Review Article

Local anesthetics in oral and maxillofacial medicine: pharmacology, adverse effects, drug interactions and clinical manifestations

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Abstract: A dentist's ability to safely and accurately deliver regional anesthesia is crucial for pain-free dental treatment. Despite local anesthetics being the most widely used drugs in the field of dentistry, patients are becoming increasingly more susceptible to adverse physiological reactions as a consequence of many potential drug interactions with local anesthetic components. This review offers an update on the basic pharmacology of local anesthesia, the types of reactions following an injection, the most notable drug interactions with vasoconstrictor-containing preparations, and common ways to manage their associated systemic complications. A thorough search for peer-reviewed journal articles was conducted utilizing databases such as PubMed, MEDLINE, ScienceDirect, and the Cochrane Library. In total, 560 articles were identified, 105 investigated and 52 cited in this review. The content was mainly formulated from scientific reviews and peer-edited manuscripts published within the last 5 years, and included relevant keywords in the search process. The exclusion and inclusion criteria regarding the search strategies were also displayed in a table. Specifically, the manuscript provides a pharmacological overview of the various adverse reactions associated with local anesthesia delivery, such as psychogenic complications, allergies, toxicity, methemoglobinemia, and paraesthesia. In addition, the use of vasoconstrictors in local anesthetic preparations, their interactions with other agents, as well as their relevant precautions and contraindications were discussed. A section examining different local anesthesia injection techniques, including infiltrations and nerve blocks in both the mandible and maxilla, with their respective clinical advantages and risks, was also included. Lastly, this paper highlights the pertinence of comprehending a patient's medication history and medical background to evaluate the potential risks and benefits of local anesthesia delivery during dental treatment. Fortunately, the distinctive signs or symptoms of adverse reactions make the diagnosis and treatment a relatively quick process, with serious physiological drug responses being rare and unlikely to result in severe harm when promptly addressed.

Keywords: Local anesthesia; dentistry; adverse effects; drug interactions; clinical management

Received: 03 September 2023; Accepted: 11 December 2023; Published online: 12 January 2024.
doi: 10.21037/joma-23-27
View this article at: https://dx.doi.org/10.21037/joma-23-27

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Introduction

Local anesthesia is a common dental procedure which involves the administration of an anesthetic drug in order to block sensations from an area within the oral cavity. Since around 10% to 30% of patients experience anxiety associated with painful dental operations, anesthesia has played a crucial role in enabling dentists to maximize patient comfort throughout the course of an appointment (1). Although anesthetics have been used for over 175 years, individual patient factors and the clinical scope of dental surgeries have drastically changed with time. Therefore, it is paramount for current dental practitioners to comprehend how these locally administered preparations interact with both exogenously delivered drugs, as well as naturally occurring compounds within the body.

Local anesthetic agents are drugs that can block the generation and propagation of nerve impulses in a reversible manner. Moreover, these preparations have the ability to depress the conduction of electrical signals in all excitable cells, including sensory peripheral nerves, motor peripheral nerves, nerves within the central nervous system, autonomic ganglia, neuromuscular junctions, smooth muscle cells, as well as cardiac muscle cells. Throughout all of history, the main purpose in administering local anesthetics was to transiently eliminate sensations at a specific location, ultimately permitting surgical treatment and relieving pain (2).

Prior to understanding how local anesthetics function, it is important to outline the nature of the pain pathway. Despite pain being dictated by many intricate sensory pathways, this unpleasant signal or feeling is also largely guided by the complex experience of perception. The first step in the pain model involves either a painful trigger or tissue damage, which ultimately activates specialized nerve cells (nociceptors). In turn, pain signals are sent to the spinal cord, where they enter the dorsal horn. Furthermore, some of these signals of pain are increased or decreased by interneurons before continuing up to the brain (3). Likewise, beliefs, feelings and thoughts can change the pain signals into the individual's experience of "pain". Certain parts of the brain create signals that may travel back down the spinal cord to either increase or decrease pain signals at the level of the interneuron. All in all, pain itself is contextual, and it can be modulated on the way up and down depending on the situation (3,4).

Over the years, the study of local anesthetics has led to the proposal of certain theories pertaining to their methods of action at the molecular level. In the membrane expansion theory, it has been suggested that local anesthetic molecules diffuse into the hydrophobic regions of excitable membranes, leading to the expansion of critical regions within the nerve cell's bilayer. When specific areas of the membrane are expanded, an increase in permeability to sodium channels is impaired. In other words, the membrane expands to compress this space, therefore blocking ions (5). Despite what this theory postulated, the hypothesis surrounding the membrane expansion theory has largely given way to the specific receptor theory. This newer and more widely accepted idea suggests that local anesthetic molecules bind directly to specific receptors on sodium channels. Interestingly, this theory states that local anesthetics operate within sodium channels and that there are four potential sites of action. Therefore, the general mechanism of action of local anesthesia directly and selectively involves a nerve membrane's sodium channels, in which there is an induction of a reversible and dose-dependent reduction in local currents while the electrical potential remains unchanged. Evidently, blockage of these sodium channels can progress until there is a total inhibition of ion flow, where the net result would be the blockage of action potential propagation (5,6). Previous studies have shown that as the concentration of the local anesthetic agent increases, the firing threshold for an action potential becomes elevated, and the spread of conduction down the length of the axon is slowed significantly. In myelinated nerve fibres, these electrical phenomena only occur at the nodes of Ranvier, which are intermittent gaps along the axon that are devoid of fatty sheets. From a chemical point of view, the presence of fatty sheets on nerve fibres could affect the efficacy of local anesthetic delivery. Knowing that the sodium channels are both charged and water soluble, the fat-soluble nature of a myelinated nerve fibre would render it more difficult for the local anesthetic ions to reach their target on the axonal membrane (5,7).

The nerve membrane, through which electrical impulses travel, is composed of a double layer of phospholipids containing structural proteins, enzymes and ion channels throughout. The channels, otherwise known as ionophores, are very selective for specific ions such as sodium; these protein channels are regulated, or gated, by a membrane potential. In terms of sodium ionophores, they possess a major subunit (alpha) which is made up of four domains, each containing six helical transmembrane domains. Furthermore, each channel is linked to an inactivation

gate outside the channel, and an activation gate inside the channel. When it comes to sodium channel cycling, the ionophores involved may be present in closed, open, or inactive configurations (6). Depolarization reverses the resting membrane potential from interior negative to interior positive. As a result of this electrical change, the channel proteins change from a closed resting state to an ion-conducting state. Ionophore state changes continue from open to inactive, where the channel configuration assumes an impermeable structure. This protein channel cycling is a fundamental principle pertaining to the function and action of all local anesthetics; these agents become physically lodged within the ionophores and block the flow of ions across the membrane, ultimately inhibiting action potential conduction (5,6,8).

Two theories have been previously proposed to describe the nature of nerve impulse inhibition via local anesthetic administration: the use-dependent block and the differential nerve block. In the use-dependent block, the efficacy of local anesthesia can be increased following the repeated stimulation of a nerve fibre. Likewise, it has been discovered that local anesthetic preparations are more effective at inhibiting high-frequency impulses compared to single action potentials. This is because, with a greater electrical impulse rate, the ionophores are in an open configuration more often, thus allowing the local anesthetic molecules to access their binding site more readily (9). All in all, the use-dependent block suggests that freezing is faster when the target nerve is stimulated prior to local anesthesia (9,10). In the differential nerve block, it is believed that nerves with different functions have variable sensitivities to local anesthetics. For instance, sympathetic fibres, such as smaller B and C fibres, are most sensitive to the numbing effect of local anesthesia. Similarly, pain and touch fibres are moderately sensitive, while motor fibres (e.g., larger A fibres) are the least sensitive. In terms of critical length, the differential nerve block theory states that smaller nerves are easier to freeze because the nodes of Ranvier are closer together. On the other hand, larger nerves are harder to freeze because local anesthetic molecules need to traverse longer diffusion distances to achieve the desired numbing effect. In general, there is a mixed population of nerve fibres with different rates of impulse conduction and diameters, which can lead to a differential blockade altogether (11).

Despite their undisputed importance, studies have shown that vasoconstrictor-containing local anesthetics may cause undesirable effects in patients who have been recently exposed to controlled substances or drugs of addiction. This paper will highlight the pharmacokinetics and pharmacodynamics of commonly used local anesthetic agents, as well as the potential adverse drug interactions between anesthetic preparations, endogenous hormones, recreational drugs and prescription medications.

Methods

A thorough review was conducted to identify the most relevant adverse interactions with common local anesthetic agents used by general dentists and specialists. Likewise, the information collection process involved a detailed search for peer-reviewed journal articles from the University of Toronto Library System, which were thoroughly read and interpreted prior to compiling the data displayed in this article. The main electronic databases used from the library system were PubMed, MEDLINE, ScienceDirect and the Cochrane Library. Furthermore, physical-copy textbooks from the University of Toronto Dentistry Library were used as a supplementary tool to confirm the accuracy and relevancy of certain clinical details. A total of 560 articles were identified, 105 investigated and 54 cited in this review. Some of the major keywords that were searched in the online databases included “local anesthesia”, “local anesthetic agents”, “adverse interactions”, “clinical outcomes” and “dentistry”. In addition, over 70% of the content outlined in this paper is derived from scientific reviews and peer-edited manuscripts that were published up to 5 years ago. For a comprehensive depiction of the exclusion and inclusion criteria for choosing pertinent reference articles, refer to *Table 1*.

Discussion

Basic pharmacology of commonly used local anesthetics

In terms of molecular structure, local anesthetic molecules share three common features: a lipophilic (aromatic) group, an intermediate chain with an amide or ester linkage, and a hydrophilic (tertiary amine) group. It is the intermediate group that defines whether an anesthetic agent is an amide or an ester by classification. Further, the amphipathic nature of these molecules ensures that the local anesthetic will soak through the nerve’s hydrophobic myelin sheath and bind to the hydrophilic protein channel within the membrane (11). Of the amide local anesthetic agents, the three subcategories include the xylidine derivatives, the toluidine derivative,

Table 1 Inclusion and exclusion criteria for selecting the references utilized in this article

Inclusion criteria
Peer-reviewed articles
Written in English, or possess a copy translated to English
Preference for publications released from 2017 onward
Papers displaying objectively measured outcomes of study
Exclusion criteria
Papers which were not peer-reviewed
Not written in English, or do not possess a copy translated to English
Journals not accessible online
Duplicate publications
Editorials and letters
Papers displaying self-reported outcomes of study

and the thiophene derivative. Specifically, the xylidine derivatives are lidocaine, bupivacaine and mepivacaine, while the toluidine and thiophene derivatives are prilocaine and articaine respectively. Though classified as an amide local anesthetic, it is important to note that articaine contains an additional ester linkage, giving it the shortest elimination time of the amides (11,12). With respect to the ester local anesthetics, they include procaine, benzocaine, tetracaine and cocaine. Even though both amide and ester preparations possess the same mechanisms of action, they are differentiated by their slightly dissimilar metabolic pathways, which will be described later. In dentistry, the majority of invasive procedures are preceded by the administration of an amide local anesthetic; ester preparations are used mainly as topical agents to minimize the pain associated with needle puncture through mucosal surfaces (11,13).

Studies have revealed a variety of factors which could directly affect the onset of action of local anesthetic drugs. Precisely, the agent's concentration plays a key role, as the number of molecules administered close to the target nerve could influence the ion flow through sodium channels. In addition, the anesthetic's lipid solubility and its proximity to the nerve of interest can either increase or decrease the time it takes to obtain a numbing effect. Moreover, the nerve's morphology, the pH of the tissue being frozen, and the ionization constant (pKa) of the drug must be considered when evaluating local anesthesia efficacy. For example, a wider nerve trunk would lead to a longer onset time as the drug molecules would need to cover a larger diffusion distance to reach their binding site on the sodium channels. Also, the greater the difference between the tissue's pH and the drug's pKa, the slower the onset of action, and vice versa (12,14). Within the prepared cartridge, the local anesthetic base is considered stable when it exists in a water-soluble form, being a hydrochloride salt. However, the molecules' charged state makes penetrating the neuron's sheath extremely difficult. Therefore, the onset of action is related to the anesthetic's pKa, which is calculated using the Henderson-Hasselbalch calculation. Particularly, it is the proportion of molecules that are converted to the lipid-soluble state at a pH of 7.4 which determines the onset time of local anesthesia. The aforementioned idea suggests that the higher the pKa of the agent, the greater the number of molecules are present in a water-soluble state, thus slowing down the onset of numbing (15). This chemical concept can be observed clinically in patients with an infection, as dentists may find it harder to anesthetize such cases. Since the pH of the oral cavity becomes more acidic in the presence of inflammation, the water-soluble form of the preparation is favoured, which would ultimately lead to less molecules infiltrating the nerve and reaching their target site on the ionophores (16,17). Despite knowing that all of these physiological variables can alter the onset times, other patient factors may also prove to be large threats to the overall success of local anesthesia.

The length of time that a local anesthetic dose lasts directly depends on how long the agent can stay near the nerve of interest in order to block sodium channels. As a result, it could be argued that the local anesthetic's ability to diffuse from its intended location is the most important factor that dictates its duration of action. Apart from cocaine, which is the only vasoconstrictive local anesthetic, all of the other amide and ester agents have vasodilation properties. This means that, when given alone, these preparations rapidly redistribute away from the site of injection. The incorporation of a vasoconstrictor such as epinephrine, however, has shown to drastically slow down this diffusion rate and increase the period of anesthesia (18). Along with proximity to the anatomical target, the duration of action is also influenced by protein binding, which is an inherent pharmacological characteristic. A protein-bound drug is considered inactive, but when liberated from its substrate, the local anesthetic becomes active. Correspondingly, a drug with a higher protein binding rate would sustain a longer neural blockage, thus achieving a

longer duration of activity. Similarly, the concentration of local anesthetic directly influences duration of action, as described by the dose-response curve. Moreover, the more lipid-soluble the drug is, the less likely that it will dissolve away because of its tendency to stay in fat tissue. Ultimately, all of the previously listed factors are crucial in defining the time span of anesthesia in the oral cavity (14,18).

The metabolism of amides is primarily completed in the liver, where hepatic microsomal enzymes aid in the formation of water-soluble metabolites. Lidocaine is N-dealkylated to monoethylglycinexylidide, which is the anesthetic's active metabolite and is about 80% as potent as the pre-transformed agent. Prilocaine is also biotransformed in the kidney and plasma, but its metabolite, ortho-toluidine, can potentially induce methemoglobinemia in predisposed patients (19). Since articaine contains an ester link, the hydrolysis of this agent occurs primarily in the plasma. Lastly, bupivacaine is largely metabolized in the liver, where it is N-dealkylated to pipecolylxylidine. The metabolism of the esters is mainly completed in the plasma by an enzyme called pseudocholinesterase. From a clinical perspective, the biotransformation of local anesthetics should not be a concern unless the patient presents with severe liver dysfunction or pseudocholinesterase deficiency (19,20). Nevertheless, a prudent practitioner should be aware of the total amount administered, while not necessarily worrying about changing the amount per injection. With respect to elimination, both amides and esters are excreted in the urine.

A scientific theory has recently been proposed regarding the reasoning as to why recreational drug use is associated with recalcitrant local anesthesia. A recreational drug is typically defined as a chemical substance that is taken for psychoactive effects rather than for medical reasons. Further, these agents can be found naturally, or they can be synthesized in a laboratory setting. Some examples of recreational drugs used worldwide include, but are not limited to, marijuana, cocaine, morphine, 3,4-methyle nedioxymethamphetamine (MDMA), heroin, lysergic acid diethylamide (LSD), ketamine, amphetamines, methamphetamines, psilocybin mushrooms, as well as volatile substances such as gases, aerosols and glues. Difficulty in achieving effective local anesthesia has been observed clinically in recreational drug users. The pharmacodynamic factors of regional numbing have effects on both peripheral nerve sensitization and central sensitization. Some researchers believe that past or current drug use may alter the emotional perception of pain, leading to patients normalizing their pain threshold to a new set point. Another theory suggests that, since many recreational drugs produce dysphoric states of mind, patients consuming such drugs may enter a state of hyperalgesia (21). All in all, experts believe that patients who are current or past users of recreational drugs may have an altered sensory system and a lower overall pain threshold, meaning that they often require more local anesthesia and are predisposed to local anesthetic toxicity (21-23).

Types of adverse reactions

Following the intra-oral delivery of an anesthetic, the likelihood that a patient would experience an abnormal response is relatively rare. Although viewed as a safe procedure, local anesthesia can sometimes induce an adverse physiological reaction, especially considering the high number of annual injections performed by dentists worldwide.

Psychogenic reactions are observed when mental stressors initiate the physical symptoms of different disorders. In fact, anxiety is often the most common culprit leading to the development of adverse reactions associated with local anesthetics. Of the various types of psychogenic responses, syncope is regarded as the most frequently occurring medical emergency in the dental office (19). In addition to fainting, other examples of adverse events include nausea and vomiting, hyperventilation, changes in blood pressure, as well as changes in heart rate. Interestingly, many psychogenic symptoms can mimic allergic reactions, such as skin rashes, throat itchiness, numbness around the lips, bronchospasm and generalized edema (19,24).

Allergic responses to local anesthesia, albeit common, are often induced by psychological distress (19,24). Studies have shown that a true allergy to one ester compound excludes the use of any other ester agents, since the metabolism of all esters yields the main allergenic component (para-aminobenzoic acid) (25). Likewise, patients that carry a true allergy to para-aminobenzoic acid should avoid methylparabens, which are antifungal preservatives that were previously used in multi-dose anesthetic vials. Due to its allergenicity, and with the advent of single-use cartridges, methylparaben has been removed from all preparations. In addition to being exceedingly rare, an allergy to an amide compound does not necessarily rule out the use of a different amide anesthetic. Also, it has been suggested to avoid vasoconstrictive agents in patients who are truly allergic to sulfites; metabisulfites are added to

Table 2 Signs of local anesthetic toxicity

Low
Analgesia
Sedation
Antidysrhythmic
Intermediate
Slurred speech
Light-headedness
Drowsiness
Diplopia
Euphoria
Dysphoria
Muscle fasciculations
Sensory disturbances
High
Respiratory depression
Tremors
Tonic clonic seizures
Disorientation
Lethal
Respiratory arrest
Cardiovascular system collapse
Coma

Table 3 Sample calculation for the amount of local anesthetic solution per cartridge

Given variables	Calculation
• 1 dental anesthetic cartridge contains 1.8 mL of solution	1.8 mL × 20 mg/mL = 36 mg
• The concentration of a 2% solution is 20 mg/mL	
• 1 dental anesthetic cartridge contains 1.8 mL of solution	1.8 mL × 40 mg/mL = 72 mg
• The concentration of a 4% solution is 40 mg/mL	

preparations containing vasoconstrictors since they operate as antioxidants (19,25).

The toxicity of local anesthesia is directly related to the amount of compound absorbed into systemic circulation. This phenomenon, termed Local Anesthetic Systemic Toxicity (LAST), is a dose-dependent concept that affects children more often than adults. For the majority of cases, the correct administration of these agents does not lead to any noteworthy side effects. However, in the event of injecting too many concurrent doses or introducing an accidental intravascular injection, certain organ systems could endure negative consequences (19). Several key signs and symptoms of LAST are outlined in *Table 2*. The central nervous system is usually affected first, where the inhibitory neurons become blocked and excitatory symptoms emerge, such as involuntary muscle fasciculations, seizures and diplopia. Subsequently, and as the plasma concentration of the agent increases, depressive symptoms such as unconsciousness, respiratory arrests and comas may ensue (19,26). After the neurological responses, the cardiovascular system is next most susceptible to experiencing adverse effects. Bradycardia is often the first reaction, as rising concentrations begin to block sodium channels within the myocardium. Ultimately, prolonged systemic absorption of local anesthetics could lead to atrioventricular blocks, ventricular dysrhythmias and cardiac arrest altogether (27). Additionally, a sample calculation for the amount of local anesthetic solution per cartridge is portrayed in *Table 3*. The recommended maximum doses for commonly administered local anesthetics with or without a vasoconstrictor is shown in *Table 4*, even though toxicity depends on many

Table 4 Recommended maximum doses of local anesthetic agents with or without a vasoconstrictor

Preparation	Maximum dose
Articaine (4%; 1:100,000)	7 mg/kg (up to 500 mg); 5 mg/kg in pediatric cases
Articaine (4%; 1:200,000)	7 mg/kg (up to 500 mg); 5 mg/kg in pediatric cases
Lidocaine (2%)	4.5 mg/kg (up to 300 mg)
Lidocaine (2%; 1:50,000)	3.5 mg/kg (up to 250 mg)
Lidocaine (2%; 1:100,000)	7 mg/kg (up to 500 mg)
Bupivacaine (0.5%; 1:200,000)	2 mg/kg (up to 200 mg)
Mepivacaine (3%)	6.6 mg/kg (up to 300 mg)
Mepivacaine (2%; 1:20,000)	6.6 mg/kg (up to 400 mg)
Prilocaine (4%)	8 mg/kg (up to 400 mg)
Prilocaine (4%; 1:200,000)	8 mg/kg (up to 600 mg)

interrelated factors, including the speed of injection, the site of delivery and the presence or absence of a vasoconstrictor. Lastly, it is important to note that the maximum doses for pediatric patients should be calculated according to body weight, not age.

Methemoglobinemia is a condition in which cyanosis develops in the absence of respiratory or cardiac abnormalities. Explicitly, it is a blood disorder where an abnormally large amount of methemoglobin is produced. It may manifest as a consequence of a congenital abnormality, or as a result of consuming certain drugs and chemicals. When this ailment arises, the patient becomes unresponsive to oxygen, and the blood appears chocolate brown in colour. Thankfully, the intravenous administration of 1% methylene blue usually resolves this condition. Clinically, it has been revealed that high doses of prilocaine, benzocaine or tetracaine can induce this cyanotic state approximately 3–4 hours after local anesthetic administration (27). In terms of prilocaine, its metabolite (ortho-toluidine) can block MetHb reductase, thus leading to high levels of methemoglobin. All in all, research suggests avoiding the use of prilocaine, benzocaine or tetracaine in patients with an inherited form of methemoglobinemia (19,28).

Paraesthesia is a broad term defining prolonged anesthesia or variable sensations, exceeding the expected duration of action of a local anesthetic preparation. Of the altered sensations a patient could experience, the three main ones are dysesthesia, hyperaesthesia and allodynia. Simply put, dysesthesia is an unpleasant sensation that does not necessarily involve pain. Hyperaesthesia is defined as excessive physical sensitivity to a stimulus, while allodynia occurs when pain is induced by a stimulus that normally does not cause pain. Most cases of paraesthesia are transient, with the majority of patients reporting complete recovery within a 2-month time frame. Even though the precise cause of this condition has not been confirmed, some speculate that it could arise as a result of intraneural hematoma formation, direct nerve trauma, neurotoxicity or scar formation. Unfortunately, paraesthesia has no definitive treatment and it could remain indefinitely in some cases (19,29,30). Several retrospective studies have shown that, although speculative, most incidents of paraesthesia occur following the use of articaine or prilocaine. The reason for this is not due to the drug per se, but it is believed that higher concentrations may simply predispose patients to a greater effect. Likewise, results have demonstrated that the tongue is most frequently affected by this ailment, since the lingual nerve is the anatomical target at risk (29).

Vasoconstrictors in local anesthetic preparations

Administering a local anesthetic solution with a vasoconstrictive agent has become a consistent method to ensure hemostasis during dental surgery, reduce systemic toxicity, and to increase the length and depth of anesthesia. In dentistry, the main vasoconstrictors that are added to local anesthetic preparations are epinephrine and levonordefrin (31).

Epinephrine itself displays a rapid onset and a short duration of action, being approximately 5 to 10 minutes following an intravenous injection and 10 to 20 minutes after an intraoral injection. This compound, otherwise known as adrenaline, is a sympathomimetic catecholamine which exerts its actions on alpha- and beta-adrenergic receptors via a G protein-linked secondary messenger cascade (32). Physiologically, vasoconstriction occurs due to epinephrine's activity on alpha-1 receptors within vascular smooth muscle. Furthermore, this hormone stimulates beta-1 receptors in the heart, leading to an increased contraction strength, heart rate and oxygen consumption within the myocardial tissue. The beta-2 receptors are also targeted, ultimately inducing the vasodilation of blood vessels within skeletal muscle. With low-dose administrations (e.g., 1 to 2 cartridges of 1:100,000 epinephrine), physiological observations would include decrease in total peripheral resistance, an increase in cardiac output, and an unaltered mean blood pressure reading. In terms of metabolism, exogenously-administered epinephrine is mainly bio-transformed by an enzyme called catechol-O-methyltransferase (COMT) (32,33).

Levonordefrin is a sympathomimetic amine whose activity is similar to that of epinephrine, although it is considered to be more stable than the aforementioned hormone. Likewise, this compound is approximately one-sixth as potent as epinephrine, and it exhibits more alpha receptor activity (75%) than beta receptor activity (25%). As with adrenaline, levonordefrin is metabolized and eliminated from the body with the help from COMT and monoamine oxidase (MAO). Specifically, COMT breaks down exogenous epinephrine located within the bloodstream, while MAO breaks down intraneuronal epinephrine (32).

Key drug interactions with vasoconstrictors

Although epinephrine has served a functional purpose since its inception in anesthesia, studies have identified a handful of hallmark interactions between this exogenous

hormone and certain drugs. Historically, epinephrine within local anesthetic preparations has been found to mainly interact with non-selective beta-blockers, tricyclic antidepressants, amphetamines and vapor anesthetics (19). With the advancement of research within the field of dental anesthesia, other interactions have been found to be associated with exogenous epinephrine and levonordefrin. When these agents chemically collaborate with the aforementioned exogenous hormones, it is possible to witness a variety of adverse physiological effects.

Research has revealed that six non-selective beta-blockers, when combined with epinephrine, can promote unopposed alpha effects and an increase in mean blood pressure. These drugs include pindolol (Visken), propranolol (Inderal), oxprenolol (Trasicor), nadolol (Corgard), timolol (Blocadren) and sotalol (Sotacor). In the event that an epinephrine-containing local anesthetic is given to a patient who is taking one of the previously listed non-selective beta-blockers, the dentist is advised to monitor their patient's blood pressure and heart rate throughout the procedure (19,33,34).

The tricyclic antidepressant medications to be concerned of are amitriptyline (Elavil), nortriptyline (Aventyl), protriptyline (Vivactil), imipramine (Tofranil), desipramine (Norpramine) and doxepin (Sinequan). With the tricylic antidepressant's ability to block the non-adrenergic reuptake channels, this would lead to an elevated concentration of epinephrine, levonordefrin and serotonin within the synaptic cleft. Ultimately, this would cause an increase in cardiovascular activity as a result of summative anticholinergic effects at the neuronal level. When these agents interact with exogenous vasoconstrictors, enhanced sympathomimetic effects, increased blood pressure, and a greater risk of postural hypotension could be witnessed as well. It is also important to note that levonordefrin is contraindicated for patients taking a scheduled regimen of the aforementioned tricyclic antidepressants (34,35).

As to the amphetamines, such as cocaine, an interaction with exogenous adrenaline may lead to potentially lethal cardiac dysrhythmias and blood pressure elevation. Cocaine exhibits some tricyclic antidepressant-like activity and can enhance adrenergic neurotransmitter release and postsynaptic responses to epinephrine-like agents (35). With this knowledge, it is recommended to avoid injecting a vasoconstrictor in those who have used cocaine within 24 hours of their scheduled appointment, as the heart is especially primed to exogenous epinephrine during this timeframe. In these situations, mepivacaine or prilocaine plain can be used, since these mixtures lack vasoconstrictors (19). Similarly, norepinephrine reuptake inhibitors and amphetamine-like stimulants, such as attention deficit hyperactivity disorder medications, are able to augment the release of norepinephrine and catecholamines while also chemically blocking their reuptake. The latter two drug classes may be used in children and adults with normal heart rates and blood pressures (36).

General anesthetics, such as halothane, are known to cause some unwanted responses when combined with injectable epinephrine. On the bright side, interactions between adrenaline and other vapour preparations are less likely than with halothane, which is no longer available for human use. When a drug interaction does occur, however, it can lead to serious cardiac dysrhythmias. As a result, dental clinicians are advised to limit the dose of epinephrine in local anesthetics to less than 1 µg/kg (19,31).

With the widespread legalization of cannabis across the United States and Canada, it has become more likely that dental practitioners will come across patients who have used this drug prior to their dental appointment. Hence, clinicians need to be aware of the possible drug interactions between cannabis and sedatives, anti-inflammatories, analgesics, antibiotics or antifungals. From a physiological perspective, marijuana can lead to an increase in blood pressure and a decrease in the body's ability to carry oxygen, making patients more likely to suffer from a heart attack within the first hour of use (36,37). An increased heart rate, in addition to other cardiorespiratory effects of cannabis, makes the use of epinephrine in local anesthetics for procedural pain management potentially life-threatening. Likewise, due to the effects of cannabis on the central nervous system, frequent users of this drug may require a higher dose of local anesthetic than nonusers. All in all, recent research has concluded that the additive effects of epinephrine anddelta-9-tetrahydrocannabinol increase the overall risk of stroke or myocardial infarction in those who have used cannabis immediately prior to their dental visit (37,38).

Recently, researchers have found that COMT inhibitors, such as entacapone and tolcapone, can interact with vasoconstrictors in local anesthetics. These drugs act as adjuncts to levodopa/carbidopa in the management of Parkinson's disease, and they work by reversibly blocking COMT, thus inhibiting levodopa inactivation in the periphery (39). Surprisingly, these adjunct agents also inhibit the inactivation of epinephrine and levonordefrin

Table 5 Precautions and contraindications to vasoconstrictors in dentistry

Precautions to vasoconstrictors
• Patients on tricyclic antidepressants
• Patients on phenothiazine compounds
• Patients on monoamine oxidase inhibitors
• Patients on non-selective Beta-blockers
• Patients on digoxin
• Patients undergoing general anesthesia (mainly with Halothane)
• Cocaine users
Contraindications to vasoconstrictors
• Heart diseases: recent myocardial infarction, recent coronary artery bypass surgery, unstable angina, untreated or uncontrolled severe hypertension, untreated or uncontrolled congestive heart failure, refractory arrhythmias
• Uncontrolled diabetes
• Uncontrolled hyperthyroidism
• Steroid-dependent asthma
• Pheochromocytoma
• Sulphite allergies

in local anesthetic solutions. Therefore, it is recommended to initially administer no more than the equivalent of one cartridge of lidocaine with 1:100,000 epinephrine, and to monitor the patient's heart rate and blood pressure prior to dispensing another dose of local anesthetic containing a vasoconstrictor (36).

It has been known for decades that alcoholic patients may exhibit a variable response to drugs commonly used in clinical dentistry (40). As these patients develop a tolerance to ethanol through routine consumption, they also raise their tolerance for sedative agents such as general and local anesthetics. In other words, this population of patients will likely require greater than average doses in order to achieve the appropriate degree of anesthesia for dental procedures. Interestingly, alcoholics may experience physiological alterations in the way drugs are metabolized, particularly for drugs which are mainly processed in the liver. The chronic consumption of alcohol-containing beverages results in a cumulative elevation of the mixed-function oxidase system enzymes, which are grouped into a super-family commonly known as cytochrome P450; these proteins are responsible for the metabolism of drugs within the liver. Ultimately, this can result in an accelerated drug metabolism cascade, leading to a shortened substance half-life and a potential reduction in the agent's effectiveness. Typically, alcoholics with healthy livers tend to metabolize drugs faster than the average population due to enzyme induction. On the other hand, those with less severe liver conditions, such as fatty liver, usually maintain normal metabolic efficiency. Further, individuals with more advanced liver diseases, such as hepatitis or chronic cirrhosis, often experience a slower-than-normal metabolic rate due to the loss of these essential enzymes (40,41). Overall, predicting the impact of these physiological differences in individual patients can be very challenging.

Some local anesthetic substances that are significantly metabolized by the liver include both lidocaine and mepivacaine, which are medications that are very commonly employed prior to routine operative dentistry. Therefore, it is important for the treating dental clinician to consult with the patient's physician to outline the safe dosages according to their liver function. Dental anesthesiologists typically advise the utilization of ester-type local anesthetics for individuals with alcoholic cirrhosis because of their more consistent metabolic processing rates. For instance, a local anesthetic cartridge containing 0.4% propoxycaine hydrochloride (Ravocaine) combined with 2% procaine hydrochloride (Novocain) is available on the market, with a total volume of 1.8 mL per cartridge. These ester formulations, which belong to the para-amino benzoic acid family, undergo rapid breakdown via plasma cholinesterase hydrolysis, and the liver processes them to a lesser extent compared to the amide-type local anesthetic agents (41).

Vasoconstrictor precautions and contraindications

There are a number of medical conditions which warrant prudency when administering local anesthetics containing vasoconstrictive agents. *Table 5* displays two separate lists for some of the most common precautions and contraindications that general practitioners and specialists should be aware of (42).

Clinical differences between local anesthesia injection techniques

With the evolution of clinical dentistry, dental practitioners have increasingly diversified their methods of achieving anesthesia within the oral cavity. Despite the large variety

of approaches discovered over the years, the choice of local anesthetic injection technique mainly depends on the type of dental procedure being performed, the risk of adverse consequences unique to each patient, and the extent of analgesia required (43).

Firstly, one of the most common techniques used to anesthetize a specific tooth or small area in the mouth is the infiltration method, which involves injecting the local anesthetic solution directly into the tissues surrounding the teeth that require treatment. Although this technique is relatively safe to execute, some common adverse effects could include, but are not limited to, post-injection swelling and damage to nearby oral tissues if the needle penetration is not precise. Secondly, nerve blocks are employed in order to achieve more profound anesthesia of multiple teeth in a quadrant and their surrounding soft tissues; this is done by injecting the anesthetic fluid near a major nerve that supplies a larger surface area of the oral cavity. Similarly, some studies have shown that nerve blocks are more effective than infiltrations in terms of providing long-lasting analgesia for procedures such as extractions or root canal therapies, but this evidence is not conclusive and varies among different research articles according to their unique experimental criteria (43). Generally speaking, current research suggests that infiltrations lead to faster analgesia and a more tolerable peri-operative pain level compared to nerve blocks, which are only more effective with respect to duration of action compared to infiltrations. Due to their more invasive and penetrative nature, nerve blocks also possess a greater risk of nerve damage, trismus, needle breakage, facial paralysis, paraesthesia, ocular manifestations, accidental intravascular injection leading to systemic effects, and possible hematoma formation (43).

In terms of the mandibular nerve blocks, the Gow-Gates technique is often deemed as the most promising injection, with a close-to 99% success rate when performed by experienced dentists. Although it is viewed as a difficult technique to master, it possesses a smaller risk of facial paralysis following imprecise technique execution, hematoma formation and vascular contact compared to the traditional inferior alveolar nerve block (IANB). With the IANB, published success rates are between 80% to 92%, and efficacy can be improved by injecting the anesthetic solution more slowly, waiting for a longer period of time post-injection for the analgesic effect to work, using an adequate needle gauge, and promoting relaxation prior to injecting (44). In addition, the Vazirani-Akinosi technique has the same indications as the Gow-Gates technique and the IANB, but it is often recommended when the patient has trismus or cannot open their mouth wide enough, when it is difficult to visualize the anatomic landmarks, when there is a history of failure with other mandibular blocks, and when there is accessory innervation present. Lastly, maxillary nerve blocks are considered to be extremely effective in anesthetizing regions of the maxillary jaw when appropriately administered, but they do present with their own risks and clinical complications, such as trismus, hematoma formation, intravascular injection, and ocular disturbances. The latter risk is especially important to note for maxillary nerve block techniques such as the greater palatine approach, the high tuberosity approach and the posterior superior alveolar approach, whereby diplopia (double vision), esotropia (cross-eyed) and amaurosis (blindness) have been previously reported (45).

Interactions between different local anesthetics

In general, the majority of studies state that the combination of different local anesthetic preparations does not produce an interaction of clinical significance (19,41). Despite this finding, there is some evidence suggesting that combining such agents during local anesthesia delivery may lead to additive toxicity; it is recommended to stay well below maximum doses during combination dosing (41).

Relevance to the dental practice

With the insight of this review, general practitioners and specialist dentists should come to understand the importance of knowing which drugs the patient is taking prior to administering local anesthetic solutions intraorally. This is because, occasionally, an adverse interaction can occur between a drug and the vasoconstrictive agent contained within the preparation. In most cases, carefully injecting small doses of vasoconstrictors, avoiding the use of gingival retraction cords possessing epinephrine, and monitoring vital signs will permit the use of most drugs with little to no risk of serious complications. In general, the use of vasoconstrictors like epinephrine can be permitted for most dental operations, but the doses may need to be minimized for patients with cardiovascular disease or for those currently enrolled in specific drug regimens, whether warranted or not (42).

Recent studies have indicated that dentists and specialists within the field who incorporate substance abuse screening tools into their practices, and who possess a thorough understanding of the addiction process, are more likely to

make inquiries related to substance misuse when interacting with their patients on a day-to-day basis (46). As a result, a demand exists for comprehensive education among dental clinicians with respect to the pre-, peri- and post-operative management of the addicted patient (47).

In the event that a patient consumed illicit substances prior to a dental appointment, and has not informed the dentist about it, a cascade of negative events could occur if the clinician has not been trained to detect the physiological signs and symptoms of an adverse reaction. In order to effectively manage these types of situations, such as when a patient has cocaine in their system, the dentist should begin by assessing the patient's physical condition. Specifically, the clinician should focus on signs such as tachycardia, excessive perfusion, hypertension, anxiety, restlessness and confusion (48). Following this initial emergency assessment, the dentist or surrounding staff should call for immediate assistance, especially if the patient's physical status appears to be severely compromised or deteriorating rapidly; this may include contacting nearby emergency medical services or a local hospital department. While waiting for medical assistance to arrive to the dental office, it is important to keep the patient calm, conscious if possible, and to reassure them that help is on the way. If the patient's physical status worsens drastically and they become totally unresponsive, it may be necessary to commence basic life support techniques, such as cardio pulmonary resuscitation (CPR) (48). After the patient receives the appropriate medical attention, the treating dentist should attempt to communicate with the patient in a supportive and empathetic manner. This form of doctor-patient interaction can help promote open and honest dialogue about the substance use, which could aid in ensuring the continuity of dental care following the incident. For the prevention of unforeseeable medical emergencies involving illicit drug consumption, dental offices should consider incorporating a routine and non-judgmental substance use screening program as part of their new patient intake process. By doing so, this can help identify those who could be at risk for adverse reactions in the dental office due to their undisclosed substance abuse (46,49,50).

Administering local anesthetics for acute pain management a promising alternative to the traditional practice of prescribing opioids to patients, both within the dental and medical sectors (51,52). In clinical dentistry, one notable solution for alleviating pain is the use of long-acting local anesthetic agents, such as bupivacaine, tetracaine and etidocaine. Since these drugs have a longer duration of action (i.e., between 2 to 4 hours), they can effectively offer pain relief for an extended period of time, making them especially advantageous for post-procedural pain management following endodontic therapies, tooth extractions, or periodontal surgeries. Interestingly, bupivacaine has been shown to be superior with respect to the amount of post-operative analgesic consumption and time to analgesic consumption compared to short-acting anesthetics such as lidocaine with epinephrine and mepivacaine (51). This suggests that, compared to short-acting local anesthetics, bupivacaine yields a substantially lower pain response after invasive operations. Therefore, it is clear that the advent of long-acting local anesthetics like bupivacaine has now allowed for general dentists and specialist clinicians to enhance patient comfort while also minimizing the need for opioid prescriptions (51). Similarly, in clinical medicine, long-acting local anesthetics are frequently used to address acute or sporadic pain in a wide array of scenarios, ranging from minor surgical interventions to generalized post-operative discomfort. Likewise, this approach aligns with the medical community's growing commitment to reduce opioid dependence and overprescribing, which has become a widespread issue over the last few decades as seen with the opioid crisis. Local anesthetics such as ropivacaine, with its extended analgesic effect, are valuable options in many contexts within the field of medicine (52). Ropivacaine has been shown to last between 2.5 to 6 hours when administered epidurally, while its effective analgesia could last between 8 to 13 hours when used for peripheral nerve blocks. While long-acting local anesthetic agents are extremely effective in a diverse amount of situations, they should be used with extreme care because overdose or improper administration can lead to severe complications. Thus, healthcare providers are required to possess the necessary clinical knowledge and training in order to safely use this strategy for pain alleviation (51,52).

Conclusions

Drug interactions in local anesthesia are one of the most avoidable causes of inadvertent patient harm in clinical dentistry (33,34). As new classes of therapeutic and non-therapeutic agents enter the market, the likelihood of experiencing an adverse drug response involving adrenergic vasoconstrictors will only continue to rise. As a result, dental clinicians are encouraged to practice vigilance and recognition of such interactions. A reliable place to start would be to comprehend a patient's current medication

intake and medical history, as this provides clues to the potential risks and benefits of local anesthesia during invasive dentistry (42). Moreover, drug reactions with exogenous vasoconstrictors should be considered when prescription changes are made, or when interpreting a differential diagnosis of symptoms. Luckily, the signs and symptoms of the various unfavorable reactions associated with local anesthetics are very distinctive, making diagnosis and treatment a relatively rapid process. Also, serious drug reactions are extremely rare and, when treated promptly, are unlikely to lead to significant morbidity or mortality (42).

Acknowledgments

Funding: None.

Footnote

Peer Review File: Available at https://joma.amegroups.com/article/view/10.21037/joma-23-27/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://joma.amegroups.com/article/view/10.21037/joma-23-27/coif). A.O. serves as an unpaid editorial board member of *Journal of Oral and Maxillofacial Anesthesia* from September 2023 to August 2025. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/joma-23-27
Cite this article as: Janev N, Ouanounou A. Local anesthetics in oral and maxillofacial medicine: pharmacology, adverse effects, drug interactions and clinical manifestations. J Oral Maxillofac Anesth 2024;3:2.