Local Anesthetic Agents in Dentistry

Video Transcript

Hello, everyone. My name is Tom Viola. I am the founder and CEO of Pharmacology Declassified and this is another dentalcare.com continuing education course entitled Local Anesthetic Agents in Dentistry.

Cocaine was the first recognized local anesthetic agent. Its addictive properties and toxicity, psychological and physical dependence, mood alteration, central nervous system and cardiac excitation, and intense facial constriction, preclude its clinical use. Procaine, a cocaine analog, has short duration of action, but high allogenicity and is no longer available in dental cartridges. Today, local anesthetics that are available in dental cartridges include lidocaine, ropivacaine, prilocaine, articaine, and bupivacaine.

Local anesthetics consist of an aromatic group connected by an ester or amide linkage to an aliphatic chain with a secondary or tertiary amine group. Procaine has an ester-like linkage connecting the aromatic group to the amine group, and is the prototypical ester or amino ester local anesthetic. Agents primarily used by dentists have an amide linkage and lidocaine is the prototypical amide or amino amide local anesthetic agent. These structural domains affect local anesthetics' pharmacologic characteristics.

Homeostatic mechanisms and excitable neuronal cells maintain a chemical radiant with high extracellular sodium and high intracellular potassium concentrations such that the inside of neuronal cells is electro negative and the outside is electro positive. Nociceptive or painful stimuli alter the distribution of these ions and briefly reverse the electrical polarity, which may lead to neuronal membrane depolarization. The energy generated by neuronal depolarization may activate voltage gated sodium channels. If the threshold energy level of the activation or voltage gated sodium channels is reached, sodium ions flow into neuronal cells and the action potential is generated.

Local anesthetics 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 local anesthetic agents are located on the cytosolic side of these large membrane proteins, following administration local anesthetics must diffuse across those lipophilic neuronal membranes.

Local anesthetic agents cross neuronal membranes by passive diffusion. Since local anesthetic agents are weak basis in an aqueous environment, they exist as a mixture of protonated or positively charged ionized, and deprotonated or neutral unionized or non-ionized molecules. The ratio of ionized to non-ionized forms of local anesthetic agent is predicted by its PKA, or dissociation constant, and the pH of the drug's milieu, the environment at the site of the drug administration. The PKA is the pH at which the drug is 50% ionized and 50% non-ionized. Only non-ionized, or therefore fat soluble local anesthetic molecules, can cross biologic membranes. Ionized local anesthetic 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 is deposited in an infected or an inflamed site with a pH less than 7.9, more than 50% of its molecules become protonated and will be unable to diffuse across biologic membranes. This is the mechanism by which infection and inflammation interfere with the activity of local anesthetic agents.

When the threshold number of local anesthetic molecules interact with their receptors, when enough have crossed the membrane, the action potential becomes temporarily blocked. Because of differential functional blockade and its predictability on the degree of myelination of nerve fibers and the local anesthetic's concentration gradient, different fiber types are blocked at different times. The general order of function deficit progresses sequentially as follows: pain, temperature, touch, proprioception, and finally motor functions.

The rate of the local anesthetic's absorption from the site of administration into the systemic circulation is also predicted by passive diffusion. Once in the vascular compartment, local anesthetic agents bind to albumin, alpha-1-acid glycoproteins, and erythrocytes. Consequently, the protein binding capacity of a local anesthetic agent affects drug distribution from the vascular compartment to other bodily fluids or tissues, including local anesthetic's ability to reach their receptors on the voltage gated sodium channels.

The distribution of a drug from the vascular c- compartment has three different phases. Phase one reflects the rapid decline in the drug's plasma levels due to the drug's distribution to the well-perfused tissues: brain, liver, heart, kidneys, lungs. That's where you will find the adverse effects of a local anesthetic agent. Wanna know where an anesthetic agent's gonna cause its most side effects? Look at the most well perfused organs.

Phase two reflects the decline in drug plasma levels due to the drug's slow but inevitable distribution to less well perfused tissues, such as skeletal muscles and fat, and therefore mow- mirrors a drug's distribution half-life.

Phase three of drug distribution reflects the decline in drug plasma levels due to clearance. So this is where the drug is being metabolized and excreted. And again, that mirrors a drug's elimination half-life. The degree of tissue uptake of the local anesthetic agent is expressed as a volume of distribution, as with all drugs. Local anesthetic agents with greater lipid solubility and lower plasm protein capacity have a greater additional volume of distribution. Therefore, a drug's volume of distribution is the primary determinant of a drug's elimination half-life.

What does that mean in easy to understand terms, my friend? That means that the more fat soluble and less plasma protein binding a local anesthetic agent is, the greater will be its volume of distribution.

Okay. The metabolism of most amino amide type local anesthetic agents, like lidocaine, take place primarily in the liver by cytochrome P450 enzymes, which you know are like CYP3A4 and CYP1A2. The excretion of their metabolites, and unchanged drug, takes place in the kidneys.

Prilocaine is a little different. Prilocaine is metabolized in both the liver and the kidneys. It's metabolites and any unchanged drug molecules are also excreted in the kidneys. As a rule, amino amide type local anesthetic agents require five elimination half-lives for systemic clearance. To give you some idea, lidocaine's half-life is about 90 minutes. 90 times 5 is 450 minutes. That's a little over six hours it takes, therefore, for lidocaine to be excreted directly from the body.

While articaine is a member of the amino amide group of local anesthetic agents, it's unique in that it contains a thiophene or a [thiopentene 00:08:10] based nucleus, as well as an ester linkage connecting a side chain. As a result, articaine is rapidly inactivated via hydrolysis in the blood stream by plasma cop- cholinesterases. Only about 5 to 10% of articaine, therefore, is actually metabolized

at- in the liver by hepatic microsomal CYP450 enzymes. These metabolites, and any unchanged drug, are excreted by the kidneys.

When we talk about the adjuvants in local anesthetic agents, realize that the vehicle for local anesthetic agents is usually sterile water. Now, some local anesthetics, uh, in cartridges contain citric acid, which is an antioxidant, [inaudible 00:08:55] calcium disodium, a stabilizer, and sodium chloride, obviously to produce isotonicity.

Now, sodium hydroxide and/or hydrochloric acid are added to adjust the pH. Usually acid is added to adjust the pH range down to 3.4 to 6.5. This favors the formation of a stable water soluble local anesthetic salt in solution. Aqueous solution. However, once injected into the intratissual space, the buffering capacity of the extracellular fluid, physiologic pH of 7.4, favors the formation of a free base local anesthetic agent and therefore greater diffusion.

So, in other words, the cartridges contain acid to bring the pH down to make a stable, water soluble salt. But keep in mind, every time you add a cartridge of anesthetic agent, you're really adding acid. Now, when you inject, the buffering capacity of the tissue neutralizes that acid and therefore favors the formation of a fat soluble local anesthetic agent in its free base form, and that fat soluble free base will cross the membrane and have activity.

Most local anesthetic formulations include epinephrine for vasoconstriction. Why? Well, it decreases the rate of the local anesthetic agent's systemic absorption and thereby reduces the risk of any systemic toxicity. It localizes the local anesthetic agent, locks it in, thereby prolonging the local anesthetic agent's duration of action, and especially with infiltration anesthesia, reduces superficial bleeding from arterials and capillaries in the operative field.

The vasoconstrictor that's sometimes found with mepivacaine is levonordefrin. In that combination the concentration of mepivacaine reduces from 3% normally found in its plain formulation, to 2%. What is levonordefrin? It's a derivative of norepinephrine and it has mostly alpha activity, not so much beta. So therefore it doesn't really cause palpitations, but it can cause an increase in blood pressure.

What about some therapeutic considerations? Well, local anesthesia, at the end of the day, is a reversible sensory loss in a defined area of the body associated with what? Transient inhibition of peripheral nerve conduction. The use of a local anesthetic agent should be followed by complete recovery. There should be no evidence of structural or functional nerve damage. The ideal local anesthetic agent formulation therefore should provide profound reversible local anesthesia with rapid onset and satisfactory duration of action with minimal adverse effects.

Well, what about the potency?

The structural domain of local anesthetic agents responsible for either their fat solubility or water solubility, is ultimately in the aromatic group. The lipid solubility with a partition coefficient of local anesthetics, determines their ability to pass through biologic membranes and reach their sites of action. They gotta be fat soluble to cross one of our phospholipid membranes.

Therefore, the primary determinant of an anesthetic agent's potency is the partition coefficient. A local anesthetic agent with higher potency will require a lower dose to achieve the same degree of neuronal blockade as that which would be achieved by an agent with a low potency.

Okay. The structural domain of local anesthetic agents responsible for their water solubility is the amine group. In aqueous solution, the primary determinant of the ratio of ionized to unionized molecules is, as we say, the local anesthetic agent's PKA or dissociation constant. A local anesthetic agent with a PKA closer to 7.4, which our physiologic pH, will have a greater fraction of neutral molecules, fat soluble, at the site of drug administration that can then diffuse across the neuronal membrane and therefore results in a faster onset of action.

Okay. What about the duration of action? Well, local anesthetic agent's receptors on the voltage gated sodium channels are the integral membrane proteins. Now predictably the primary determinant of a local anesthetic agent's duration of action is its protein binding capacity. Can it lock on to the proteins in the membrane? Local anesthetic agents with a high protein binding capacity bind more tightly to and dissociate more slowly from their receptor sites, and therefore have a longer duration of action. Think bupivacaine.

Other factors, though, do affect the duration of action of local anesthetic agents, and they include the lipid solubility, the vascularity at the injection site, the presence of a vasoconstrictor in the formulation, and of course the dose.

Let's talk about dosing. So local anesthetic agents' non selective, voltage gated, sodium channel blockade is responsible not only for its therapeutic effect, its mechanism of action, but also its adverse effects. High plasma levels, other than overdose, may be caused by what? Repeated dosing. We can't always chase neuronal blockade or profound anesthesia with volume. Rapid absorption, especially in the absence of a vasoconstrictor. Intravascular injection. That's all about accuracy and technique. Low plasma protein binding and slow clearance.

The dosage for healthy adults is based on body weight. However, if a patient's weight is greater than or equal to 150 pounds, no more than the MRD should be administered. Dosing must take into consideration the dose of epinephrin, or in the case of ropivacaine, levonordefrin. That's also included in the local anesthetic formulation.

To minimize medication errors, it's prudent to think of a dosage strength in milligrams per mL, rather than ratio expressions like 1:100,000. The maximum recommended dose, or MRD, of epinephrine in a healthy adult, ASA class one, is 0.2 milligrams per visit. Levonordefrin 0.5 milligrams is bioequivalent to epinephrine at 0.01 milligrams. Consequently, the MRD for levonordefrin is one milligram. In high risk populations, those with significant cardiovascular risk for example, a dose of 0.02 to 0.05 milligrams of epinephrine is recommended.

Well, local anesthetic agents, like most drugs, seldom exert beneficial effects without also causing adverse drug reactions. For example, local anesthetic agents and their metabolites can sometimes be inherently toxic and produce cytotoxic reactions. Other reactions may be immune mediated or even idiosyncratic. In general, adverse drug reactions associated with the administration of local anesthetic agents, like lidocaine, mepivacaine, prilocaine, articaine and ropivacaine, are similar and therefore we may consider them together. However, some unique toxicities deserve to be highlighted.

Epithelial and vascular reactions may be due to a local anesthetic agent's dosage related, cytotoxic nature. Or they may be vasoconstrictor induced. These reactions may manifest as edema, desquamation, and ischemia necrosis, and are usually transient in nature. Injection at the muscles may result in local anesthetic agent associated mild toxicity, and vasoconstrictor associated necrosis. Clinical manifestations include acute pain and trismus, and healing with fibrosis may lead to chronic trismus.

Neurologic deficit may reflect a local anesthetic agent's dose related neurotoxicity, but it could also be related to the technique employed. For example, infiltration versus block. Most cases of neurologic deficit involve the lingual nerve. Signs and symptoms include transient anesthesia or paresthesia, characterized as a sensation of pricking or tingling of the lip, tongue, or other oral tissues that may sometimes take two to six months to resolve. In rare instances the neurologic deficit may be permanent.

The reported deficit or 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. These findings are consistent with those reported from other countries. So clinicians should consider this evidence when assessing the risk versus benefit of

administering a 4% local anesthetic formation for mandibular nerve block anesthesia.

Okay, what about some more systemic events? Well, central nervous system effects of local anesthetic agents can either be excitatory or depressant in nature. Excitatory effects are usually brief and include lightheadedness, restlessness, anxiety, apprehension, euphoria, confusion, dizziness, tinnitus, blurred or double vision, twitching, tremors, and rarely convulsions. But depressant effects can also occur and they include drowsiness, which can progress to unconsciousness, respiratory depression, and finally even respiratory arrest. Other central nervous system effects include nausea, vomiting, chills, and miosis.

How about some cardiovascular effects? Well, signs and symptoms of depressed cardiovascular function are the direct effect of the local anesthetic's action on cardiac induction, excitability, and chronic tactility. So early signs of reduced cardiac output include sweating, faintness, and altered mentation, followed by bradycardia, hypotension, and progressively cerebral hypoxia which can lead to seizures. Depressed cardiac induction, excitability and contractility, can progress to ventricular arrhythmia, atrial ventricular block and cardiac arrest.

Uh, how about allergies? Well, hypersensitivity reactions are allergic reactions may manifest in lots of ways. Uh, pruritus or erythema, rash, urticaria, angioedema, wheezing, asthma, coughing or, you know, difficulty breathing, and rarely but possible, anaphylaxis. Allergic reactions to the ester type local anesthetic agents have been confirmed. Ester type anesthetic agents are metabolized by plasma cholinesterases.

Now, one of the metabolites that's formed is ara-aminobenzoic acid, or PABA, and it's highly antigenic. It's a highly antigenic compound. It's capable of sensitizing lymphocytes and therefore eliciting the formation of antibodies, IgE antibodies.

True allergy to amides is rare. However, local anesthetic agents with a vasoconstrictor containing metabisulfite may precipitate an allergic reaction. It's not the anesthetic agent here, it's the sulfite that's being used as an antioxidant or preservative.

The prevalence of sulfite allergy in the general population is unknown, but sulfite sensitivity is seen more frequently in patients with asthma. That's important to know. Patients allergic to ester type local anesthetic agents have not shown cross sensitivity to amide type local anesthetic agents. And cross sensitivity among members of the amide type local anesthetic agents has not been reported. So someone may be allergic to lidocaine, but may not be allergic to mepivacaine. However, we tend to be cautious with that because, while we haven't seen it, it doesn't mean it doesn't happen.

Okay, so give me some idiosyncratic reactions. Methemoglobinemia. Methemoglobinemia is an uncommon idiosyncratic reaction most notably to prilocaine and, believe it or not, topical benzocaine. Their metabolites bind to hemoglobin and interfere with the hemoglobin's ability to carry oxygen. Signs and symptoms usually appear three to four 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.

Any drug interactions to worry about? Well, local anesthetic agents' dosage should be reduced in patients taking other central nervous system depressants, as they are additive in that effect. We normally recommend caution when administering local anesthetic agents with a vasoconstrictor to a patient who is taking a tricyclic antidepressant, like amitriptyline, some beta-1 adrenergic receptor antagonists that are non-selective, like propranolol, and some general anesthetics. These agents may cause severe hypertension, cardiac arrhythmias, and even cerebrovascular accident. Evidence of interactions with antipsychotic agents or psychotherapeutic agents, and even thyroid hormone, currently are less compelling.

What about safety in pregnancy? Well, in 2014 the FDA amendment to regulations governing

the content and format for labeling human prescription drugs and biologic products became effective on the 30th of June, 2015. And they require the removal of what we used to call the pregnancy categories, category A, B, C, D, and X, from all drug product labeling. Information about local anesthetic related risk to fetus and mom, and recommendations a- about the use of local anesthetic agents during pregnancy, can now be found in the new pregnancy subsection of specific package inserts.

Well, if we're gonna talk about the local anesthetic agent effect on pregnancy, we're gonna have to talk about the effect on breastfeeding. Well, the same 2014 FDA amendment to the regulations governing the content and the format of the labeling for both human prescription drugs and biologic products, which became effective, again, on the 30th of June, 2015, now requires the inclusion of a lactation subsection in the patient package insert.

So, information about the local anesthetic agent related risks to the breastfeeding child, and recommendations about the use of local anesthetic agents in breastfeeding mothers, can now be found in that special lactation subsection of the specific package insert.

We've been focusing a lot on the local anesthetic agent. Let's focus a little now on the reactions to epinephrine. Epinephrine has a narrow therapeutic window. It reaches peak plasma levels in about 5 to 10 minutes. Since it doesn't cross the blood/brain barrier, the adverse effects associated with epinephrine are really the result of peripheral effects. Now, they may occur even within therapeutic doses.

Okay, give me some signs and symptoms of effects related to epinephrine. There's a whole list. Restlessness, agitation, anxiety, tremor, and tachycardia. And patients with Parkinson's disease may actually increase in... experience increased tremor and rigidity. The particularly vulnerable population to the effects of, uh, epinephrine, even in therapeutic doses, include both pediatric and geriatric patients, as well as those with high blood pressure, severe cardiovascular disease like unstable angina pectoris, recent MI, decompensated heart failure, severe valvular disease, supraventricular tachycardia with uncontrolled ventricular rate, and even symptomatic ventricular arrhythmia, patients with uncol- controlled hypothyroidism and even those taking certain drugs.

So we know epinephrine should be used with caution, especially in patients who are taking other agents that are sympathomimetic, because we know that effect is additive, as well as patients who are taking non-selective beta antagonists. Because we know that blocking the beta-2 receptor, and therefore its vasodilation, results in unopposed alpha effect, which therefore results in vasoconstriction and hypertension. Wait, epinephrine's a vasodilator? Yes, in the beta-2 receptor. But if you block that beta-2 receptor, now there's nothing left to balance the vasopressive or vasoconstrictive effects on the alpha receptors.

Of course epinephrine should be avoided in patients on cocaine (laughs), since it inhibits the re-uptake of epinephrine and increases both the heart rate and blood pressure. We do know that epinephrine should be used with caution in patients under the influence of general anesthesia, especially those that sensitized the myocardium to epinephrin, causing no more than the usual ventricular arrhythmia, both premature ventricular contractions, tachycardia, fibrillation. But what about levonordefrin? Well, levonordefrin should be avoided in patients on tricyclic antidepressants. It can inhibit the re-uptake of norepinephrine, 'cause that could increase the heart rate. That's at least theoretical.

Epinephrine should be used with caution in patients with supraphysiologic thyroid levels, or what we call thyroid overdose or simply hyperthyroidism. Because that upregulates the beta receptors in vascular smooth muscles. That sensitizes the myocardium to the beta adrenergic effects of epinephrin, and that increases the heart rate and the blood pressure. Caution is also recommended when patients are on digoxin and diuretics. Why? Because they can increase the cardio sensitivity

and potentiate the anti, uh, arrhythmogenic effects of both epinephrin, uh, respectively.

The beta-1 adrenergic activity of epinephrine may decrease uterine contraction and prolong labor. It's doubtful you're gonna be performing dental procedures with epinephrine on a woman who's likely to give birth quickly, but remember that the alpha-1 adrenergic activity can decrease uterine blood flow and fetal circulation. However, it's been shown that bolus doses of epinephrin, 0.1 milligram, did not prolong the duration of labor and did not adversely affect per- uh, placental blood flow and fetal circulation. Thank goodness. Investigators consider the addition of epinephrine to local anesthetic agents beneficial, 'cause it reduces the dose of local anesthetic agent required for pain relief, and also reduces its, you know, systemic outflow, at least temporarily.

Levonordefrin in the mepivacaine 2% formulation activates alpha-2 receptors and vascular smooth muscles and causes vasoconstriction. Wonderful. But it also activates alpha-2 receptors in the cardiovascular control center of the central nervous system, and thereby suppresses sympathetic output from the brain and actually lowers blood pressure. So consequently, levonordefrin is less likely than epinephrine to cause arrhythmia, which is good, but it may also cause reflex bradycardia, especially if the blood pressure is elevated.

The pharmacologic properties of local anesthetic agents vary from agent to agent. To compensate for these differences, manufacturers have adjusted the concentration of various local anesthetic agents such that they all produce nearly the same effect. Consequently, local anesthetic agents selected in each clinical situation and the dose administered [inaudible 00:30:26] predicated on the potentially toxic effects or other adverse drug effects. In most instances, lidocaine 2% with epinephrine at 1 to 100,000 is as effective and less toxic than other agents. That's why we love it so much. Infiltration anesthesia with lidocaine 2% with epinephrine 1 to 50,000, twice as strong, may be useful to provide surgical hemostasis. Mepivacaine 3% plain provides a longer duration of action that lidocaine 2% plain, even though it's no longer available, and therefore it's a good option when the use of a vasoconstrictor is contraindicated.

Infiltration anesthesia with articaine 4% with epinephrine 1 to 100,000 may provide for greater probability of achieving pulpal anesthesia with long duration, in comparison to lidocaine 2% with epinephrine 1 to 100,000. That may be due to the fact that articaine is more fat soluble. Could be due to the fact that articaine at 4% is twice as concentrated as lidocaine 2%.

Ah, bupivacaine and its high fat solubility and high protein binding capacity produces the longest duration of pulpal anesthesia. This could be useful in lengthy procedures. However, because it will also produce prolonged soft tissue analgesia, it should be used with caution in the elderly and debilitated patients to minimize self-inflicted soft tissue injury. And its use in patients younger than 12 years of age is not recommended. Bupivacaine is also the most cardiotoxic of all local anesthetic agents because of its protein binding capacity.

The use of epinephrine with local anesthetic agents is now a 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 milligrams per mL of the local anesthetic agent, rather than the ratio expressions 1 to 100,000 or 1 to 200,000. In general the MRD of epinephrine for local anesthetic agents, uh, containing epinephrine for healthy adults is 0.2 milligrams per visit. But in high risk populations, a less amount, 0.02 milligram to 0.05 milligrams is generally recommended.