Local Anesthetic Agents in Dentistry

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Conflict of Interest Disclosure Statement

- Dr. Terézhalmy has done consulting work for Procter & Gamble and has served on the dentalcare.com Advisory Board. He has no relevant financial relationships to disclose.

Introduction – Local Anesthetic Agents

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

Course Contents

Overview

Participants in this course will be introduced to evidence-based information related to 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; and precautions to consider with the use of LAs.

Learning Objectives

Upon completion of this course, the dental professional should be able to:

- Discuss the pharmacology of LAs.
- Discuss the factors to consider in selecting the most effective and least toxic LA for perioperative pain management.
- Discuss precautions to consider with the use of LAs.

Introduction

Cocaine was the first recognized local anesthetic agent (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.[1] **Procaine**, a cocaine analog, has short duration of action, high allergenicity, and is no longer available in dental cartridges. Today, LAs available in dental cartridges include **lidocaine mepivacaine**, **prilocaine**, **articaine**, and **bupivacaine**.

LAs consist of an aromatic group connected by an ester- or an amide-linkage to an aliphatic chain with a secondary or a tertiary amine group (Figure 1).[2-10] Procaine has an ester-linkage connecting the aromatic group to the amine group and is the prototypical ester or aminoester LA. Agents primarily used by dentists have an amide-linkage and lidocaine is the prototypical amide or aminoamide LA. These structural domains affect LAs pharmacological characteristics.[2-10]

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.[2,11,12] Nociceptive or painful stimuli alter the distribution of these ions and briefly reverse electrical polarity, which may lead to neuronal membrane depolarization. The energy generated by neuronal depolarization may activate voltage-gated sodium channels (Figure 2).

If the threshold energy level for the activation of voltage-gated sodium channels is reached, sodium ions flow into neuronal cells and an action potential is generated.[2,11,12] LAs, reversibly and in a dose-dependent manner, reduce the amplitude and conduction velocity of action potentials by interacting with their receptors located on the voltage-gated sodium channels. Since the sites of action of LAs are located on the cytosolic side of these large membrane proteins, following administration, LAs must diffuse across lipophilic neuronal membranes.[2,11,12]

LAs cross neuronal membranes by **passive diffusion**. Since LAs are weak bases, in an aqueous environment they exist as a mixture

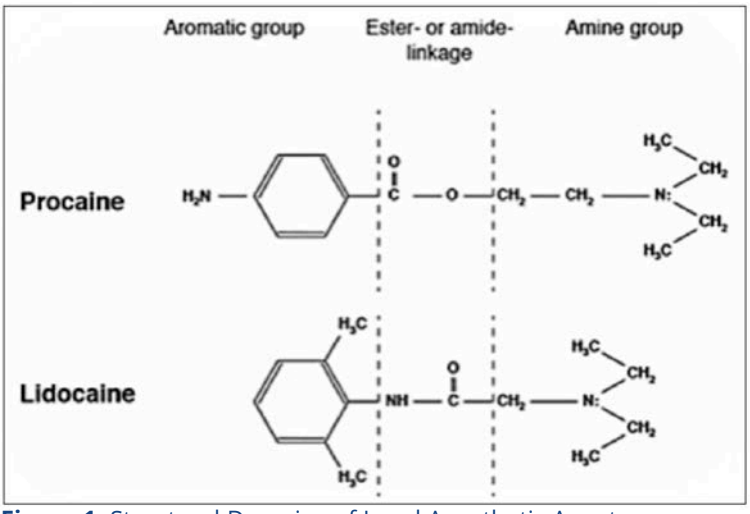

Figure 1. Structural Domains of Local Anesthetic Agents.

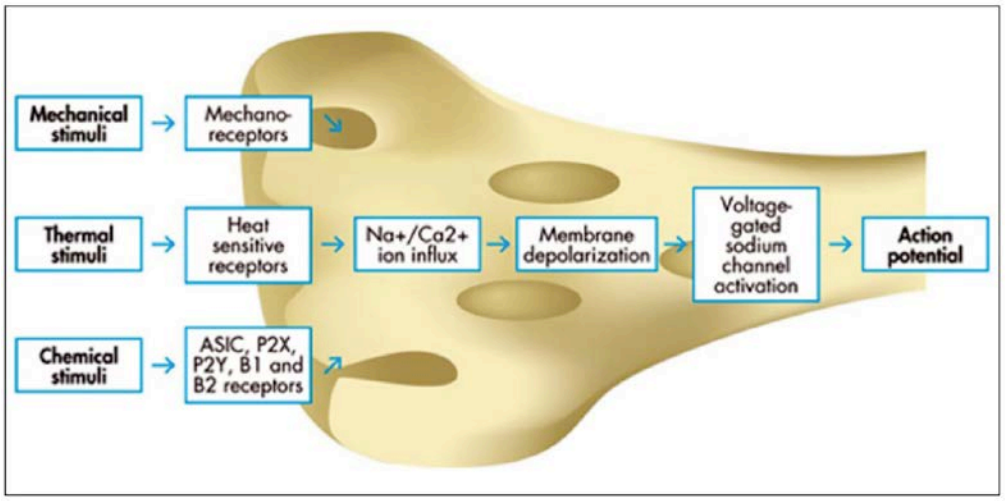

Figure 2. Activation of Peripheral Sensory Terminals.

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 **pKa** or **dissociation constant** 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.

Only unionized LA molecules can translocate across biological membranes. 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**. Predictably, 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.

When a threshold number of LA molecules interact with their receptors, the action potentials will be temporarily blocked.[2,11,12] Because of differential functional blockade is 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: pain, temperature, touch, proprioception, and finally motor functions.

Table 1. The elimination half-life of LAs is predicated on their lipid solubility and protein-binding capacity.

	Lidocaine	Mepivacaine	Prilocaine	Articaine	Bupivacaine
Lipid solubility	43	21	25	17	346
Plasma protein-bound fraction	60-80	75	55	60-80	95
Elimination half-life ($T_{1/2\beta}$)	≈2.0	≈1.9	≈2.0	≈1.8	≈5.5

The rate of LAs' **absorption** from the site of administration into the systemic circulation is also predicated on **passive diffusion**.[2-10] Once in the vascular compartment, LAs bind to albumin, α-1 acid glycoproteins, and erythrocytes. Consequently, the **protein-binding capacity** of a LA affects drug distribution from the vascular compartment to other body fluids or tissues, including LAs' ability to reach their receptors on the voltage-gated sodium channels (Table 1).[2-10]

The distribution of a drug from the vascular compartment has three distinct phases. Phase 1 reflects the rapid decline in drug plasma levels due to the drug's distribution to well-perfused tissues (i.e., brain, liver, heart, kidneys, and lungs). Phase 2 reflects the decline in drug plasma levels due to the drug's slow distribution to less well-perfused tissues (i.e., skeletal muscles and fat) and mirrors a **drug's distribution half-life** ($T_{1/2\alpha}$).[3-10]

Phase 3 of drug distribution reflects the decline in drug plasma levels due to **clearance**, i.e., metabolism and excretion of the drug and mirrors the drug's **elimination half-life** or $T_{1/2\beta}$.[3-10] The degree of tissue uptake of LAs is expressed as their **volume of distribution** (V_d).[3-10] LAs with greater lipid solubility and lower plasma protein-binding capacity have a greater V_d. Therefore, a drug's V_d is the primary determinant of the drug's elimination half-life ($T_{1/2\beta}$) (Table 1).[3-10]

The **metabolism** of most aminoamide-type LAs takes place primarily in the liver by cytochrome P450 isoenzymes CYP3A4 and CYP1A2.[2-10] The **excretion** of their metabolites and any unchanged drugs takes place in the kidneys.[2-10] Prilocaine is metabolized both in the liver and the kidneys, its metabolites and any unchanged drug molecules are also exerted in the kidneys. As a rule, aminoamide-type LAs require 5 elimination half-lives, i.e., $T_{1/2\beta}$ x 5, for systemic clearance.

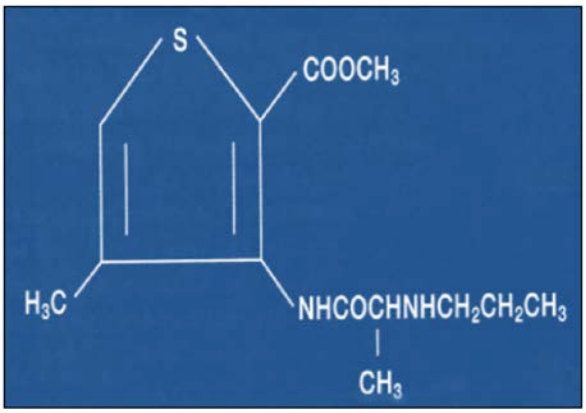

Figure 3. Structural Domains of Articaine.

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 sidechain by plasma carboxylesterases. 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.

Adjuvants in Local Anesthetic Agents

The vehicle for LAs is sterile water. Some LAs contain citric acid, an antioxidant; edetate calcium disodium, a stabilizer; and sodium

chloride to produce isotonicity. Sodium hydroxide and/or hydrochloric acid are added to adjust the pH, to a pH range of 3.4 to 6.5, favoring the formation of stable water-soluble LA salts in the solution. Once injected into the interstitial space, the buffering capacity of the extracellular fluid (physiological pH of 7.4) favors the formation of free base LA and greater diffusion.

Most LA formulations include epinephrine for vasoconstriction.[13-16] It decreases the rate of LAs' systemic absorption, thereby, reducing the risk of LAs' systemic toxicity; it localizes LAs, thereby, prolonging LAs' duration of action; and, with infiltration anesthesia, reduces superficial bleeding from arterioles and capillaries in the operative field.[13-17] The vasoconstrictor in the mepivacaine 2% formulation is levonordefrin, a derivative of norepinephrine.[16]

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 formulation should provide profound, reversible local anesthesia with rapid onset and satisfactory duration of action, and minimal adverse effects.[4]

Potency

The structural domain of LAs responsible for their lipophilicity is the aromatic group. The **lipid solubility** or **partition coefficient** of LAs determine their ability to pass through biological membranes and reach their sites of action.[2-10] Therefore, the primary determinant of an agent's potency is its partition coefficient. A LA with higher potency will require a lower dose to achieve the same degree of neuronal blockade as that achieved by an agent with lower potency (Table 2).

Onset of Action

The structural domain of LAs responsible for their hydrophilicity is the amine group. In aqueous solution, the primary determinant of the ratio of ionized to unionized LA molecules is the LA's **pKa** or the **dissociation constant**.[2-10] A LA with a pKa closer to 7.4 (physiologic pH) will have a greater fraction of neutral molecules at the site of drug administration that can diffuse across neuronal membranes, and, therefore, a faster onset of action (Table 3).

Duration of Action

LAs' receptors on the voltage-gated sodium channels are integral membrane proteins. Predictably, the primary determinant of a LA's duration of action is its **protein-binding capacity** (Table 1). LAs with high protein-binding capacity bind more tightly to and dissociate more slowly from their receptor sites and, therefore, have a longer duration of action (Table 4).[2-13] Other factors affecting the duration of action of LAs include their lipid solubility, vascularity at the injection site, the presence of a vasoconstrictor in the formulation, and dosing.

Dosing

LAs' nonselective voltage-gated sodium channel blockade is responsible not only for its therapeutic effect but also for most of its adverse 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.[2,6-10,19-21] The dosage for healthy adults is based on body weight; however, if a patient's weight is ≥150 lbs. no more than the maximum recommended dose (MRD) should be administered (Table 5).[4-10,19-21]

Dosing must also take into considerations the dose of epinephrine or levonordefrin in a LA formulation. To minimize medication errors, it is prudent to think of dosage strengths in mg/mL rather than ratio expressions, e.g., 1:100,000 (Table 5). The maximum recommended dose (MRD) of epinephrine in healthy adults is 0.2 mg per visit.[13] Levonordefrin, 0.05 mg, is bioequivalent to epinephrine, 0.01 mg; consequently, the MRD of levonordefrin is 1 mg.[17] In high-risk populations, a dose of 0.02 to 0.05 mg of epinephrine is recommended.[13]

Precautions Related to the Administration of LAs

Drugs seldom exert their beneficial effects without also causing adverse drug reactions (ADRs). For example, some LAs or their

Table 2. Lipid solubility determines a LA's relative potency, which is reflected in the drug's formulation.

	Lidocaine	Mepivacaine	Prilocaine	Articaine	Bupivacaine
Lipid solubility	43	21	25	17	346
Relative potency	≈2	≈1	≈1	≈1	≈8
Formulations	2%	2% or 3%	4%	4%	0.5%

Table 3. A LA's pKa determines the fraction of free base at the site of drug administration, which is reflected in the drug's onset of action.

	Lidocaine 2%	Mepivacaine 2%	Prilocaine 4%	Articaine 4%	Bupivacaine 0.5%
pKa (Dissociation constant)	7.9	7.7	7.9	7.8	8.1
Fraction of free base at pH 7.4	25%	33%	25%	29%	1.7%
Onset of action	2-4 min.	2.4 min.	2.4 min.	2-4 min.	4.8 min.

Table 4. Range of Duration of Action of Various Local Anesthetic Agent Formulations.*[18]

	Infiltration: Pulpal Anesthesia	Nerve Block: Pulpal Anesthesia	Soft Tissue Anesthesia
Lidocaine 2 %, plain	5 min.	—	120 min.
Mepivacaine 3 %, plain	20-30 min.	45-65 min.	120-180 min.
Prilocaine 4 %, plain	10-15 min.	45-65 min.	180-240 min.
Lidocaine 2 %, w/epi.	55-70 min.	80-90 min.	180-300 min.
Mepivacaine 2 %, w/lev.	40-60 min.	60-90 min.	180-300 min.
Articaine 4 %, w/epi.	60-75 min.	120 min.	180-300 min.
Prilocaine 4 %, w. epi.	30-45 min.	50-70 min.	180-360 min.
Bupivacaine 0.5 %,	7 hrs.	47 hrs.	12 hrs.

*Based on data from Brandt RC, Anderson PF, McDonald NJ, et al. The pulpal anesthetic efficacy of articaine versus lidocaine in dentistry – a meta-analysis. JADA 2011;142(5):493-504.

Table 5. Dosage strengths of local anesthetic agents in mg/mL of LA and epinephrine in mg/mL in LA and maximum safe doses in mL of LA.[6-10]

LA formulations		MRD of LA in mg	LA in mg/mL	500 mg of LA in mL of LA	MRD of EPI in mg	EPI in mg/mL	0.2 mg of EPI in mL of LA
Lidocaine 2%	w/ epinephrine 1:100,000	500	20	25	0.2	0.01	20*
	w/ epinephrine 1:50,000	500	20	25	0.2	0.02	10*
Mepivacaine 2%	w/levonordefrin 1:20,000	400	20	20*	1.0 (levonordefrin)	0.02	20*
Prilocaine 4%	w/epinephrine 1:200,000	600	40	15*	0.2	0.005	40
Articaine 4%	w/epinephrine 1:100,000	500	40	12.5*	0.2	0.01	20
	w/epinephrine 1:200,000	500	40	12.5*	0.2	0.005	40
Bupivacaine 0.5%	w/epinephrine 1:200,000	90	5	18*	0.2	0.005	40

*Maximum safe dose of LAs in mL per visit predicated on the MRD of LA or MRD of epinephrine or levonordefrin

metabolites are inherently toxic and produce cytotoxic reactions; other reactions may be immune mediated or idiosyncratic.[2-10,18-25,49-51] In general, ADRs associated with the administration to lidocaine, mepivacaine, prilocaine, articaine, and bupivacaine are similar and may be consider together.[2-10] However, some unique toxicities will be highlighted.

Local Reactions

Epithelial and vascular reactions may be due to LAs' dosage-related cytotoxic nature or they may be vasopressor-induced.[2,5] These reactions may manifest as edema, desquamation, and ischemic necrosis (Figure 4) and 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.[2,5]

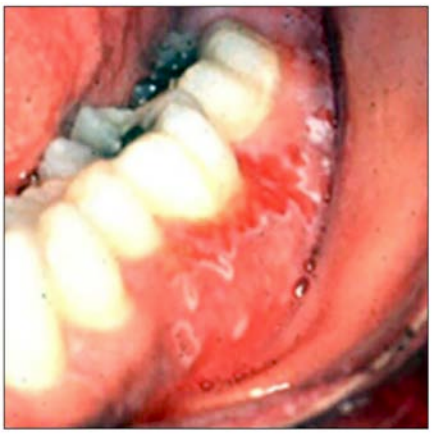

Figure 4. Edema and Desquamation Secondary to the Repeated Topical Application 10% Lidocaine Stray.

Neurologic deficit may reflect a LA's dose-related neurotoxicity and/or the technique employed (e.g., infiltration versus nerve block).[2,5,22-24] 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. The reported incidence of permanent paresthesia in the U.S. following mandibular nerve block with prilocaine 4% and articaine 4% is 7.3 and 3.6 times greater, respectively, than expected.[22] These findings are consistent with those reported from other countries.[23,24] 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.[2,4-10,19-21,26,27] Excitatory effects are usually brief and include lightheadedness, restlessness, anxiety, apprehension, euphoria, confusion, dizziness, tinnitus, blurred or double vision; twitching, tremors, and rarely convulsions. Depressant effects include drowsiness progressing to unconsciousness, 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 are the direct effect of LAs on cardiac conduction, excitability, and contractility.[2,4-10,19-21,26,27] Early signs of reduced cardiac output include sweating, faintness, and altered mentation; followed by bradycardia, hypotension, and progressive cerebral hypoxia leading to seizures. Depressed cardiac conduction, excitability, and contractility may progress to ventricular arrhythmias, atrioventricular block, and cardiac arrest.

Hypersensitivity Reactions

Allergic reactions may manifest as pruritus, erythema, rash, urticaria, angioedema, wheezing, asthma (coughing, difficulty breathing); and, rarely, anaphylaxis.[2,4-10,20,21,28-31] Allergic reactions to ester-type LAs have been confirmed. Ester-type anesthetic agents are metabolized by plasma cholinesterase. One of the metabolites, 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.[2,4-10,20,21,28-31] However, LAs with a vasoconstrictor contain metabisulfite that may precipitate an allergic reaction.[6-10,32,33] The prevalence of sulfite allergy in the general population is unknown, but sulfite sensitivity is seen more frequently is patients with asthma. 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.

Idiosyncratic Reactions

Methemoglobinemia is an uncommon idiosyncratic reaction most notably to prilocaine and topical benzocaine.[6-10,20,21,34-38] Their metabolites bind to hemoglobin and interfere with its oxygen-carrying capacity. Signs and symptoms usually appear 3 to 4 hours after exposure and may include cyanosis, fatigue, weakness, nausea, sedation, seizures, and coma. Young patients and those with congenital methemoglobinemia or glucose-6-phosphate deficiency are the most susceptible.

Drug-drug Interactions

LA's dosage should be reduced in patients taking other CNS depressants as they are additive. Caution is recommended when administering LAs with a vasoconstrictor to the patient taking tricyclic antidepressants, some β_1-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.[6-10]

Local Anesthetic Agents and Pregnancy

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, required the removal of the old pregnancy categories A, B, C, D, and X from all drug product labeling.[39] 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.[6-10]

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, required the inclusion of a "Lactation" subsection in the package insert.[40] Information about LA-related risks to the breastfeeding child and recommendations about the use of LAs in breastfeeding mothers can be found in the "Lactation" subsection of specific package inserts.[6-10]

Sympathetic Reactions

Epinephrine has a narrow therapeutic window, reaching peak plasma levels in 5-10 minutes.[17,40-44] Since it does not cross the blood-brain barrier, adverse reactions are the result of peripheral effects and may occur even with therapeutic doses. Signs and symptom may include restlessness, agitation, anxiety, tremulousness, headache, dizziness, pallor, palpitation, and tachycardia; and patients with Parkinson's disease may experience increased tremor and rigidity.[6-10,45-48]

Particularly vulnerable populations to the effects of therapeutic doses of epinephrine include the young and the old; those with high BP, severe cardiovascular disease (i.e., unstable angina pectoris, recent myocardial infarction (MI), decompensated heart failure, severe valvular disease, supraventricular arrhythmias with uncontrolled ventricular rate, and symptomatic ventricular arrhythmias); patients with uncontrolled hyperthyroidism; and those taking certain drugs.[6-10,45-48]

Epinephrine should be used with caution in patients on other sympathomimetic agents because of additivity in patients on nonselective β-adrenoceptor antagonists, which block β_2-adrenoceptor-mediated vasodilation resulting in unopposed α-adrenoceptor-induced vasoconstriction and high BP.[17,45-50] Epinephrine should be avoided in patients on cocaine, since it inhibits the reuptake of epinephrine increasing HR and BP.[50]

Epinephrine should be used with caution in patients under the influence of general anesthetics (e.g., halothane and cyclopropane) that sensitize the myocardium to epinephrine causing ventricular arrhythmias (premature ventricular contractions, tachycardia, or fibrillation).[17,45-50] Levonordefrin should be avoided in patients on tricyclic antidepressants (e.g., amitriptyline) that inhibit the reuptake of norepinephrine increasing HR.[17,45-50]

Epinephrine should be used with caution in patients with supraphysiological thyroid levels (i.e., thyroid overdose or hyperthyroidism) that upregulate β-adrenoceptors in vascular smooth muscles sensitizing the myocardium to β-adrenergic effects of epinephrine increasing HR and BP.[17,45-50] Caution is also recommended when patients are on digoxin and diuretics, which may increase cardiosensitivity and potentiate the arrhythmogenic effects of epinephrine, respectively.[17]

The β_1-adrenergic activity of epinephrine may decrease uterine contraction and prolong labor; its α_1-adrenergic activity may decrease uterine blood flow and fetal circulation. However, it has been shown that bolus doses of epinephrine, 0.1 mg, did not prolonged the duration of labor and did not adversely affect placental blood flow and fetal circulation.[51-62] Investigators considered the addition of epinephrine to LAs beneficial for it reduced the dosage of LA required for pain relief.

Levonordefrin, in the mepivacaine 2% formulation, activates peripheral α_2-adrenoceptors in vascular smooth muscles and causes vasoconstriction.[49] It also activates α_2-adrenoceptors in the cardiovascular control center of the CNS, thereby, suppresses sympathetic output from the brain and lowers BP. Consequently, levonordefrin is less likely than epinephrine to cause cardiac arrhythmias but it may cause reflex bradycardia.

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 each clinical situation and the dosage administered should be predicated on potential toxic and other ADEs. In most

instances, lidocaine 2% w/epinephrine 1:100,000 is as effective as, and less toxic than, other agents.

Infiltration anesthesia with lidocaine 2% w/ epinephrine 1:50,000 may be useful to provide surgical hemostasis. Mepivacaine 3% plain provides for longer duration of action than lidocaine 2% plain and it is a good option when the use of a vasoconstrictor is contraindicated. Infiltration anesthesia with articaine 4% w/ epinephrine 1:100,000 may provide for a greater probability of achieving pulpal anesthesia with longer duration in comparison to lidocaine 2% w/epinephrine 1:100,000.

Bupivacaine, because of its high lipid solubility and high protein-binding capacity, 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 in patients younger than 12 years of age is not recommended. Bupivacaine is also the most cardiotoxic of all LAs.

The use of epinephrine with LAs is standard dental practice. The question to ask is not whether epinephrine should be used – the question to ask is how much epinephrine can be used safely. To minimize serious medication errors, think of dosage strengths of epinephrine in mg/mL of LA rather than ratio expressions (e.g., 1:100,000). In general, the MRD of epinephrine with LAs for healthy adults is 0.2 mg per visit; in high-risk populations, 0.02 to 0.05 mg is recommended.

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/ce646/test*

1. All the following statements related to LAs are correct EXCEPT which one?

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 primarily used by dentists have an amide-linkage and lidocaine is the prototypical amide or aminoamide LA.
C. Procaine produces psychological and physical dependence, mood alteration, CNS and cardiac excitation, and intense vasoconstriction.
D. The structural components of LAs affect their pharmacological characteristics.

2. All the following statements related to homeostatic mechanisms in excitable neuronal cells are correct EXCEPT which one?

A. Excitable neuronal cells maintain a chemical gradient with low extracellular sodium and low intracellular potassium concentrations.
B. In resting state, the inside of neuronal cells is electronegative (-50 to -90 mV) and the outside is electropositive.
C. Nociceptive or painful stimuli alter the distribution of sodium and potassium ions and briefly reverse electrical polarity.
D. The energy generated by neuronal depolarization may activate voltage-gated sodium channels.

3. All the following statements related to action potential generation and LAs' interaction with its receptors are correct EXCEPT which one?

A. If the threshold energy level required for the activation of voltage-gated sodium channels is reached, sodium ions flow into the cell and an action potential is generated.
B. LAs irreversibly reduce the amplitude and conduction velocity of action potentials by interacting with their receptors located on voltage-gated sodium channels.
C. The sites of action of LAs on voltage-gated sodium channels are located on the cytosolic side of these large membrane proteins.
D. From the site of administration, to interact with their receptors, LAs must diffuse across lipophilic neuronal membranes.

4. All the following statements related to the ability of LAs to cross biological membranes are correct EXCEPT which one?

A. LAs cross neuronal membranes by passive diffusion as function of its pKa or dissociation constant and the pH of the environment at the site of drug administration.
B. 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. Unionized LA molecules are unable to reach their receptors or diffuse into the circulation and become trapped at the site of 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 ionized.

5. All the following statements related to LAs' absorption into and distribution from the vascular compartment are correct EXCEPT which one?

A. The rate of absorption of LAs into the systemic circulation is predicated on passive diffusion.
B. In the vascular compartment, LAs bind to albumin, α-1 acid glycoproteins, and erythrocytes.
C. The protein-binding capacity of an LA affects drug distribution from the vascular compartment to other body fluids or tissues, including LAs' ability to reach their receptors.
D. The rapid decline in drug plasma levels due to the drug's distribution to well-perfused tissues (i.e., brain, liver, heart, kidneys, and lungs) reflect the drug's distribution half-life.

6. All the following statements related to LAs' volume of distribution (V_d) and elimination half-life ($T_{1/2\beta}$) are correct EXCEPT which one?

A. The degree of LAs' tissue uptake is expressed as its V_d.
B. LAs with lower plasma protein-binding capacity have a greater V_d.
C. A LA's lipid solubility has no effect on its Vd.
D. The V_d of LAs is the primary determinant of its elimination half-life ($T_{1/2\beta}$).

7. All 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 rule, aminoamide-type LAs require 5 half-lives, i.e., $T_{1/2\beta}$ x 5, for systemic clearance.

8. All the following statements related to adjuvants in LAs are corrects EXCEPT which one?

A. Adjuvants include citric acid and edetate calcium, an antioxidant and a stabilizer, respectively.
B. The adjuvant sodium chloride produces isotonicity.
C. Sodium hydroxide and/or hydrochloric acid is/are added to increase the pH of the solution.
D. The vasoconstrictors epinephrine or levonordefrin are added to decrease LAs' rate of diffusion into excitable neuronal cells.

9. All 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.

10. All the following statements relative to a LAs' 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 ration of protonated to deprotonated forms is predicated on the drug's dissociation constant (pKa) and the pH of the environment.
C. The closer is a LA's pKa to the pH at the site of its administration (physiologic pH of 7.4), greater is its ionized fraction 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 LAs onset of action.

11. All the following statements related to LAs' 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. LAs' protein-binding capacity is the primary determinant of its duration of action.
D. The duration of action of LAs is also modulated by their lipid solubility, vascularity at the injection site, and the presence of a vasoconstrictor in the formulation, and dosing.

12. 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

13. 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's weight is ≥150 lbs. no more than the maximum recommended dose (MRD) should be administered.

A. True
B. False

14. All the following statements related to vasoconstrictors in LAs formulations are correct EXCEPT which one?

A. To minimize medication errors, it is prudent to think of dosage strengths in ratio expressions, e.g., 1:100,000, rather than mg/mL of the vasoconstrictor in the formulation.
B. The maximum recommended dose (MRD) of epinephrine in healthy adults is 0.2 mg per visit.
C. Levonordefrin, 0.05 mg, is bioequivalent to epinephrine, 0.01 mg; consequently, the MRD of levonordefrin is 1 mg.
D. In high-risk populations, a dose of 0.02 to 0.05 mg of epinephrine is recommended.

15. All the following statements related to MRDs of LAs' are correct EXCEPT which one.

A. The maximum safe dose of 2% lidocaine w/epinephrine 1:100,000 (0.01 mg/mL) is 20 mL.
B. The MRD of 2% lidocaine (500 mg) with epinephrine 1:50,000 is reached before the MRD of epinephrine (0.02 mg/mL).
C. With mepivacaine 2% w/ levonordefrin 1:20.000, the MRD of mepivacaine (400 mg) and the MRD of levonordefrin (1 mg) are both reached at 20 mL of the LA.
D. Based on the MRD of articaine 4% (500 mg) with epinephrine 1:100,000 (0.01 mg/mL) or 1:200,000 (0.005 mg/mL), the MRD of articaine is 12.5 ml.

16. All the following statements related to LAs' local toxicity are correct ECEPT which one?

A. LA-induced epithelial and vascular reactions may include edema, desquamation, and ischemic necrosis.
B. Injection into muscles may result in LA-associated myotoxicity and vasoconstrictor-associated necrosis.
C. Most cases of LA-induced neurotoxicity manifest as permanent anesthesia or paresthesia of the lip, tongue, and other oral tissues.
D. The reported incidence of permanent paresthesia following mandibular nerve block is significantly higher with 4% LA formulations.

17. All the following statements related to LAs' CNS toxicity are correct EXCEPT which one?

A. The excitatory CNS effects of LAs are characterized by lightheadedness, restlessness, anxiety, apprehension, euphoria, confusion, dizziness, tinnitus, blurred or double vision, twitching, tremors, and rarely convulsions.
B. The excitatory manifestations of LAs' CNS toxicity are prolonged.
C. CNS depressant effects of LAs include drowsiness progressing to unconsciousness, respiratory depression, and finally, respiratory arrest.
D. LAs' CNS toxicity may include nausea, vomiting, chills, and miosis.

18. With high plasma concentration of LAs, early signs of reduced cardiac output include sweating, faintness, and altered mentation; followed by bradycardia, hypotension, and progressive cerebral hypoxia leading to seizures; and, finally, may progress to ventricular arrhythmias, atrioventricular block, and cardiac arrest.

A. True
B. False

19. All the following statements related to LA-induced allergic reactions are correct EXCEPT which one?

A. A breakdown product of ester-type LAs, para-aminobenzoic acid (PABA), can sensitize lymphocytes or eliciting the formation of IgE antibodies.
B. Allergy to amide-type LAs and cross sensitivity among members of amide-type LAs is common.
C. LAs with a vasoconstrictor contain metabisulfite that 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.

20. All the following statements related to epinephrine toxicity are correct EXCEPT which one?

A. Epinephrine has a relatively narrow therapeutic window, reaching peak plasma levels in 5-10 minutes.
B. Since epinephrine crosses the blood-brain barrier, epinephrine-associated ADRs are the result of CNS effects.
C. Signs and symptoms of epinephrine toxicity include restlessness, agitation, anxiety, tremulousness, headache, dizziness, pallor, palpitation, and tachycardia.
D. In patients with Parkinson's disease, epinephrine may increase tremor and rigidity.

21. Particularly vulnerable populations, even to the effects of therapeutic doses of epinephrine, include all the following EXCEPT which one?

A. The young and the old
B. Those with high BP and severe cardiovascular diseases
C. Patients with uncontrolled hypothyroidism
D. Patients on nonselective β-adrenoceptor antagonists, which block β_2-adrenoceptor-mediated vasodilation resulting in unopposed α-adrenoceptor-induced vasoconstriction and high BP

22. All the following statements related to the use of LAs containing a vasoconstrictor during pregnancy are correct EXCEPT which one?

A. There is general concern that the β_1-adrenergic activity of epinephrine may decrease uterine contraction and prolong labor.
B. There is general concern that epinephrine's α_1-adrenergic activity may decrease uterine blood flow and fetal circulation.
C. Investigators have found that bolus doses of epinephrine up to 0.1 mg do not prolong labor.
D. Investigators have found that the use of LAs with epinephrine in healthy pregnant women does affect placental blood flow and fetal circulation.

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Additional Resources

- No Additional Resources Available.

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