensitive calcium channels, which leads to synaptic release of glutamate, and subsequent action potential generation in secondary neurons. Secondary afferent neurons project to the thalamus and synapse with tertiary afferent neurons. Tertiary afferent neurons project to the somatosensory cortex responsible for the localization of pain; and to the limbic system responsible for the emotional aspects of pain.

There are three groups of sensory fibers: groups A (A-α, A-β, A-γ, and A-δ), B, and C. Nociceptive information is conducted by myelinated A-δ and nonmyelinated C sensory neurons. Information via A-δ fibers arrives rapidly; i.e., first pain, which is perceived as sharp, bright, well-localized pain not particularly persistent, but immediately associated with tissue injury. Information via C fibers arrives slowly, i.e., second pain, which is perceived as dull, throbbing, burning, diffuse, and persistent.

Pharmacology of Local Anesthetics
Homeostatic mechanisms in excitable neuronal cells maintain a chemical gradient with high extracellular sodium and high intracellular potassium concentrations such that the inside of neuronal cells is electronegative (-50 to -90 mV) and the outside is electropositive. Nociceptive signals alter the distribution of these ions and briefly reverse electrical polarity, which leads to neuronal membrane depolarization that provides the energy to activate voltage-gated sodium channels. If the threshold for activation of voltage-gated sodium channels is reached, sodium ions flow into the cell and an action potential is generated. The duration of this inward sodium current is limited as the voltage-gated sodium channels close spontaneously behind the passing action potential. Following inactivation of voltage-gated sodium channels, Na/K ATPase pumps sodium out of the cells and the leak of potassium ions through passive ion channels restore the resting membrane potential.

![Figure 1. Activation of Peripheral Sensory Terminals.](image-source: Aminoshariae A, Terézhalmy GT. Pharmacology of analgesics: clinical considerations. January 6, 2014.)
Local anesthetics (LAs) reduce the amplitude and conduction velocity of action potentials in a reversible, dose-dependent manner. LAs’ sites of action are the voltage-gated sodium channels. They are large membrane proteins, which consist of a pore forming α-subunit and one or two β-subunits. The receptors for LAs are on the intracellular α-subunits. Consequently, to gain access to their receptors, LAs must diffuse across lipophilic neuronal membranes at the site of administration.

LAs cross biological membranes by passive diffusion. Since LAs are weak bases, in an aqueous environment they exist as a mixture of protonated or positively charged (ionized) and deprotonated or neutral (unionized) molecules. The ratio of ionized to unionized forms of a LA is predicated on its dissociation constant or pKa and the pH of the drug’s milieu, i.e., the environment at the site of drug administration. The pKa is that pH at which a drug is 50% ionized and 50% unionized.

Since only unionized molecules of drugs can translocate across biological membranes, the ionized LA molecules will be unable to reach their receptors or diffuse into the circulation and become trapped at the site of administration. This phenomenon is known as ion trapping. For example, when lidocaine with a pKa of 7.9 is deposited into an infected/inflamed site with a pH less than 7.9, more than 50% of its molecules become protonated and will be unable to diffuse across biological membranes.

If, however, sufficient numbers LA molecules can interact with voltage-gated sodium channels, the action potentials will be temporarily halted. Because of differential functional blockade predicated on the degree of myelination of the nerve fibers and the LAs’ concentration gradient, different fiber-types are blocked at different times. The general order of functional deficit progresses sequentially as follows: first pain, second pain, temperature, touch, proprioception, and finally motor functions.

Cocaine was the first recognized LA. Its addictive properties and toxicity, i.e., psychological and physical dependence, mood alteration, CNS and cardiac excitation, and intense vasoconstriction preclude its clinical use in dentistry. Procaine, an analog of cocaine, has short duration of action, high allergenicity, and it is no longer available in dental cartridges. Today, the gold standard for LAs is lidocaine; other available LAs include mepivacaine, prilocaine, articaine and bupivacaine.

LAs consist of three structural domains: an aromatic group connected by an ester- or an amide-linkage to an aliphatic chain containing a secondary or a tertiary amine group (Figure 2). For example, procaine has an ester-linkage connecting the aromatic group to the amine group and is referred to as an ester or aminoester LA. The other agents have an amide-linkage and are called amide or aminoamide LAs. These structural components affect pharmacodynamic and pharmacokinetic processes.

The rate of LAs’ absorption into the systemic circulation is also modulated by the determinants of passive diffusion, i.e., the drug’s molecular weight, pKa, lipid solubility, formulation, concentration gradient, and the pH and vascularity of the environment. LAs in plasma bind to albumin, α-1 acid glycoproteins, and erythrocytes. The primary determinant of a LA’s ability to distribute from the vascular compartment to other body fluids or tissues is its protein-binding capacity (Table 1). There are three distinct phases of drug distribution from the vascular compartment to other body fluids and tissues. Phase 1 is characterized by rapid fall in plasma concentration as the drug is distributed to well-perfused tissues such as the brain, liver, heart, kidneys, and lungs. Phase 2 is associated with a slower decline in plasma levels as the drug is distributed to less well-perfused tissues such as skeletal muscles and fat. Phase 2 mirrors the distribution half-life or T1/2α of LAs.

The degree of tissue uptake of LAs is expressed as their volume of distribution (Vd). LAs with lower plasma protein-binding capacity and greater lipid solubility have a greater Vd. Phase 3 of drug distribution reflects the decline in LAs’ plasma concentration due to clearance,
i.e., metabolism and excretion of LAs and represents their elimination half-life or $T_{1/2\beta}$. Therefore, the primary determinant of a LA’s elimination half-life ($T_{1/2\beta}$) is its $V_d$ (Table 1).

The metabolism of aminoamide-type LAs takes place primarily in the liver by cytochrome P450 isoenzymes CYP3A4 and CYP1A2. With some exceptions, the excretion of metabolites and any unchanged LA takes place in the kidneys. Prilocaine is metabolized both in the liver and the kidneys. The metabolites and any unchanged drug are exerted via the kidneys. As a general rule, aminoamide-type LAs require 5 half-lives, i.e., $T_{1/2\beta} \times 5$, for systemic clearance (Table 1).

While articaine is a member of the aminoamide group of LAs, it is unique in that it contains a thiophene-based nucleus as well as an ester-linkage connecting a second side chain (Figure 3). As a result, articaine is rapidly inactivated via hydrolysis of the ester side-chain by plasma carboxylesterase. Only about 5 to 10% of articaine is metabolized by hepatic microsomal CYP450 isoenzymes. The metabolites and any unchanged drug are excreted by the kidneys.

**Therapeutic Considerations**
Local anesthesia is a reversible sensory loss in a defined area of the body associated with transient inhibition of peripheral nerve conduction. The use of a local anesthetic agent should be followed by complete recovery, i.e., without evidence of structural or functional nerve damage. The ideal local anesthetic agent should provide profound, reversible local

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**Figure 2. Structural Domains of Local Anesthetic Agents.**

**Table 1. Plasma-protein Binding Capacity, Lipid Solubility, and $T_{1/2\beta}$ of LAs.**

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine</th>
<th>Mepivacaine</th>
<th>Prilocaine</th>
<th>Articaine</th>
<th>Bupivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent plasma-protein binding capacity</td>
<td>60-80</td>
<td>75</td>
<td>55</td>
<td>60-80</td>
<td>95</td>
</tr>
<tr>
<td>Lipid solubility</td>
<td>43</td>
<td>21</td>
<td>25</td>
<td>17</td>
<td>346</td>
</tr>
<tr>
<td>Elimination half-life or $T_{1/2\beta}$</td>
<td>$\approx2.0$</td>
<td>$\approx1.9$</td>
<td>$\approx2.0$</td>
<td>$\approx1.8$</td>
<td>$\approx5.5$</td>
</tr>
</tbody>
</table>
anesthesia with rapid onset and satisfactory duration of action, and minimal adverse effects."

The vehicle for LAs is sterile water. Some formulations contain citric acid, an antioxidant; and edetate calcium disodium, a stabilizer; and sodium chloride is added to produce isotonicity. Sodium hydroxide and/or hydrochloric acid are added to adjust the pH; at a pH range of 3.4 to 6.5 they form stable water-soluble salts with LAs. Once injected, the buffering capacity of the extracellular fluid (physiological pH of 7.4) favors free base formation and greater neuronal penetration.

Epinephrine bitartrate or levonordefrin is included in most LA formulations. They cause vascular smooth muscle contraction at the site of LA administration, slow the rate of LA absorption into the systemic circulation, and enhance the duration of local anesthetic action. To minimize oxidation of the vasoconstrictor, sodium or potassium metabisulfite is included in these formulations. Note that epinephrine 1:100,000 is physiologically equivalent to levonordefrin 1:20,000.

**Potency**

The structural domain of LAs responsible for their lipophilicity is the aromatic group. The lipid solubility or partition coefficient of a LA determines its ability to pass through biological membranes and reach their receptor sites.

Consequently, LAs must be able to partition into, diffuse across, and finally dissociate from neuronal plasma membranes. As the lipid solubility increases, the partition of a LA through neuronal membranes also increases.

LAs with higher partition coefficients require the use of lower doses to achieve the same degree of neuronal blockade as that achieved by agents.

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**Table 2. Partition Coefficients, Relative Potencies, and Percent Concentrations of LAs**

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine</th>
<th>Mepivacaine</th>
<th>Prilocaine</th>
<th>Articaine</th>
<th>Bupivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partition coefficient (lipid solubility)</td>
<td>43</td>
<td>21</td>
<td>25</td>
<td>17</td>
<td>346</td>
</tr>
<tr>
<td>Relative potency</td>
<td>~2</td>
<td>~1</td>
<td>~1</td>
<td>~1</td>
<td>~8</td>
</tr>
<tr>
<td>Percent concentration</td>
<td>2</td>
<td>2 or 3</td>
<td>4</td>
<td>4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

---

**Figure 3. Structural Domains of Articaine.**
with lower lipid solubilities. Therefore, the primary determinant of a LA’s potency is its partition coefficient (Table 2). At some point this relationship reverses and a highly lipid soluble LA would become trapped in the neuronal membrane. The relative potencies of LAs are reflected by their concentrations in aqueous solutions.

Onset of Action
The structural domain of LAs responsible for their hydrophilicity is the amine group. As mentioned earlier, in aqueous solution LAs exist as a mixture of protonated or positively charged (ionized) and deprotonated or neutral (unionized) forms. Only the deprotonated or neutral forms of LA molecules can translocate across neuronal membranes. The ratio of protonated to deprotonated forms is predicated on the drugs’ dissociation constant (pKa) and the pH at the site of drug administration. The closer is a LA’s pKa to the pH at the site of its administration (physiologic pH of 7.4), greater is its fraction of deprotonated molecules (free base) that can translocate across neuronal membranes. Therefore, the primary determinant of a LA’s onset of action is its dissociation constant (Table 3). Once in the cytoplasm, most of the deprotonated molecules are rapidly protonated, which tend to bind voltage-gated sodium channels with higher affinity than the deprotonated molecules.

Duration of Action
As noted earlier, the receptor site for LAs, i.e., the voltage-gated sodium channels, are integral membrane proteins. Predictably, LAs with high protein-binding capacity bind more tightly to and dissociate more slowly from their receptor sites. The lower is the protein-binding capacity of a LA, the weaker is the drug-receptor bond. Therefore, the primary determinant of a LA’s duration of action is its protein-binding capacity (Table 3).

In addition to their protein-binding capacity, the duration of local anesthetic action is modulated by a number of other factors as well. For example, more lipophilic LAs tend to bind more tightly to their receptors because of receptor site-associated structural fatty acids and protonated forms of LAs tend to dissociate more slowly from their receptor site. Still other variables include the dosage of the LA administered, vascularity of the injection site, and the presence of a vasoconstrictor in the formulation.

Lidocaine formulations are available as 2% plain, and as 2% w/epinephrine 1:100,000 and 1:50,000. Mepivacaine formulations are available as 3% plain and 2% w/ levonordefrin 1:20,000. Prilocaine formulations are available as 4% plain and as 4% w/epinephrine 1:200,000. Articaine formulations are available as 4% w/epinephrine 1:100,000 and 1:200,000. Bupivacaine is available as a 0.5% formulation w/epinephrine 1:200,000.

Lidocaine 2% plain has ultrashort duration of action. Lidocaine 2% w/epinephrine 1:100,000 and 1:50,000 has a somewhat longer duration of action than mepivacaine 2% w/levonordefrin 1:20,000 and prilocaine 4% w/epinephrine 1:200,000; and a somewhat shorter duration of action than articaine 4% w/epinephrine 100,000 and bupivacaine, 0.5% w/epinephrine 1:200,000, produces longer duration of pulpal (up to 7 hours) and soft tissue (up to 12 hours) anesthesia than any other LA.

Table 3. Dissociation Constant, Percent Free Base at pH 7.4, and Onset of Action of LAs.

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine</th>
<th>Mepivacaine</th>
<th>Prilocaine</th>
<th>Articaine</th>
<th>Bupivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissociation constant (pKa)</td>
<td>7.9</td>
<td>7.7</td>
<td>7.9</td>
<td>7.8</td>
<td>8.1</td>
</tr>
<tr>
<td>Percent free base at pH 7.4</td>
<td>25</td>
<td>33</td>
<td>25</td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td>Onset of action in minutes</td>
<td>2-4</td>
<td>2-4</td>
<td>2-4</td>
<td>2-4</td>
<td>4-8</td>
</tr>
</tbody>
</table>

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Figure 4. Range of Duration of Action of Various Formulations of Local Anesthetic Agents.*

Infiltration anesthesia with lidocaine 2% w/ epinephrine 1:50,000 may be useful to provide surgical hemostasis. Mepivacaine 3% plain formulation provides for longer duration of action than lidocaine 2% plain and it is the option when the use of a vasoconstrictor is contraindicated.\textsuperscript{26} Meta-analysis has shown that infiltration anesthesia with articaine 4% w/ epinephrine 1:100,000 provides for a greater probability of achieving pulpal anesthesia in comparison to lidocaine 2% w/epinephrine 1:100,000.\textsuperscript{26}

Bupivacaine has the greatest lipid solubility and the greatest protein-binding capacity; as a result, it produces the longest duration of pulpal anesthesia. This may be useful for lengthy procedures. However, because it will also produce prolonged soft-tissue analgesia, it should be used with caution in the elderly and the debilitated to minimize self-mutilation; and its use is not recommended for patients younger than 12 years of age.\textsuperscript{26} Bupivacaine is also the most cardiotoxic of all LAs.

**Dosing**

LAs' nonselective voltage-gated sodium channel blockade is responsible for most of their adverse drug effects. High plasma levels, other than overdose, may be caused by (1) repeated doses, (2) rapid absorption, (3) intravascular injection, (4) low plasma protein binding, and (5) slow clearance.\textsuperscript{26,27,30,32} Determine the dosage for healthy adults based on body weight; however, if a patient weighs ≥ 150 lbs. no more than the maximum recommended dose (MRD) should be administered (Table 4).\textsuperscript{19-25,27-29}

Since the MRD of LAs vary and there is wide variation in weight among pediatric patients, the maximum dose for each child should be carefully calculated.\textsuperscript{21-25,27-32} Although there are many rules and formulae to calculate dosages, manufacturers’ recommendations provide a reasonable approach.\textsuperscript{21-25,27,30,32} Using the information in Table 4, the MRD of lidocaine 2% w/epinephrine 1:100,000 that can be safely administered to a child of 25 lbs. is as follows:

<table>
<thead>
<tr>
<th>LA formulations</th>
<th>mg/mL</th>
<th>mg/cartridge</th>
<th>MRD – mg/lb.</th>
<th>MRD in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine, 2% plain</td>
<td>20</td>
<td>36</td>
<td>2</td>
<td>300</td>
</tr>
<tr>
<td>Lidocaine, 2% w/epinephrine</td>
<td>20</td>
<td>36</td>
<td>3.2</td>
<td>500</td>
</tr>
<tr>
<td>Mepivacaine, 2% plain</td>
<td>30</td>
<td>54</td>
<td>3</td>
<td>400</td>
</tr>
<tr>
<td>Mepivacaine, 2% w/levonordefrin</td>
<td>20</td>
<td>36</td>
<td>3</td>
<td>400</td>
</tr>
<tr>
<td>Prilocaine, 4% plain</td>
<td>40</td>
<td>72</td>
<td>4</td>
<td>600</td>
</tr>
<tr>
<td>Prilocaine, 4% w/epinephrine</td>
<td>40</td>
<td>72</td>
<td>4</td>
<td>600</td>
</tr>
<tr>
<td>Articaine, 4% w/epinephrine</td>
<td>40</td>
<td>72</td>
<td>3.2</td>
<td>500</td>
</tr>
<tr>
<td>Bupivacaine, 0.5% w/epinephrine</td>
<td>5</td>
<td>9</td>
<td>0.6</td>
<td>90</td>
</tr>
</tbody>
</table>
Similarly, using the information in Table 4 to calculate the MRD of mepivacaine 3% plain that can be safely administered to a child of 25 lbs. is as follows:

**Step 1:** Determine MRD in mg

MRD in mg/lb. x weight of patient in lbs = Total MRD in mg
i.e., 3.2 mg/lb. x 25 lbs = 80 mg

**Step 2:** Determine MRD in mL

Total MRD in mg + mg per mL = Total MRD in mL
i.e., 80 mg + 20 mg = 4.0 mL

**Step 3:** Determine MRD in cartridges

Total MRD in mg + mg per cartridge = Total MRD in cartridges
i.e., 80 mg + 36 = 2.22 cartridges

**Technical Issues, Sterilization, and Storage**

Dental formulations of LAs are available in glass cartridges, which contain either 1.7 ml or 1.8 ml of local anesthetic solution. The cartridges are sealed with a plunger at one end and a diaphragm at the opposite end. The plunger is a filler, coloring agent, and paraffin-impregnated rubber compound. A lubricant is added to allow for greater ease of plunger movement during aspiration. The diaphragm is a rubber-filler compound sealed with an aluminum cap that accommodates the disposable needle.

Cartridges should be stored at room temperature, i.e., about 25°C (77°F). Solutions that are pinkish or darker than slightly yellow, those that are cloudy, and solutions that contain crystal precipitates or particulate contaminants suggest exposure to extreme temperatures and manufacturing problems, and potential loss of sterility.

To minimize oxidation and changes in pH, LAs with a vasoconstrictor should be protected from sunlight, ultraviolet or infrared radiation, or fluorescent light.

Cartridges should not be sterilizer or immersed in chemicals. They cannot withstand temperatures and pressures associated with steam sterilization; many disinfectants/sterilants contain and release metallic ions (e.g., mercury, zinc, copper, etc.), which may produce swelling and edema; some antirust solutions contain sodium nitrate or other similar agents, which are also capable of releasing metallic ions; and quaternary ammonium compounds are electrolytically incompatible with the aluminum cap.

If disinfection of a cartridge is desired, it can be accomplished by wiping the cap with a pledget of cotton impregnated with either 91% isopropyl alcohol (USP) or 70% ethyl alcohol (USP) just prior to use. It is of note that most commercial brands of isopropyl alcohol (rubbing alcohol) and ethyl alcohol solutions are not USP grade; such formulations often contain denaturants, which can adversely affect the rubber components of the diaphragm and plunger.

When loading the syringe the needle should penetrate the center of the diaphragm. An off-center penetration produces an oval shaped puncture, which under pressure allows leakage around the needle. Leakage may also result when using a badly worn syringe, an aspirating syringe with a bent harpoon, a syringe not intended to take 1.8 mL cartridges, or inadvertent freezing of a cartridge. Cracking of a cartridge is often the result of an extruded plunger being forced back into the cartridge.

**Reducing Needle-insertion Pain**

Factors that modulate the efficacy of topical anesthetic agents to reduce needle-insertion pain include (1) concentration and formulation of the topical anesthetic agent, i.e., viscous, ointment, liquid, spray, patch; (2) duration of application; (3) site of application, i.e., keratinized versus non-keratinized tissue and maxillary versus mandibular sites; and (4) technical issues related to the administration
of the LA, e.g., the depth of needle placement, the gauge of needle used, and contact with the periosteum.34

Four studies found lidocaine 5%, benzocaine 20%, and EMLA patch (lidocaine 2.5% w/ prilocaine 2.5%), to be more effective than placebo.35-38 Three other studies concluded that benzocaine 20%, benzocaine 18%, tetracaine 2% w/benzocaine 20%, and lidocaine 5% were no more effective than a placebo.39-41 While there were other variables, it is of note that the needles used in the first four studies were no larger than 27 gauge; while in the last three studies the needles were 25 gauge.

Two randomized, double-blind, placebo-controlled studies evaluated the efficacy of lidocaine patches containing lidocaine 10% (23 mg) and lidocaine 20% (46.1 mg) placed on the buccal mucosa of the maxillary premolar area, and maxillary and mandibular premolar areas, respectively, prior to the insertion of a 25-gauge needle intentionally contacting the periosteum.42,43 Both formulations were superior to the placebo, but the 20% patch produced more profound anesthesia of longer duration.

Two cm² mucoadhesive lidocaine (20%) patches containing 46.1 mg of lidocaine base are available (DentiPatch™, Noven Pharmaceuticals, Inc.).44 Anesthesia occurs within 2.5 minutes of application and after an application period of 15 minutes anesthesia persists for approximately 30 minutes. Peak plasma concentration with the 20% patch, after an application period of 15 minutes, is 10 times less than that associated with the administration of lidocaine 2% (36 mg) w/1:100,000.42,43

Reversal of Soft-tissue Anesthesia
Epinephrine and levonorgestrel are α₁-adrenergic-receptor agonists. They delay the uptake of LAs into the vascular compartment and contribute to prolonged soft-tissue anesthesia, i.e., anesthesia of the lip and tongue, and associated functional deficits.45 Phenylephrine mesylate, 0.4 mg in 1.7 mL cartridges (OraVerse™, Novalar Pharmaceuticals) is a non-selective α₁-adrenergic-receptor antagonist. When injected at the site of LA administration, it shortens post-treatment duration of soft-tissue anesthesia.45

Studies concluded that phenylephrine mesylate administered at the same volume and at the same site as a LA with a vasoconstrictor significantly and safely reduces the duration of soft-tissue anesthesia and associated functional deficits.46-48 However, its use is not approved by the FDA in children under the age of 6 years or in children who weigh less than 33 lbs. (15 kg). Clinicians should also consider the risks/benefits of reversal when a longer period of postoperative pain is anticipated.

Precautions Related to the Administration of LAs
Drugs seldom exert their beneficial effects without also causing adverse drug reactions (ADRs). In addition to overdose, ADRs may be caused by therapeutic doses of drugs because of drug-drug, drug-food, drug-herbal, and drug-disease interaction-related to pharmacokinetic or pharmacodynamic processes. Drugs or their metabolites may also be inherently toxic and produce cytotoxic reactions. Other LA-related ADRs may be immune mediated or are idiosyncratic.14,18-25,27-29

ADRs associated with the administration to lidocaine, mepivacaine, prilocaine, articaine, and bupivacaine, in general, are similar and may be considered together.14,18-25 However, some LAs with unique toxicities will be highlighted. For example, prilocaine is more likely to induce methemoglobinemia in susceptible patients;23 prilocaine and articaine are more likely to produce paresthesia following mandibular nerve blocks;49-51 and bupivacaine is the most cardiotoxic.14,18-25

Local Reactions
Epithelial and vascular reactions may be due to dosage-related cytotoxic nature of LAs or they may be vasoconstrictor-induced.14,20 Clinical manifestations may include edema, desquamation, and ischemic necrosis (Figure 5). These ADEs are usually transient in nature. Injection into muscles may result in LA-associated myotoxicity and vasoconstrictor-associated necrosis. Clinical manifestations include acute pain and trismus. Healing with fibrosis may lead to chronic trismus.14,20

Neurologic deficit may be LA-induced neurotoxicity related to the total dose of the LA administered,
the particular LA used, and the technique employed (e.g., infiltration versus nerve block).

Most cases of neurologic deficit involve the lingual nerve. Signs and symptoms include transient anesthesia or paresthesia characterized as sensation of pricking or tingling of the lip, tongue, and other oral tissues and may take 2 to 6 months to resolve.

In rare instances, the neurologic deficit may be permanent. Based on LA usage by U.S. dentists, the reported incidence of permanent paresthesia following mandibular nerve block with prilocaine 4% and articaine 4% is 7.3 and 3.6 times greater, respectively, than expected. These findings are consistent with those reported from other countries. Clinicians should consider this evidence when assessing the risks and benefits of administering 4% LA formulations for mandibular nerve block anesthesia.

**CNS Effects**

CNS effects of LAs may be excitatory and/or depressant in nature. Excitatory effects may be brief and include lightheadedness, restlessness, nervousness, anxiety, apprehension, euphoria, confusion, dizziness, tinnitus, blurred or double vision; twitching, tremors, and rarely convulsions. Depressant effects include drowsiness progressing to unconsciousness, to respiratory depression, and finally, respiratory arrest. Other CNS effects may include nausea, vomiting, chills, and miosis.

**Cardiovascular Effects**

Signs and symptoms of depressed cardiovascular function may be the direct effect of LAs, which depress cardiac conduction, excitability, and contractility. Premonitory signs of reduced cardiac output include sweating, faintness, and altered mentation; followed by bradycardia, hypotension, progressive cerebral hypoxia, and seizures. Depressed cardiac conduction, excitability, and contractility may progress to ventricular arrhythmias, atrioventricular block, and cardiac arrest.

**Hypersensitivity Reactions**

Allergic reactions to LAs may manifest as pruritus, erythema, rash, urticaria, angioedema, wheezing, asthma (coughing, difficulty breathing); and, rarely, anaphylaxis. Allergic reactions to ester-type LAs have been confirmed. Ester-type anesthetic agents are metabolized by plasma cholinesterases. One of the breakdown products, para-aminobenzoic acid (PABA) is a highly antigenic compound capable of sensitizing lymphocytes or eliciting the formation of IgE antibodies.

True allergy to amide-type LAs is rare. Patients allergic to ester-type LAs have not shown cross sensitivity to amide-type LAs and cross sensitivity among members of the amide-type LAs has not been reported. However, LAs formulated with a vasoconstrictor contain metabisulfite may precipitate an allergic reaction. The prevalence of sulfite allergy in the general population is unknown, but sulfite sensitivity is seen more frequently is patients with asthma.

**Idiosyncratic Reactions**

Methemoglobinemia is an uncommon idiosyncratic reaction most notably to prilocaine and topical benzocaine. Their metabolites bind to hemoglobin and interfere with its oxygen-carrying capacity. Signs and symptoms
usually appear 3 to 4 hours after exposure to large doses and may include cyanosis, fatigue, weakness, nausea, sedation, seizures, and coma. Very young patients and those with congenital methemoglobinemia or glucose-6-phosphate deficiency are the most susceptible.

**Sympathetic Reactions**

LA formulations may contain epinephrine or levonordefrin. Healthy adults can safely receive up to 0.2 mg of epinephrine or 1.0 mg of levonordefrin per visit. The inadvertent intravascular injection of a LA containing a vasoconstrictor, the use of a LA containing high concentration of vasoconstrictor, the potentiation of the injected vasoconstrictor by endogenous catecholamines, and concomitant therapy with other sympathomimetic agents may contribute to adverse sympathetic effects (Table 5).19-25,28,29

Vasoconstrictors must be avoided in patients under the influence of cocaine. Other instances requiring prudence with the use of a vasoconstrictor include patients with blood pressure in excess of 180/110, severe cardiovascular disease (i.e., recent MI, unstable angina pectoris, decompensated heart failure, severe valvular disease, supraventricular arrhythmias with uncontrolled ventricular rate, symptomatic ventricular arrhythmias, and high-grade AV block), and patients with uncontrolled hyperthyroidism.19-25

The medical history should seek to determine the patient's functional capacity (FC).63 An individual's capacity to perform a spectrum of common daily tasks has been shown to correlate well with maximum oxygen uptake by treadmill testing. FC is expressed in metabolic equivalents (METs). The oxygen consumption of a 70-kg, 40-year-old man at rest is 3.5 ml per kg per minute, which requires a FC of 1 MET. Cardiac risk is increased in patients unable to meet a 4-MET demand for oxygen.64

The hemodynamic effect of 0.045 mg of epinephrine was reported to be less than that produced by ergometric stress testing at 25 watts in young patients and at 15 watts in older subjects.37 The workload of ergometric stress testing at these levels is about 4 METs, which is approximately equivalent to the work load produced by climbing two flight of stairs, walking 4.8 km/hr., doing light yard work (raking leaves, weeding, or pushing a power mover), painting, or doing light carpentry work.

Based on this report, 0.045 mg of epinephrine can be safely administered to patients who can tolerate the activities noted above with minimal or no symptoms, e.g., diaphoresis, fatigue, shortness of breath, and/or chest pain. Epinephrine, 0.045 mg, is equivalent to the amount of epinephrine 1:100,000 found in 4.5 mL of any LA formulation. This study provides evidence that a practical determinant for a safe dose of vasoconstrictor is the patient's FC, i.e., the ability to tolerate physical/emotional stress.

**Local Anesthetic Agents and Pregnancy**

In 2014, the FDA amended its regulations governing the content and format of labeling for human prescription drugs and biological products.65 The amendment, which became effective on 30 June 2015, required the removal of the old pregnancy categories A, B, C, D, and X from all drug product labeling. Information about LA-related risks to the fetus and recommendations about the use of LAs during pregnancy can now be found in the new “Pregnancy” subsection of specific package inserts.21-25

### Table 5. Clinical Manifestations of Sympathetic Toxic Reactions.

<table>
<thead>
<tr>
<th>Mild reactions</th>
<th>Severe reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restlessness</td>
<td>Palpitation</td>
</tr>
<tr>
<td>Headache</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Tremors</td>
<td>Chest pain</td>
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<tr>
<td>Dizziness</td>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td>Pallor</td>
<td>Cardiac arrest</td>
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</tbody>
</table>
Epinephrine and Pregnancy
Epinephrine, by β₁-adrenergic activity may decrease uterine contraction and prolong labor; and by α₁-adrenergic activity may decrease uterine blood flow and fetal circulation. However, it has been shown that bolus doses epinephrine, 0.1 mg, did not prolonged the duration of labor and did not adversely affect placental blood flow and fetal circulation.66-77 It is of note that investigators considered the addition of epinephrine to LAs beneficial for it reduced the dosage of LA required for pain relief.

Local Anesthetic Agents and Breastfeeding
The 2014 FDA amendment to regulations governing the content and format of labeling for human prescription drugs and biological products, which became effective on 30 June 2015, also requires the inclusion of a “Lactation” subsection in the package insert.65 Information about LA-related risks to a breastfeeding child and recommendations on how to minimize drug exposure when a drug is administered to the mother can be found in the “Lactation” subsection of specific package inserts.21-25

Drug-drug Interactions
The dosage of LA's should be reduced in patients taking other CNS depressants as they are additive. Caution is also recommended when administering LAs with a vasoconstrictor and the patient is taking tricyclic antidepressants, some β₁-adrenergic receptor antagonists, and some general anesthetics. These agents may cause severe hypertension, cardiac arrhythmias, and cerebrovascular accidents. Evidence of interactions with antipsychotic agents and thyroid hormone is less compelling.21-25,78

Summary
The pharmacological properties of LAs vary from agent to agent. To compensate for these differences, manufactures have adjusted the concentration of various LAs such that they all produce nearly the same effect. Consequently, the LA selected in a given clinical situation and the dosage administered should be predicated on potential toxic and other ADEs. Lidocaine 2% w/epinephrine 1:100,000 is the gold standard, in available formulations it is as effective as and less toxic than other agents.
Course Test Preview
To receive Continuing Education credit for this course, you must complete the online test. Please go to: www.dentalcare.com/en-us/professional-education/ce-courses/ce449/start-test

1. **Nociception or pain perception is _______.**
   a. the sensory detection of noxious events in the CNS
   b. transduction of noxious events to the CNS
   c. neuronal transmission of noxious events to the CNS
   d. All of the above.

2. **Which of the following are noxious stimuli that affect “high-threshold” primary afferent sensory neurons or nociceptors?**
   a. Intense mechanical stimuli
   b. Intense thermal stimuli
   c. Chemical activators
   d. All of the above.

3. **Which of the following are chemical activators of nociceptors?**
   a. Ischemia- and inflammation-associated protons.
   b. Cellular injury-associated extracellular ATP.
   c. Tissue damage- and inflammation-associated kinins.
   d. All of the above.

4. **Which of the following statements associated with the kinins (bradykinin) is correct?**
   a. Kinins directly excite primary afferent fibers.
   c. PGE2 increases the sensitivity of primary afferent sensory neurons to chemical activators.
   d. All of the above.

5. **Which of the following statements is correct with reference to the activation of peripheral sensory neurons?**
   a. Activation of peripheral sensory terminals by noxious stimuli leads to intracellular sodium and calcium ion influx and neuronal depolarization.
   b. Membrane depolarization leads to action potential generation if the activation threshold of voltage-sensitive sodium channels is reached.
   c. Four types of voltage-sensitive sodium channels are expressed in primary afferent sensory fibers and two of these only respond to high-threshold peripheral stimuli.
   d. All of the above.

6. **Which of the following statements is correct with reference to neuronal transmission in the trigeminal nucleus?**
   a. Incoming action potentials activate pre-synaptic voltage-sensitive calcium channels.
   b. Calcium ion influx into the primary sensory neuron terminal leads to synaptic release of glutamate.
   c. Glutamate receptor activation leads to action potential generation in secondary relay neurons.
   d. All of the above.
7. Which of the following statement is correct with respect to secondary or tertiary afferent neurons?
   a. Secondary afferent neurons project to the thalamus where they synapse with tertiary afferent neurons.
   b. Tertiary afferent neurons project to the somatosensory cortex, which is responsible for the localization of pain.
   c. Tertiary afferent neurons project to the limbic system, which is responsible for the emotional aspects of pain.
   d. All of the above.

8. Pain arising slowly after injury, which is perceived as burning, aching, dull, poorly localized, and persistent, i.e., second pain, is most likely due to the activation of ________.
   a. A-delta fibers
   b. C fibers
   c. B fibers
   d. A-gamma fibers

9. Pain arising rapidly after tissue injury, which is perceived as sharp, bright, well-localized, but not particularly persistent, i.e., first pain, is most likely due to the activation of ________.
   a. A-delta fibers
   b. C fibers
   c. B fibers
   d. A-gamma fibers

10. Which of the following statements is correct with respect to homeostatic mechanisms in excitable neuronal cells?
    a. Excitable neuronal cells maintain a chemical gradient with high extracellular sodium concentrations.
    b. Excitable neuronal cells maintain a chemical gradient with high intracellular potassium concentrations.
    c. The inside of neuronal cells is electronegative (-50 to -90 mV) and the outside is electropositive.
    d. All of the above.

11. Which of the following statements is correct with respect to the ionic disequilibrium associated with action potential generation?
    a. Nociceptive signals alter the distribution of sodium and potassium ions and briefly reverse electrical polarity, which leads to neuronal membrane depolarization.
    b. If the threshold for activation of voltage-gated sodium channels is reached, sodium ions flow into the cell and an action potential is generated.
    c. Following inactivation of voltage-gated sodium channels, Na/K ATPase pumps sodium out of the cells and the leak of potassium ions through passive ion channels restore the resting membrane potential.
    d. All of the above.
12. Which of the following statements is correct with respect to the mechanism of action of local anesthetic agents (LAs)?
   a. LAs reduce the amplitude and conduction velocity of action potentials in a reversible, concentration-dependent manner.
   b. The site of action of LAs is the voltage gated-sodium channels, which are integral membrane proteins.
   c. To gain access to their receptors, LAs must diffuse across lipophilic neuronal membranes at the site of administration.
   d. All of the above.

13. All of the following statements related to the ability of LAs to cross biological membranes are correct EXCEPT which one?
   a. LAs cross biological membranes by passive diffusion.
   b. Since LAs are weak bases, in an aqueous environment they exist as a mixture of protonated or positively charged (ionized) and deprotonated or neutral (unionized) molecules.
   c. The ratio of ionized to unionized forms of a LA is predicated on its dissociation constant or pKa and the pH of the drug's milieu, i.e., the environment at the site of drug administration.
   d. When lidocaine with a pKa of 7.9 is deposited into an infected/inflamed site with a pH less than 7.9, more than 50% of its molecules become unionized.

14. Which of the following statements is correct with respect to the mechanism of action of local anesthetic agents (LAs)?
   a. LAs consist of an aromatic group connected by either an ester- or amide-linkage to an aliphatic chain, which contains a secondary or tertiary amine group.
   b. Agents that have an ester-linkage connecting the aromatic group to the amine group are referred to as ester or aminoester LAs.
   c. The structural components of LAs affect their potency, onset of action, and duration of action.
   d. All of the above.

15. The rate of absorption of LAs into the systemic circulation is determined by __________.
   a. the vascularity of the injection site, i.e., the density of capillaries
   b. physiochemical properties of LAs, i.e., lipid solubility, pKa, inherent vasoactivity
   c. the presence of a vasoconstrictor
   d. All of the above.

16. Which of the following statements is correct relative to the volume of distribution (Vd) of LAs?
   a. The degree of tissue uptake of a LA is expressed as its Vd.
   b. LAs with lower plasma protein-binding and greater lipid solubility have a greater Vd.
   c. The Vd of a LA is the primary determinant of its elimination half-life or T_{1/2}\beta
   d. All of the above.

17. All of the following statements are correct with respect to the metabolism of LAs EXCEPT which one.
   a. The metabolism of aminoamide-type LAs takes place primarily in the liver by cytochrome P450 isoenzymes CYP3A4 and CYP1A2.
   b. With some exceptions, the excretion of metabolites and any unchanged LA takes place in the kidneys.
   c. Prilocaine is unique in that it contains a thiophene-based nucleus and is rapidly inactivated via hydrolysis by plasma carboxylesterase.
   d. As a general rule, aminoamide-type LAs require 5 half-lives, i.e., T_{1/2}\beta x 5, for systemic clearance.
18. While the vehicle of LAs is sterile water, formulations may contain _______.
   a. citric acid, an antioxidant; and edetate calcium, a stabilizer
   b. sodium chloride to produce isotonicity
   c. sodium hydroxide and/or hydrochloric acid to adjust the pH
   d. All of the above.

19. Which of the followings statements related to vasoconstrictors in LAs is correct?
   a. Vasoconstrictors cause vascular smooth muscle contraction at the site of LA administration, slow the rate of LA absorption into the systemic circulation, and enhance the duration of local anesthetic action.
   b. To minimize oxidation of the vasoconstrictor, sodium or potassium metabisulfite is included in LA formulations containing a vasoconstrictor.
   c. Epinephrine 1:100,000 is physiologically equivalent to levonordefrin 1:20,000.
   d. All of the above.

20. All of the following statements relative to a LA’s potency are correct EXCEPT which one?
   a. Lipid solubility, which is a function of the aromatic group, affects the ability of LAs to pass through biological membranes.
   b. As lipid solubility increases, the partition of drugs through the neuronal membrane decreases.
   c. The primary determinant of a LA’s potency is its partition coefficient.
   d. The relative potencies of LAs are reflected by their concentrations in aqueous formulations.

21. All of the following statements relative to a LA’s onset of action are correct EXCEPT which one?
   a. The amine group confers hydrophilicity and in aqueous solutions LAs exist as a mixture of protonated and deprotonated forms.
   b. The ratio of protonated to deprotonated forms is predicated on the drug’s dissociation constant (pKa) and the pH of the environment.
   c. The closer a LA’s pKa to the pH at the site of its administration (physiologic pH of 7.4), greater is its fraction of protonated that can translocate across neuronal membranes.
   d. Since only the deprotonated form can translocate across neuronal membranes, the pKa is the primary determinant of a LA’s onset of action.

22. All of the following statements relative to a LA’s duration of action are correct EXCEPT which one?
   a. The receptor site for LAs, i.e., the voltage gated sodium channel, is an integral membrane protein.
   b. LAs with low protein-binding capacity bind more tightly and dissociate slowly from their receptor sites.
   c. A LA’s protein-binding capacity is the primary determinant of its duration of action.
   d. The duration of a LA’s action is also modulated by its lipid solubility, the dosage of the LA administered, vascularity of the injection site, and the presence of a vasoconstrictor in the formulation.

23. In general, which of the following is the LA of choice, because of its longer duration of action, when the use of a vasoconstrictor is contraindicated?
   a. Lidocaine 2% plain
   b. Mepivacaine 3% plain
   c. Prilocaine 4% plain
   d. Mepivacaine 2% with levonordefrin 1:20,000
24. **All of the following statements relative to LAs are correct EXCEPT which one?**  
   a. Infiltration anesthesia with lidocaine 2% w/epinephrine 1:50,000 may be useful to provide surgical hemostasis.  
   b. Meta-analysis has shown that when administered by infiltration, articaine provides for a greater probability of achieving anesthesia in comparison to lidocaine.  
   c. Articaine is the most cardiotoxic of all LAs.  
   d. Bupivacaine has the greatest lipid solubility and the greatest protein-binding capacity; as a result, it produces the longest duration of pulpal anesthesia.

25. **Which of the following statements are correct with respect to bupivacaine when compared to other LAs?**  
   a. Bupivacaine should be used with caution in the elderly and the debilitated to minimize self-mutilation.  
   b. The use of bupivacaine is not recommended for pediatric patients younger than 12 years of age.  
   c. Bupivacaine is the most cardiotoxic of all LAs.  
   d. All of the above.

26. **A practical approach to determine the dosage of LAs in healthy adults is based on weight, e.g., milligram of drug per pound of body weight; however, if a patient weighs ≥150 lbs. no more than the maximum recommended dose (MRD) should be administered.**  
   a. True  
   b. False

27. **Although there are many rules and formulae, manufacturer's recommendations provide a reasonable approach to calculating pediatric dosages.**  
   a. True  
   b. False

28. **All of the following statement related to technical issues, storage, and sterilization/disinfection of LA cartridges are correct EXCEPT which one?**  
   a. Both the plunger and the diaphragms of LA cartridges contain rubber (latex).  
   b. Cartridges of LAs should be stored at room temperature, i.e., about 25°C (77°F).  
   c. Cartridges of LAs should be sterilizer or immersed in chemical disinfectants before use.  
   d. Leakage from a LA cartridge may also result when using a badly worn syringe, an aspirating syringe with a bent harpoon, a syringe not intended to take 1.8 mL cartridges.

29. **Technical issues related to the administration of LAs that modulate the efficacy of intraoral topical anesthetic agents to reduce needle-insertion pain include _______.**  
   a. needle gauge  
   b. depth of needle placement  
   c. needle contact with periosteum  
   d. All of the above.

30. **Which of the following statements is correct with respect to phentolamine mesylate for the reversal of soft-tissue anesthesia?**  
   a. Phentolamine mesylate is a non-selective α₁-adrenergic-receptor antagonist.  
   b. Studies concluded that phentolamine mesylate administered at the same volume and at the same site as a LA with a vasoconstrictor significantly and safely reduces the duration of soft-tissue anesthesia and associated functional deficits.  
   c. The use of phentolamine mesylate is not approved by the FDA in children under the age of 6 years or in children who weigh less than 33 lbs. (15 kg).  
   d. All of the above.
31. Which of the following statements is correct with respect to local toxicity of LAs?
   a. LA-induced epithelial and vascular reactions may include edema, desquamation, and ischemic necrosis; myotoxicity may manifest as acute pain and trismus.
   b. Most cases of LA-induced neurotoxicity manifest as anesthesia or paresthesia of the lip, tongue, and other oral tissues and may take 2 to 6 months to resolve.
   c. The reported incidence of permanent paresthesia following mandibular nerve block is significantly higher with 4% LA formulations.
   d. All of the above.

32. Which of the following statements is correct with respect to LA-associated CNS toxicity?
   a. CNS effects of LAs may be excitatory and/or depressant in nature.
   b. The excitatory manifestations may be brief or absent.
   c. The depressant effect may progress from drowsiness to unconsciousness, to respiratory depression, and finally, to respiratory arrest.
   d. All of the above.

33. Which of the following settlements is correct with respect to LAs’ cardiovascular toxicity?
   a. Signs and symptoms of depressed cardiovascular function may be the direct effect of LAs, which depress cardiac conduction, excitability, and contractility.
   b. Signs of reduced cardiac output include sweating, faintness, altered mentation, bradycardia, hypotension, progressive cerebral hypoxia, and seizures.
   c. With high plasma concentration of LAs, cardiovascular toxicity may progress to ventricular arrhythmias, atrioventricular block, and cardiac arrest.
   d. All of the above.

34. All of the following statements are correct with respect to LA-induced allergic reactions EXCEPT which one?
   a. A breakdown product of ester-type LAs, para-aminobenzoic acid (PABA), is capable of sensitizing lymphocytes or eliciting the formation of IgE antibodies.
   b. True allergy to amide-type LAs is rare, but cross sensitivity among members of amide-type LAs is common.
   c. LA formulated with a vasoconstrictor contain metabisulfite may precipitate an allergic reaction in susceptible patients.
   d. The prevalence of sulfite sensitivity in the general population is unknown, but sulfite sensitivity is seen more frequently in patients with asthma.

35. Which of the following statements related to methemoglobinemia is correct?
   a. Methemoglobinemia is an uncommon idiosyncratic reaction most notably to prilocaine and topical benzocaine.
   b. Signs and symptoms of methemoglobinemia usually appear 3 to 4 hours after exposure to large doses and may include cyanosis, fatigue, weakness, nausea, sedation, seizures, and coma.
   c. Very young patients and those with congenital methemoglobinemia or glucose-6-phosphate deficiency are the most susceptible.
   d. All of the above.

36. Which of the following statements is correct with respect to the use of vasoconstrictors in conjunction with LAs?
   a. It is generally accepted that a healthy adult can safely receive up to 0.2 mg of epinephrine.
   b. Vasoconstrictors must be avoided in patients under the influence of cocaine; in other clinical situations, the patient's functional capacity should be the guide.
   c. Cardiac risk is association with noncardiac procedures is increased in patients unable to meet a 4-MET demand for oxygen.
   d. All of the above.
37. **Which of the following statements is correct with respect to the use of LAs during pregnancy?**
   a. In 2014, the FDA amended its regulations governing the content and format of labeling for human prescription drugs and biological products.
   b. The amendment, which became effective on 30 June 2015, required the removal of the old pregnancy categories A, B, C, D, and X from all drug product labeling.
   c. Information about LA-related risks to the fetus and recommendations about the use of LAs during pregnancy can now be found in the new “Pregnancy” subsection of specific package inserts.
   d. All of the above.

38. **Which of the following statements is correct with respect to the use of LAs containing a vasoconstrictor during pregnancy?**
   a. There is general concern that epinephrine may decrease uterine contraction and prolong labor; and that it may decrease uterine blood flow and fetal circulation.
   b. Bolus doses of epinephrine up to 0.1 mg do not prolong labor and in healthy pregnant women does not affect placental blood flow and fetal circulation.
   c. Investigators considered the addition of epinephrine to LAs beneficial for it reduced the dosage of LA required for pain relief.
   d. All of the above.

39. **Which of the following statements is correct with respect to the use of LAs and the nursing woman?**
   a. In 2014, the FDA amended its regulations governing the content and format of labeling for human prescription drugs and biological products.
   b. The FDA requires the inclusion of a “Lactation” subsection in the package insert with information about LA-related risks to a breastfeeding child.
   c. The “Lactation” subsection of package insert makes recommendations on how to minimize drug exposure when a drug is administered to the mother.
   d. All of the above.

40. **All of the following statements related to LA-related drug-drug interactions are correct EXCEPT which one?**
   a. The dosage of LA's should be reduced in patients taking other CNS depressants as they are additive.
   b. Vasoconstrictors in LAs interact with tricyclic antidepressants, some β<sub>1</sub>-adrenergic receptor antagonists, and some general anesthetics.
   c. Vasoconstrictor-related drug-drug interactions may cause severe hypertension, cardiac arrhythmias, and cerebrovascular accidents.
   d. Evidence of drug-drug interactions between vasoconstrictors in LAs with antipsychotic agents and thyroid hormone is compelling.
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