Prepared by Amber Schilling, PharmD

Date:	June 2019
Requestor's Name:	Dr. XXX (Associate Professor, XXX University)
Request Classification:	Therapy Evaluation
Request:	What drugs are used in dental anesthesia and what are the product characteristics that may lead to increased or decreased efficacy in some patients and disease states over others?

Response to Question:

- **Pertinent Background Information**

Experiencing full or partial nerve sensation during a dental procedure can be extremely uncomfortable for the patient and can also complicate the procedure for the clinician. Local anesthetics (such as lidocaine, mepivacaine, bupivacaine, or articaine) are routinely used to anesthetize the area before and during the procedure; however, there are many factors that can influence their efficacy.

All currently available local anesthetics on the market are sodium-channel blockers. Sodium channels are embedded within the phospholipid membrane of nerve cells. Under normal circumstances, an external stimulus causes sodium ions (Na^+) to rush into the cell through these sodium channels. This rapid flow of positive charge propagates a signal along the entire length of the nerve cell, ultimately arriving at the spinal cord and brain for processing. When a local anesthetic antagonizes (or blocks) these sodium channels, sodium ions are blocked from flowing into the cell and a signal cannot be transmitted along the nerve as quickly, or at all.

- **Pertinent Patient Factors**

Some patient populations may report disproportionately higher local anesthetic failure than is observed in the general population. Patient factors that can influence the efficacy of local anesthetics during a dental procedure include area of the oral cavity being anesthetized (lower jaw versus upper jaw), the presence or absence of inflammation, genetic factors, and disease states.

The inflammatory process involves vasodilation to allow increased blood flow to the area and to allow delivery of inflammatory mediators (cells and chemicals) to the site. Vasodilation will hasten the diffusion of local anesthetic drugs away from the area, thus reducing local anesthetic efficacy.

Inflammatory mediators may interfere with anesthetic success by competing for binding sites on the sodium channel within the nerve fiber (competitive inhibition) and by lowering the pH of the surrounding tissues (non-competitive inhibition). Inflammation-induced acidity can affect the efficacy of local anesthetics because a sodium channel blocker's ability to access the sodium channel is pH-dependent. With alkali molecules (including all local anesthetics), increasing tissue acidity will make it harder for the drug molecule to cross the cell membrane and access its binding site. Thus, local inflammation decreases the efficacy of the local anesthetics, making it more difficult to anesthetize those tissues. This may explain why mepivacaine (most acidic local anesthetic) is a good choice when pulpal tissues are inflamed (1, 2).

If individuals have genetic differences in the structure or function of their sodium channels, then drugs that affect sodium channels may have reduced ability to bind to their target, thus imparting lower efficacy.

Genetic polymorphisms in drug metabolizing enzymes are already known to affect the duration of action of several drugs such as warfarin and codeine (3, 4), and more are being discovered. In addition, decreased or impaired liver function can prolong the effect of some drugs which are hepatically metabolized.

Patients suffering from chronic pain often experience a phenomenon known as wind-up pain, which makes pain management particularly difficult to control. Wind-up pain results in the setting of prolonged, persistent release of neurotransmitters involved in pain pathways. This results in the up-regulation of physiologic pathways that ultimately cause patients to experience pain from otherwise non-painful stimuli (allodynia) and an exaggerated amount of pain during painful episodes (hyperalgesia). The wind-up pain phenomenon in and of itself may make achieving adequate anesthesia difficult for patients who deal with chronic pain.

- **Pertinent Medication Factors**

Medication factors that can influence efficacy of local anesthetics include its relative acidity, how it is metabolized, delivery technique (infiltration or block), and whether a vasoconstrictor (commonly epinephrine) is co-administered.

Refer to **Table**.

Dental procaine (tradename Novocain®) has been discontinued in the U.S. and is now only commercially available in combination with injectable penicillin to reduce the pain associated with this antibiotic injection at the intramuscular injection site. Its use as a dental anesthetic began to decline in the 1960s due to the allergenicity of one of its metabolites (PABA, para-amino-benzoic acid) and by the 1980s, most dentists had stopped using it all together.

Lidocaine, mepivacaine, bupivacaine, and articaine are all commercially available within the U.S. for dental procedures (5). Lidocaine was approved for use within the U.S. by the Food and Drug Administration (FDA) in 1948; both mepivacaine and bupivacaine were approved in 1984; and articaine was approved in 2000.

With the exception of mepivacaine, the commercially available preparations of local anesthetics for dental use are co-formulated with epinephrine (a vasoconstrictor) (5). This usually restricts blood flow enough to keep the local anesthetic at the site for the duration of the procedure. Mepivacaine is not co-administered with epinephrine because it does not naturally cause vasodilation to the extent that the other agents do (6).

The duration of action of sodium channel blockers is affected by how rapidly they are metabolized. If metabolism occurs at the site of injection, then the duration of action will be rapid; if, however, the metabolism occurs through complex biotransformation within the liver, the drug will first have to diffuse away from the site and enter systemic circulation before it can be inactivated. The latter process takes more time and hence, the drug will have a longer duration of action. Local anesthetics containing an ester functionality (procaine, and articaine) are rapidly hydrolyzed (cleaved) by esterases in the blood and surrounding tissue directly at the site, giving them a very short duration of action. In contrast, lidocaine, mepivacaine, and bupivacaine, are hepatically metabolized and typically have a longer duration of action. Of these three agents, lidocaine is metabolized the fastest and bupivacaine the slowest (7).

- **Review of pertinent literature**

Clendenen et al. reported that a family with local anesthetic resistance shared the A572D mutation in the SCN5A gene which may indicate a genetic etiology for local anesthetic resistance (8). Several investigators (1, 2, 9, 10) have noted that the presence or absence of inflammation may alter the efficacy of a local anesthetic.

In a recent review by Badr and Aps, the efficacy of local anesthetics used in dentistry was compiled from research conducted within the past decade (11). Eleven (11) of the 30 studies included found that articaine provided better analgesia versus lidocaine; 3 studies found articaine superior to bupivacaine; and 2 studies found articaine superior to mepivacaine. Comparing mepivacaine to lidocaine, 3 studies found them to be similar, while 2 studies found mepivacaine superior. Two studies found bupivacaine superior to lidocaine. A 2018 Cochrane review by George et al. presented similar findings(12). Marhofer et al. (2014) considered an anesthetic failure rate of 30% to be clinically relevant in dentistry (13)

- **Analysis and Synthesis**

Dental procaine (tradename Novocain®) has been discontinued in the U.S. Lidocaine, mepivacaine, bupivacaine, and articaine are all commercially available within the U.S. for local anesthesia during dental procedures (5).

Some patient factors beyond a dentist's control may significantly decrease the efficacy of local anesthetics.

Mepivacaine (most acidic local anesthetic) may be a good choice when pulpal tissues are inflamed (1, 2).

Procaine and articaine have the shortest duration of action of all dental local anesthetics because they are rapidly hydrolyzed by esterases in the blood at the site. Lidocaine, mepivacaine, and bupivacaine, are hepatically metabolized and typically have a longer duration of action. With the exception of mepivacaine, all commercially available local anesthetics for dental use in the US are co-formulated with epinephrine, a vasoconstrictor, to slow their diffusion away from the site and increase their duration of action (5).

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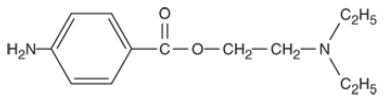
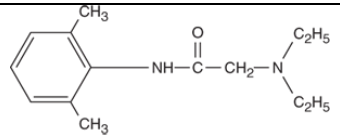
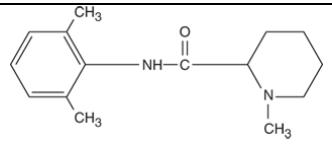
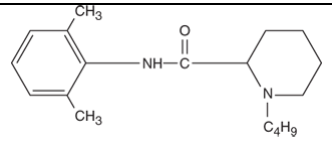
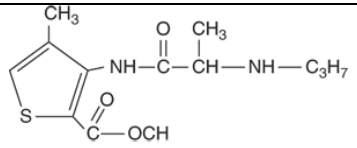
Table. Local anesthetics that have historically been (or are currently being) used in dentistry.

Generic Name *(Trade Name)*	**Chemical Structure**[1]	**How Supplied for Dental Use**	**Molecular Weight** (g/mol)	**pKa** *(& relative acidity)*	**Protein Binding** (%)	**Onset of Action** (mins)	**Duration of Action** (hrs)	**Primary Metabolic Pathway**
Amino Esters								
Procaine *(Novocain)*		discontinued	236	8.8 *(least acidic)*	<10	2-5	0.5-1	Plasma esterases
Amino Amides								
Lidocaine/ Lignocaine *(Xylocaine)*		2% w/ 1:50,000 epinephrine 2% w/ 1:100,000 epinephrine	234	7.8	70-75	2-4	2.5-3.5 (w/ epinephrine) 10-20 mins (w/o epinephrine)	Hepatic
Mepivacaine *(Carbocaine)* *(Polocaine)* *(Scandonest)*		3%	246	7.6 *(most acidic)*	75	0.5-2 (upper jaw) 1-4 (lower jaw)	0.3 (upper jaw) 0.6 (lower jaw)	Hepatic
Bupivacaine *(Marcaine)* *(Sensorcaine)* *(Vivacaine)*		0.25% w/ 1:200,000 epinephrine 0.5% w/ 1:200,000 epinephrine	288	8.1	84-95	2-10	1.5-8.5	Hepatic
Articaine *(Articadent)* *(Orabloc)* *(Septocaine)* *(Zorcaine)*		4% w/ 100,000 epinephrine 4% w/ 1:200,000 epinephrine	284	7.8	76	1-9	1-3.5	Plasma esterases

[1]Chemical Structures taken from (7)

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