

Local Anesthetics: Pharmacology and Toxicity

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KEYWORDS

• Local anesthetics • Pharmacology • Toxicity reaction • MRD

The development of safe and effective local anesthetic agents has been possibly the most important advancement in dental science to occur in the last century. The agents currently available in dentistry are extremely safe and fulfill most of the characteristics of an ideal local anesthetic (**Box 1**). These local anesthetic agents can be administered with minimal tissue irritation and with little likelihood of inducing allergic reactions. A variety of agents are available that provide rapid onset and adequate duration of surgical anesthesia. The agents provide anesthesia that is completely reversible, and systemic toxicity is rarely reported. An ideal local anesthetic agent, one that would induce regional analgesia by selectively inhibiting pain pathways without interrupting transmission of other sensory modalities, has not yet been discovered.

This issue of *Dental Clinics of North America* updates the advancements in local anesthesia therapeutics currently available in dentistry and provides an insight into a wide range of concerns related to the agents used for local anesthesia. This introductory article provides a brief update of the clinical pharmacology of local anesthetic agents and formulations used in dentistry at present. Following this update, a review of the dosing strategies needed to prevent local anesthetic toxicity reactions is presented.

CLINICAL PHARMACOLOGY OF LOCAL ANESTHETICS

For the last 20 years, amides are predominantly used in dentistry as local anesthetic agents. Lidocaine and mepivacaine, 2 of the most commonly used amide local

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Box 1 Characteristics of an ideal local anesthetic	
1.	Administration of the agent is nonirritating
2.	The anesthetic has little or no allergenicity
3.	A rapid onset and adequate duration of anesthesia
4.	Anesthesia is completely reversible
5.	Minimal systemic toxicity
6.	Anesthesia is selective to nociception (pain) pathways

anesthetic agents in dentistry, have a 50-year history of effectiveness and safety in providing regional anesthesia for dental therapies. Practitioners prefer the amide local anesthetic agents to the ester agents (ie, procaine and propoxycaine) because amides produce profound surgical anesthesia more rapidly and reliably, with fewer sensitizing reactions than ester anesthetics. The availability of various dental formulations of amide agents (Table 1) that provide anesthesia of varying duration has dramatically improved patient care, permitting the development of many of the sophisticated surgical outpatient procedures that are now available in dentistry.¹

Variations in the clinical characteristics of the local anesthetic agents can be attributed to differences in chemical properties of their molecular structures. An anesthetic's dissociation constant (pKa) determines the pH at which the drug's ionized (charged) and nonionized (uncharged) forms are in equal concentrations. This value is critical for effective anesthesia because the uncharged form of a local anesthetic molecule is essential to permit diffusion across lipid nerve sheaths and cell membranes.

Table 1 Local anesthetic formulations			
Anesthetic Agent	Brand Names	Formulations Available in Dental Cartridges	Duration of Anesthesia
Articaine	Ultracaine, Septocaine, Articaident, Zorcaine	4% Articaine, 1:100,000 epinephrine	Medium
		4% Articaine, 1:200,000 epinephrine	Medium
Bupivacaine	Marcaine, Vivacaine	0.5% Bupivacaine, 1:200,000 epinephrine	Long
Lidocaine	Xylocaine, Octocaine, Lignospan, Alphacaine	2% Lidocaine, 1:100,000 epinephrine	Medium
		2% Lidocaine, 1:50,000 epinephrine	Medium
		2% Lidocaine plain	Ultrashort
Mepivacaine	Carbocaine, Polocaine, Scandonest	3% Mepivacaine plain	Short
		2% Mepivacaine, 1:20,000 levonordefrin	Medium
Prilocaine	Citanest, Citanest Forte	4% Prilocaine plain	Short
		4% Prilocaine, 1:200,000 epinephrine	Medium

Conversely, only the charged form can dissolve in water and diffuse through extracellular fluid and intracellular cytoplasm. Therefore, an agent's pKa is the most important factor in determining its diffusion properties and subsequently, the rate of onset. Procaine, with a pKa of 8.9, is 98% ionized at a normal tissue pH of 7.4. After procaine injection, most of the molecules exist in its charged state at normal pH and is therefore unable to cross cell membranes. The onset of anesthesia using procaine and other ester local anesthetics is thus unacceptably prolonged. Amide anesthetics having pKa values in the range of 7.6 to 8.0 have less of the drug in an ionized state, diffuse through tissue more readily, and have acceptably rapid onset times.²⁻⁴

The lipid solubility characteristics of a local anesthetic best predict its potency. Procaine is one of the least lipid-soluble and least potent local anesthetics, whereas bupivacaine is highly lipid soluble and most potent. Protein binding characteristics are a primary determinant of the duration of anesthesia. Agents that attach to protein components of nerve membranes are less likely to diffuse from the site of action and enter the systemic circulation. Lidocaine's short duration and bupivacaine's long duration of action are due, in part, to their distinctly different protein binding characteristics.^{2,5}

It is clear that lipid solubility, ionization, and protein binding properties contribute to the clinical characteristics of local anesthetics. However, factors such as the site of injection, drug and vasoconstrictor concentration, volume of injection, and inherent vasodilating properties of the anesthetic also influence the clinical performance of a local anesthetic.

Local Anesthetics: Current Practice

Because anesthesia induced using ester anesthetics is less effective than with amides, and because ester anesthetics have a higher incidence of allergic reactions, dental anesthetic formulations containing ester agents are no longer marketed. Lidocaine remains the predominant local anesthetic agent used in the United States. In Canada, formulations of articaine have surpassed lidocaine in popularity, thus becoming the most frequently used dental anesthetic. A survey of US oral surgeons regarding their preferences for local anesthetic agents found bupivacaine, a long-acting local anesthetic, to be commonly administered to manage postoperative pain. Formulations used by less than 2% of the surveyed oral surgery practitioners included mepivacaine with 1:20,000 levonordefrin (Neo-Cobefrin), lidocaine with 1:50,000 epinephrine, 3% mepivacaine plain, and 4% prilocaine plain (**Table 2**).⁶

Until 1989, a combination of ester anesthetics, procaine and propoxycaine, was available in dental cartridges. This formulation was a combination of 0.4% propoxycaine (Ravocaine) and 2% procaine (Novocain) with 1:20,000 levonordefrin as a vasoconstrictor. As stated earlier, ester anesthetics are generally less effective than amides because they have poor diffusion properties. Procaine is a potent vasodilator and is not effective if used without a vasoconstrictor. The metabolism of esters is through hydrolysis by the plasma and tissue esterases, yielding para-aminobenzoic acid (PABA) and diethylamino alcohol. PABA seems to be the allergen associated with procaine's significant allergenicity. The concern regarding patient reporting of allergy to local anesthetics is addressed in an accompanying article by Speca and colleagues elsewhere in this issue.

Lidocaine hydrochloride

Lidocaine was introduced into practice in the 1950s and, because of its excellent efficacy and safety, has become the prototypic dental local anesthetic in North America. Besides having excellent anesthetic efficacy, lidocaine has limited allergenicity, with

Table 2 Local anesthetics administered for third molar extraction	
Local Anesthetic Formulation	Frequency (%)
2% Lidocaine, 1:100,000 epinephrine	70.4
0.5% Bupivacaine, 1:200,000 epinephrine	11.3
4% Articaine, 1:100,000 epinephrine	7.3
4% Prilocaine, 1:200,000 epinephrine	3.1
2% Mepivacaine, 1:20,000 levonordefrin	1.9
2% Lidocaine, 1:50,000 epinephrine	1.8
3% Mepivacaine	0.7
4% Prilocaine	0.2

fewer than 20 confirmed cases of serious allergic anaphylactic reactions (ie, anaphylactoid) reported in the last 50 years. Given the frequent use of local anesthesia in dentistry (500,000–1,000,000 injections a day throughout the United States and Canada), the rare incidence of serious life-threatening hypersensitivity reactions associated with lidocaine is an extremely important clinical advantage.

Lidocaine is formulated in cartridges as 2% lidocaine with 1:50,000 epinephrine, 2% lidocaine with 1:100,000 epinephrine, and 2% lidocaine plain. The 2% lidocaine with 1:100,000 epinephrine formulation is considered the gold standard when evaluating the efficacy and safety of newer anesthetics.

Mepivacaine hydrochloride

Mepivacaine has an important role in dental anesthesia because it has minimal vaso-dilating properties and can therefore provide profound local anesthesia without being formulated with a vasoconstrictor such as epinephrine or levonordefrin (see [Table 1](#)). The availability of a 3% mepivacaine formulation without a vasoconstrictor is a valuable addition to a dentist's armamentarium. It is available in dental cartridges as 3% mepivacaine plain or 2% mepivacaine with 1:20,000 levonordefrin.

Mepivacaine plain is often reported to have a shorter duration of soft tissue anesthesia, making it potentially useful in pediatric dentistry in which children are known to chew their lips after dental procedures. However, one investigation suggests that although pulpal durations of mepivacaine plain are shorter than that of 2% lidocaine with epinephrine, duration of soft tissue anesthesia for mepivacaine and lidocaine with epinephrine are nearly identical.⁷

Alternatively, shortening of the duration of soft tissue anesthesia after completion of a dental procedure has been shown using the α -adrenergic receptor antagonist phen-tolamine. Local anesthesia reversal, a recent advancement in dental anesthesia ther-apeutics, is addressed in an article by Hersh and Lindemyer elsewhere in this issue.

Prilocaine hydrochloride

Prilocaine, like mepivacaine, is not a potent vasodilator and can provide excellent oral anesthesia with or without a vasoconstrictor. It is available in preparations of 4% pri-locaïne plain and 4% prilocaine with 1:200,000 epinephrine. The formulation contain-ing epinephrine has anesthetic characteristics similar to 2% lidocaine with 1:100,000 epinephrine. The 4% prilocaine plain formulation provides a slightly shorter duration of surgical anesthesia. Prilocaine plain solution in dental cartridges has a somewhat less acidic pH. Although not confirmed by clinical trials, there is some indication that prilo-caïne causes less discomfort on injection.⁸

One of prilocaine's metabolic products has been associated with the development of methemoglobinemia. Methemoglobinemia has also been reported with overdoses of the topical anesthetic, benzocaine. The significance of this adverse reaction is addressed in an article by Trapp and Will elsewhere in this issue.

Articaine hydrochloride

Similar to most dental anesthetics available to the dental practitioner, articaine is classified as an amide anesthetic. However, the molecular structure of articaine is somewhat unique, containing a thiophene (sulfur-containing) ring and an ester side chain. As articaine is absorbed from the injection site into the systemic circulation, it is rapidly inactivated via hydrolysis of the ester side chain to articainic acid. Consequently, articaine has the shortest metabolic half-life (estimated to be between 27–42 minutes) of the anesthetics available in dentistry.^{9,10} Formulations containing 4% articaine hydrochloride with 1:100,000 epinephrine and 4% articaine with 1:200,000 epinephrine are available in dental cartridges. Studies evaluating mandibular block and maxillary infiltration anesthesia have generally found that onset time, duration, and anesthetic profundity of articaine are comparable to that of 2% lidocaine with 1:100,000 epinephrine.^{11–16} The relative efficacy of lidocaine and articaine formulations is thoroughly reviewed in an article by Paxton and Thome elsewhere in this issue.

Articaine does not seem to have a greater allergenicity than other available amide anesthetic agents, probably because the ester metabolite is not the allergen PABA. Reports of toxicity reactions after the use of articaine for dental anesthesia are extremely rare. The rapid inactivation of articaine by plasma esterases may explain the apparent lack of overdose reactions reported after its administration.

Articaine and prilocaine have been associated with inferior alveolar and lingual nerve paresthesias. This controversial topic is addressed in an article by Moore and Haas elsewhere in this issue.

There is a developing clinical research literature supporting the claim that articaine has superior diffusion properties and that anesthesia can be induced after buccal infiltration in the mandible. The efficacy of articaine to provide mandibular pulpal anesthesia after buccal infiltration is critically reviewed in an article by Meechan elsewhere in this issue.

Bupivacaine hydrochloride

In the last few decades, the long-acting amide local anesthetic bupivacaine has found a place in dentists' armamentarium. This long-acting agent plays a valuable role in the overall management of surgical postoperative pain associated with dental care.⁶ The molecular structure of bupivacaine (1-butyl-2',6'-pipecoloxylidide) is identical to mepivacaine except for a butyl (4 carbon) substitution of the methyl (1 carbon) group at the amino terminus of the molecule. The addition of a butyl group to the chemical structures of mepivacaine provides enhanced lipid solubility and protein binding properties.^{17,18}

Although bupivacaine may provide adequate surgical anesthesia, it is most useful for postoperative pain management.^{19,20} Clinical trials have shown that bupivacaine, having an elevated pKa of 8.1, has a slightly longer onset time than conventional amide anesthetics. Onset times and profundity are optimized when preparations of bupivacaine include epinephrine.^{5,21}

A combination strategy for managing postoperative pain using a nonsteroidal anti-inflammatory drug before surgery and a long-acting anesthetic may provide maximum patient comfort.²² The management of postoperative and chronic pain using

long-acting local anesthetics is the focus of a review article by Gordon and Dionne elsewhere in this issue.

TOXICITY REACTIONS ASSOCIATED WITH LOCAL ANESTHESIA

A dentist's ability to safely administer local anesthesia is essential for dental practice. Local anesthetic solutions used in North America for dental anesthesia are formulated with several components: an amide local anesthetic (ester local anesthetic drugs are no longer available in dental cartridges), an adrenergic vasoconstrictor, and a sulfite antioxidant. In susceptible patients, any of these components may induce systemic, dose-dependent, adverse reactions. Although extremely rare, allergic and hypersensitivity reactions to local anesthetics and sulfites may occasionally occur (see the article by Specca and colleagues elsewhere in this issue for further exploration of this topic). Signs and symptoms of the various adverse reactions associated with local anesthetics, such as methemoglobinemia, are quite distinctive, permitting rapid diagnosis and treatment. A critical review of acquired methemoglobinemia is provided in an article by Trapp and Will elsewhere in this issue. Significant cardiovascular stimulation can occur after rapid administration of agents containing an adrenergic vasoconstrictor.

Serious reactions are extremely infrequent and when treated properly, they are unlikely to result in significant morbidity or mortality. The most serious and life threatening of adverse reactions are toxicities caused by relative excessive dosing of the local anesthetic or vasoconstrictor. These reactions are preventable with proper patient assessment and dosage calculations.

When the anesthetic agent contained in a dental cartridge diffuses away from the site of injection, it is absorbed into the systemic circulation where it is metabolized and eliminated. The doses needed for local anesthesia in dentistry are usually minimal, and systemic effects after absorption of the drug are quite uncommon. However, if an inadvertent vascular injection occurs, if repeated injections are administered, or if relatively excessive volumes are used in pediatric dentistry, then blood levels of a local anesthetic may become significantly elevated. The addition of epinephrine to local anesthetic formulations can significantly reduce the absorption of the anesthetics.

Toxicity Reactions to Excessive Local Anesthetic Dose

Initially, excitatory reactions to local anesthetic overdose are seen, such as tremors, muscle twitching, shivering, and clonic-tonic convulsions.²³⁻²⁵ These initial excitatory reactions are thought to be disinhibition phenomena resulting from selective blockade of small inhibitory neurons within the limbic system of the central nervous system (CNS).² Whether this initial excitatory reaction is apparent or not, a generalized CNS depression with symptoms of sedation, drowsiness, lethargy, and life-threatening respiratory depression follows if blood concentrations of the local anesthetic agent continue to increase. With extremely high toxic doses, myocardial excitability and conductivity may also be depressed, particularly with the highly lipid-soluble long-acting local anesthetic bupivacaine.²⁶ Cardiac toxicity to local anesthetic overdose is most often manifested as ectopic cardiac rhythms and bradycardia. With an extreme local anesthetic overdose, cardiac contractility is depressed and peripheral vasodilation occurs, leading to significant hypotension.

Compliance with local anesthetic dosing guidelines is the first and most important strategy for preventing this adverse event. Dosing calculations used to avoid systemic reactions to local anesthetics are dependent on the agent administered and the patient's body weight (**Table 3**). True dose-dependent toxicity reactions

Table 3
MRDs of injectable local anesthetics

Agents (Brand Name)	Concentration of Local Anesthetic		Concentration of epi/levo mg/Cartridge ^c	Maximum Dosing		Maximum Number of Cartridges		
	mg/mL ^a	mg/cartridge ^b		Adult MRD (mg)	MRD/lb ^d (mg/lb)	Adults ^e	50 lb Child	25 lb Child
2% Lidocaine, 1:100,000 epi	20	36	0.018	500	3.3	13.8	4.6	2.3
2% Lidocaine, 1:50,000 epi	20	36	0.036	500	3.3	13.8	4.6	2.3
2% Lidocaine plain	20	36	—	300	2.0	8.3	2.8	1.4
4% Articaine, 1:100,000 epi	40	72	0.018 ^e	500	3.3	6.9	2.3	1.1
4% Articaine, 1:200,000 epi	40	72	0.009 ^e	500	3.3	6.9	2.3	1.1
3% Mepivacaine	30	54	—	400	2.6	7.4	2.5	1.2
2% Mepivacaine, 1:20,000 levo	20	36	0.09	400	2.6	11.1	3.7	1.8
4% Prilocaine	40	72	—	600	4.0	8.3	2.8	1.4
4% Prilocaine, 1:200,000 epi	40	72	0.009	600	4.0	8.3	2.8	1.4
0.5% Bupivacaine, 1:200,000 epi	5	9	0.009	90	0.6	10	NR	NR

All cartridges are assumed to contain approximately 1.8 mL.

Abbreviations: epi, epinephrine; levo, levonordefrin; MRD, maximum recommended dose; NR, not recommended.

^a Calculation for drug concentration. For example, 2% lidocaine solution = 2 g/100 mL = 2000 mg/100 mL = 20 mg/mL.

^b Calculation of mg/cartridge. For example, 2% lidocaine: 20 mg/mL $\times$ 1.8 mL/cartridge = 36 mg/cartridge.

^c Calculation of mg/cartridge of epinephrine: for example, 1:100,000 = 1 g:100,000 mL = 1000 mg:100,000 mL = 0.01 mg/mL. A 1.8-mL cartridge contains 0.018 mg of epi.

^d Calculation of weight-based MRD: for example, 500 mg for a 150-lb adult = 500 mg/150 lb = 3.3 mg/lb.

^e Calculation of maximum number of cartridges: for example, for lidocaine/epi, the adult MRD for lidocaine/epi is 500 mg; 500 mg/36 mg per cartridge = 13.8 cartridges.

to local anesthetics are most frequently reported in pediatric patients.^{23–25} A typical case report of a local anesthetic toxicity reaction in pediatric dentistry is as follows:

A healthy five-year-old female patient, weighing 36 lb. was scheduled for multiple extractions. The child received N2O/O2 sedation via a nasal mask, followed by maxillary and mandibular injections of five cartridges of 3% mepivacaine (270 mg). Ten minutes later the child experienced “stiffening and shaking” of all extremities that lasted ten seconds. Two more convulsive episodes occurred and cardiopulmonary arrest ensued. Transport to a local hospital and resuscitation measures were unsuccessful. Death occurred four days later.²⁷

When administering local anesthetics to children, the dose must be lowered because of the child's smaller size. Clark rule predicts that this adjustment of dosing for children should be calculated as a fraction of the child's body weight (ie, child's dose = [child's weight/adult weight] × [adult dose]). In the case report presented earlier, the child's dose should have been lowered by the fraction 36 lb/150 lbs (ie, 24%). Toxicity reactions in children may occur more frequently because a child's lesser body weight does not represent a proportionate decrease in orofacial anatomy. The mandible and maxilla of a child weighing 36 lb is only 50% to 60% the size of an adult (weighing 150 lb); therefore, there is an apparent need to use relatively larger volumes when inducing local anesthesia in pediatric dental patients. The consequence of this disparity is that local anesthetic toxicity reactions occur more frequently in children. In addition, systemic drug interactions involving local anesthetics and other CNS-depressant drugs used for pediatric sedation are more likely to occur in children.^{23,24}

The local anesthetic formulation of 3% mepivacaine plain seems to be associated with a disproportionate number of local anesthetic toxicity reports.^{23–25,27–29} This toxicity may be due to the absence of a vasoconstrictor, thereby allowing more rapid systemic absorption of the anesthetic. In addition, the higher concentration of the drug used in its anesthetic formulation (3%) may result in the administration of larger relative doses. Pharmacokinetic studies by Goebel and colleagues^{30,31} have demonstrated that peak anesthetic blood levels of 3% mepivacaine occur more rapidly and exceed that of an equal volume of 2% lidocaine with 1:100,000 epinephrine by approximately 3-fold after maxillary infiltration injections (**Fig. 1**).^{30,31}

The ability of vasoconstrictors to limit the initial increase and the ultimate peak of local anesthetic drug levels is illustrated in **Fig. 1**. A higher peak serum concentration can be noted after administration of lidocaine plain than with lidocaine with epinephrine. Consequently, the maximum recommended dose (MRD) for lidocaine plain is less (300 mg for an adult) than for lidocaine with epinephrine (500 mg for an adult). Mepivacaine is a local anesthetic agent with less vasodilating properties than lidocaine. Consequently, the differences in serum levels between the mepivacaine formulations with and without a vasoconstrictor are less pronounced.

The 3% mepivacaine formulation is often chosen for children because it is considered to have a shorter duration of soft tissue anesthesia, thereby limiting severe lip biting and oral trauma seen in children after dental local anesthesia. However, the results of a double-blind randomized trial have found that onset time, peak effects, and duration of soft tissue anesthesia after mandibular block injections of 2% lidocaine with 1:100,000 epinephrine, 3% mepivacaine plain, or 4% prilocaine plain were very similar.⁷ The selection of anesthetic formulations that do not contain a vasoconstrictor, such as 3% mepivacaine, may not be a significant clinical advantage for children.

The determination of MRDs for children receiving local anesthetics is complicated by the conflicting published dosage recommendations found in the literature and the

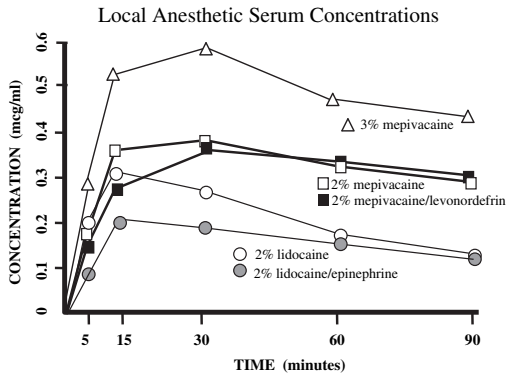


Fig. 1. Serum concentrations of lidocaine and mepivacaine after a single cartridge of each agent administered with a vasoconstrictor and without a vasoconstrictor. Open circles represent 2% lidocaine plain; closed circle, 2% lidocaine with 1:100,000 epinephrine; open squares, 2% mepivacaine plain; close squares, 2% mepivacaine with 1:20,000 levonordefrin; and open triangles, 3% mepivacaine plain. (Data from Goebel WM, Allen G, and Randall F. Circulating serum levels of mepivacaine after dental injection. *Anesth Prog* 1978;25:52–6; and Goebel WM, Allen G, and Randall F. The effect of commercial vasoconstrictor preparations on the circulating venous serum level of mepivacaine and lidocaine. *J Oral Med* 1980;35:91–6.)

various units involved in the calculation (milligram, percentage, cubic centimeter, milliliter, kilogram, pound, cartridges). The MRDs for dental local anesthetics published in the American Dental Association's guide to dental therapeutics as derived from manufacturers' package inserts are possibly the most current authoritative sources.¹ These values are summarized in **Table 3**. These recommendations permit the use of largest volume for lidocaine with epinephrine and smallest volume for mepivacaine and articaine. In addition, to prevent oral trauma after dental anesthesia, the long-acting local anesthetic bupivacaine is generally not indicated for young children.³²

The maximum volume of 3% mepivacaine plain for an anesthetic injection (7.4 cartridges for a 150 lb adult) and the maximum volume of 4% articaine with epinephrine (6.9 cartridges for a 150 lb adult) are the most restrictive of any local anesthetics used in dentistry. In comparison, the maximum volume for 2% lidocaine with epinephrine (14 cartridges for a 150 lb adult) permits the greatest volume to be administered safely. In children, the formulation of 2% lidocaine with 1:100,000 epinephrine is the least likely to cause toxicity reactions, if multiple injections are required.

A simplified alternative for calculating maximum safe doses of local anesthesia has been established resulting in the most conservative guidelines that can be applied to all anesthetic formulations used in dentistry (**Table 4**). These guidelines, "the Rule of 25" state that for healthy patients, a dentist may safely use 1 cartridge of any marketed local anesthetic for every 25 lb of patient weight, that is, 1 cartridge for a patient weighing 25 lb, 3 cartridges for a patient weighing 75 lb, and 6 cartridges for a patient weighing 150 lb or greater.

Management of Local Anesthetic Overdose

Tonic-clonic convulsions are the most common manifestation of a true overdose situation. Local anesthetic-induced convulsions are usually transient. After a convulsive episode, loss of consciousness and severe prolonged respiratory depression is likely. Immediate treatment of this emergency should address both the convulsions and the potential respiratory depression. One must monitor vital signs (particularly respiratory

Table 4 Safe dose for local anesthetics: the Rule of 25 ^a	
Body Weight in lbs (kg)	Number of Anesthetic Cartridges
25 (11.25)	1
50 (22.5)	2
75 (33.75)	3
100 (45)	4
125 (56.25)	5
150 (67.5)	6

^a An easily remembered rule for determining a safe dose of dental local anesthetics in children is to use the "Rule of 25": 1 cartridge of any anesthetic formulation can be administered safely for every 25 lb of the child's body weight.

adequacy), protect the patient from injury, place the patient in supine position, and maintain the airway. If the patient is unconscious and in respiratory arrest, positive pressure oxygen ventilation is essential. Because local anesthesia-induced convulsions are usually transient, administration of an anticonvulsant, such as intravenous diazepam, 5 to 10 mg, is rarely required.

Toxicity Reactions to Excessive Vasoconstrictors Dose

Epinephrine and levonordefrin are the 2 catecholamine vasoconstrictors formulated with local anesthetic agents in dental cartridges. As shown in Fig. 1, the use of a vasoconstrictor can improve the safety of the formulation by slowing the systemic absorption of the local anesthetic and decreasing the peak blood levels of the anesthetic. There is minimal stimulation of the cardiovascular system after submucosal injection of 1 or 2 cartridges of anesthetic containing epinephrine or levonordefrin. However, when excessive amounts of these adrenergic vasoconstrictors are administered, or when the agents are inadvertently administered intravascularly, cardiovascular stimulation, with clinically significant increases in blood pressure and heart rate, can occur. For example, the administration of 7 cartridges of 4% articaine with 1:100,000 epinephrine has been found to increase the heart rate on an average by 9 beats per minute (bpm) (from 69 to 78 bpm) and to increase systolic blood pressure by 6 mm Hg (from 125 to 131 mm Hg).¹⁰

The small amount of epinephrine in a dental cartridge was once thought to be incapable of significantly increasing epinephrine blood levels after local anesthetic administration. Most of the cardiovascular stimulation reported after local anesthesia administration was thought to be due to patient fear and anxiety or the pain of injection. However, studies have found that the epinephrine in as little as 2 cartridges of 1:100,000 formulations can significantly increase circulating epinephrine levels. Lipp and colleagues³³ administered 2 mL of 4% articaine containing tritium-labeled epinephrine (1:100,000) to determine the extent to which the increase in total epinephrine plasma levels was due to the administered tritium-labeled epinephrine. With submucosal injections (16 subjects), the total epinephrine levels increased from a baseline level of 200 pg/mL to a peak level of 631 pg/mL at 7 minutes (Fig. 2). The increase in total epinephrine levels was mostly due to the injected tritium-labeled epinephrine. Because of the apparent inadvertent intravascular local anesthetic injections in 4 subjects, a rapid increase in epinephrine levels to a mean peak level of 2645 pg/mL was seen within a minute of their injections. Although this increase was

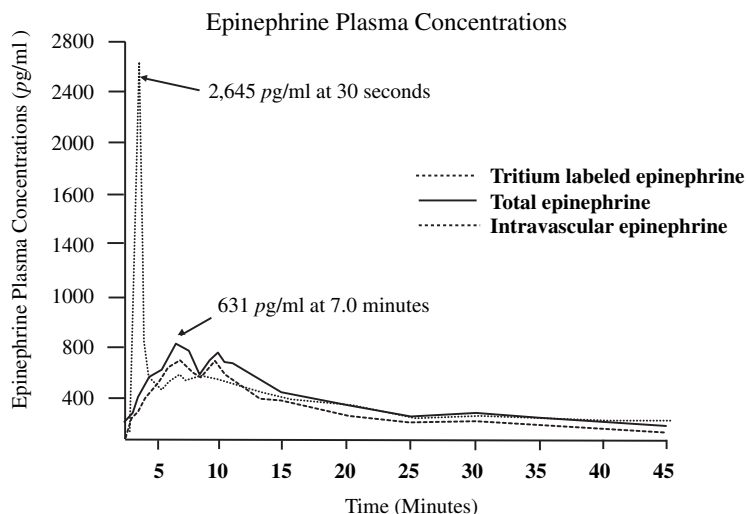


Fig. 2. Plasma concentrations of epinephrine after the administration of 2 mL of 4% articaine containing tritiated epinephrine (1:100,000). Epinephrine levels measured in the 4 patients who inadvertently received intravascular injections are shown (dotted line). Tritiated epinephrine levels (dashed line) and total epinephrine concentrations (solid line) representing subjects receiving submucosal injections are also shown. (From Lipp M, Dick W, Daubländer M, et al. Exogenous and endogenous plasma levels of epinephrine during dental treatment under local anesthesia. *Reg Anesth* 1993;18(1):6-12; with permission.)

short lived, some of these patients were found to have significant cardiovascular stimulation indicated by tachycardia and extrasystoles. It is clear that very large volumes or inadvertent intravascular injections can produce clinically significant cardiovascular responses. Using anesthetic formulations containing no or limited concentrations of vasoconstrictors, using a slow injection technique, and aspirating carefully and repeatedly are the common recommendations to prevent rapid systemic absorption of epinephrine and levonordefrin.

A patient's medical health history that indicates significant cardiovascular impairment may indicate limiting the use of vasoconstrictors. Although vasoconstrictors are rarely contraindicated, the potential stimulation of the cardiovascular system after intravascular injections should guide the dental practitioners to avoid vasoconstrictor-containing formulations if possible. A common recommendation, when a vasoconstrictor is required for a dental treatment and when there is a medical history that suggests a need for caution, is to limit the dose of epinephrine to 0.04 mg.³⁴ This dose reduction can be achieved by limiting the total anesthetics used to one of the following:

- One cartridge of an anesthetic containing 1:50,000 epinephrine
- Two cartridges of an anesthetic containing 1:100,000 epinephrine
- Four cartridges of an anesthetic containing 1:200,000 epinephrine.

In addition, practitioners must be alert to drug interactions when using local anesthetics containing the vasoconstrictors epinephrine and levonordefrin. Earlier reports suggest that vasoconstrictors should be used with caution in patients taking nonselective β -adrenoreceptor blockers, tricyclic antidepressants, cocaine, and α -adren-
 ergic blockers.³⁵ Patients taking nonselective β -adrenergic antagonists such as

propranolol may experience exaggerated systemic vasoconstrictive responses to epinephrine or levonordefrin.¹⁷ This drug interaction is critically reviewed in article by Hersh and Giannakopoulos elsewhere in this issue.

Local anesthetic administration using agents containing vasoconstrictors may also be a concern among patients who are pregnant. A review of this potential risk and treatment recommendations for this special population is presented in another article by Fayans and colleagues elsewhere in this issue.

SUMMARY

The amide local anesthetic agents currently available in dentistry are extremely safe and effective. The availability of various formulations of lidocaine, mepivacaine, prilocaine, articaine, and bupivacaine permits a practitioner to select agents that can meet treatment requirements. Many advances in local anesthesia therapeutics and armamentarium have become available to the dental practitioner in recent years. Through careful selection of agents and proper adjustment of dosing, most serious adverse reactions associated with dental local anesthetic agents can be prevented.

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