Epinephrine: Systemic Effects And Varying Concentrations In Local Anesthesia

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Summary
The range of vasoconstrictors available for use with local anesthetics in dentistry has been reviewed with emphasis on epinephrine and its physiological effects. All of the vasoconstrictors reviewed provide satisfactory results in dental anesthetic solutions when administered in appropriate concentrations and volumes. Possible drug interactions of concern to dentists include the use of vasoconstrictors with inhalational anesthetics, tricyclic antidepressants, beta blockers and, possibly, phenothiazines. Data reviewed indicates that the amounts of epinephrine used in dentistry can result in significant elevations in circulating levels of epinephrine and concomitant physiologic changes. Evidence reviewed suggests that 1:200,000 epinephrine concentration results in optional duration and depth of local anesthesia. With the potential for adverse effects from epinephrine concentrations that are needlessly increased, it appears that in most clinical situations a 1:200,000 concentration of epinephrine can be used in an efficacious manner.

Successful local anesthesia is required for performing the majority of surgical and restorative dental procedures. Many local anesthetics used today are combined with a vasoconstrictor to enhance the effects of the anesthetic.¹⁻⁴ Most dentists utilize local anesthetics in a cartridge form that includes a fixed concentration of vasoconstrictor. This report reviews the gamut of vasoconstrictors available and their physiologic action with emphasis on epinephrine. The effects of varying concentrations of epinephrine are also examined.

Vasoconstrictors added to local anesthetic solutions provide several advantages to the anesthetic. First, the addition of vasoconstrictor has been shown to increase the duration of anesthetic effect.⁵⁻⁶ Second, the vasoconstrictor can provide a margin of safety in the use of the local anesthetic by decreasing the systemic toxicity of local anesthetics. This is accomplished by retarding their absorption into the systemic circulation.³ The vasoconstrictor may also help provide hemostasis at the surgical site.⁷⁻⁸ As most local anesthetics, except cocaine, are vasodilators, the hemostatic role of the vasoconstrictor can be useful in surgical cases.⁹⁻¹⁰ Finally, the addition of vasoconstrictor can enhance the quality of the neural blockade.¹¹⁻¹²

Systemic Effects of Vasoconstrictors
The systemic actions of the sympathomimetic amines can be classified into five broad types.¹² First, a cardiac excitatory action which results in an increase in heart rate, force of contraction and stroke volume. Second, central nervous system excitation resulting from the vasoconstrictor agents. Metabolic actions, such as an increase in the rate of glycogenolysis in the liver, may occur. Peripheral excitatory action on smooth muscle groups, including those in blood vessels supplying mucous membrane and skin, provide the vasoconstrictor effect desired in local anesthesia. Finally, the sympathomimetics may cause a peripheral inhibitory action on certain other types of smooth muscle, such as those in the bronchial tree and in the wall of the gut.

There are several different types of vasoconstrictors available for clinical use. They have in common the fact that all, except for felypressin, are sympathomimetic amines.
Epinephrine

Epinephrine and levonordefrin are the most commonly employed vasoconstrictors in dentistry.\textsuperscript{13} As with the other useful vasoconstrictors, epinephrine produces its effects by stimulating the alpha adrenergic receptors located in the walls of the arteriole. Epinephrine is also a beta adrenergic stimulator and may cause vasodilatation of arterioles in skeletal muscle due to the predominance of beta receptors in this tissue. Epinephrine’s beta adrenergic responses, even at low systemic levels, include skeletal muscle vasodilatation plus increased heart rate and ionotropy. The beta adrenergic effects predominate over the alpha because of the greater sensitivity of beta adrenergic receptors to epinephrine. In the amounts commonly used in dentistry, 0.02-0.2 mg, there should be minimal effect on other organs or systems outside the arterioles in the immediate area of injection. Inadvertent intravascular administration, injections of increased volumes or concentrations, or injection into inflamed tissue may enhance the systemic uptake of vasoconstrictor (and local anesthetic) and produce toxic manifestations. The signs and symptoms of vasoconstrictor overdose include hypertension, tachycardia, tremors, headache, palpitations, and, in rare cases, ventricular fibrillation by direct effect on the myocardium.\textsuperscript{12}

Epinephrine is the most potent and efficient of the vasoconstricting drugs in dental anesthetic solutions (Table I).\textsuperscript{4,14} Three concentrations of epinephrine ranging from 1:100,000 to 1:200,000 are commercially available in dental anesthetic cartridges in the United States, depending on the type of local anesthetic used.\textsuperscript{13}

Practitioners using local anesthetic solutions with epinephrine should be aware of the signs and clinical manifestations of epinephrine overdose. Signs of epinephrine toxicity include sharp elevation of blood pressure which is chiefly systolic, elevated heart rate, and possible cardiac dysrhythmias. The clinical manifestations of epinephrine overdose are restlessness, anxiety, fear, throbbing headache, tremor, perspiration, and palpitations.\textsuperscript{4,11} According to Malamed, most instances of true epinephrine overdose are of such short duration that little or no formal management is required, especially in the ASA I patient.\textsuperscript{11} These symptoms are most often caused by intravascular administration of the anesthetic solution. Fortunately in this situation, the symptoms are of brief duration, as intravenous epinephrine has a half-life of one to three minutes.\textsuperscript{15,16}

Levonordefrin

Levonordefrin (Neo-cobefrin\textsuperscript{®}, Cooke-Waite Laboratories, NY, NY) differs from epinephrine with respect to vasoconstrictor potency and receptor specificity. Levonordefrin is considered to be from one-half to one-sixth as potent as epinephrine in terms of vasoconstrictor activity.\textsuperscript{4,11,13,14} This drug was originally thought to act through direct stimulation of alpha receptors with little or no beta activity.\textsuperscript{4,11} Milam and Giovannitti report, however, that levonordefrin may be a more potent beta agonist than previously thought. This would imply the potential for a greater degree of central nervous system and cardiac stimulation than once believed.\textsuperscript{13}

In addition, results of an animal model study by Robertson et al. suggest that accidental intravenous injection of local anesthetic solutions containing the standard concentration of levonordefrin might cause greater stress to the cardiovascular system and have the potential for greater damage than in a similar accident with epinephrine, particularly in patients whose cardiovascular and autonomic nervous systems are compromised. They also stated that, qualitatively, the response to levonordefrin resembles that to norepinephrine rather than that elicited by epinephrine.\textsuperscript{17}

Phenylinephrine

Phenylinephrine (Neo-synephrine\textsuperscript{®}) is a vasoconstrictor also available in local anesthetic cartridges.\textsuperscript{11} The vasoconstrictor effects of this drug are less pronounced than those of epinephrine and levonordefrin.\textsuperscript{4} Conversely, the duration of action is longer due to its increased stability. The systemic effects are much less severe than those seen with the other sympathomimetic drugs. Phenylinephrine is a direct alpha stimulator with little or no beta stimulation of the heart. This drug has a tendency to cause a reflex bradycardia due to reflex action of carotid baroreceptors and the vagus nerve.\textsuperscript{4,11} This decreases the chances of cardiac dysrhythmias. Phenylinephrine is used in concentrations ten to twenty times those of epinephrine, with 1:2500 being the usual concentration marketed for dental anesthesia. Total dosage should be limited to 4 mg at any single appointment. In the patient with cardiovascular disease, the dose should be limited to 1.6 mg.\textsuperscript{4}

\begin{table}
\begin{center}
\begin{tabular}{|l|c|c|}
\hline
Drug & Vasoconstrictor potency (α-receptor stimulation) & Receptor selectivity (α/β) \\
\hline
Epinephrine & 100 & 50/50 \\
Levonordefrin & 15 & 75/25 \\
Norepinephrine & 25 & 90/10 \\
Phenylinephrine & 5 & 95/5 \\
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\caption{Relative adrenergic activities of sympathomimetic amine vasoconstrictors}
\end{table}

Norepinephrine

Norepinephrine (Levophed®), like epinephrine, is a naturally occurring catecholamine and accounts for approximately 20% of the catecholamine output from the adrenal medulla. Norepinephrine is stored at the post-ganglionic nerve endings.4 This catecholamine acts directly on the alpha receptors in arterioles to produce its vasoconstrictor effect. In equal concentrations norepinephrine has approximately one-quarter the vasopressor activity of epinephrine.14 The duration of local vasoconstricting effect is also shorter than that of epinephrine. Infusions of dilute solutions of norepinephrine into the oral mucosa have been observed to produce sloughing.4,11

Unlike epinephrine, norepinephrine has little action on the beta receptors except in the heart. It exhibits a vasoconstrictor effect throughout the body without a reflex dilatation of skeletal muscle arterioles. As a result of little beta sympathetic stimulation, the net effect of the alpha receptor stimulation is to raise the mean arterial pressure and decrease the heart rate. The latter effect is a reflex response secondary to increased baroreceptor stimulation.19 Norepinephrine is available for dentistry as a 1:30,000 concentration. Malamed proposes that norepinephrine should be used only for pain control, to enhance the effectiveness of a drug and not as a hemostatic agent, due to side effects.11

Felypressin

Felypressin (Octapressin®) is a non-sympathomimetic vasoconstrictor used in Canada and abroad.7 To date it has not been approved for usage in the USA.1,20 Felypressin is a synthetic analogue of the posterior hypophyseal hormone vasopressin. This polypeptide differs from the sympathomimetic amines in that it does not affect the alpha or beta receptors. Instead, it acts directly on the vascular smooth muscle to exert its vasoconstrictor effect. In high dosages, felypressin will cause vasoconstriction of the pulmonary, general systemic, splanchnic circulations and coronary vessels.21,22 In dosages used routinely for dental anesthesia, no significant changes in blood pressure, rate and rhythm are seen.23,24 Felypressin has been found to act on the venular side of the circulation (the capacitance vessels) rather than on the arterioles.25,26 This accounts for its satisfactory use in prolonging the duration and potency of the anesthetic block, but may be responsible for its apparent poor control of hemorrhage during surgery. In a study using an analogue of vasopressin similar to felypressin, the onset of sufficient vasoconstriction was reached after twenty minutes.10,26 This is in contrast to epinephrine where the onset of vasoconstriction occurs immediately.10,26 Early studies reported unsatisfactory results using felypressin to reduce surgical hemorrhage; however, the early investigators appear to have improperly observed the onset time. Felypressin does offer a significant advantage over epinephrine in that it has not been found to induce dysrhythmias. This would appear a significant advantage when used with general anesthesia and for patients with cardiovascular disease.15,24,27

All of the vasoconstrictors discussed provide satisfactory results in dental anesthetic solution, assuming the recommended concentrations and volumes are used. Epinephrine is the most effective of these drugs4,14 and by far the most commonly used sympathomimetic amine for local and regional anesthesia.

Adverse Effects of Vasoconstrictors

In general, adverse effects of vasoconstrictors, excluding drug interaction, occur due to increased dosages or intravascular injection. Although some of the evidence is contradictory, patients with cardiovascular disease appear to be more prone to cardiac dysrhythmias after injection of local anesthetic with vasoconstrictor.

The presence of pheochromocytoma (a tumor involving cells that produce catecholamines) is an absolute contraindication to the use of epinephrine. Patients who have this disease may have an overproduction of endogenous epinephrine or norepinephrine. A sympathetic response to the increased level of circulating catecholamines results in the common manifestations of headache, excessive perspiration and palpitations in 75% of these cases.25,26 These tumors can be persistently or paroxysmally secreting catecholamines. Both situations result in the patient being hypertensive. Due to the excessively high levels of circulating catecholamines already present, exogenous epinephrine in local anesthetics could only have adverse effects and might precipitate a crisis.

Thyrotoxicosis is also a contraindication for the use of vasoconstrictors in local anesthesia.4,29 Thyrotoxicosis may be present in patients with primary or secondary hyperthyroidism. The clinical manifestations of thyrotoxicosis include increased heart rate and systolic blood pressure, marked irritability, fine tremor and elevated body temperature. "Thyroid storm" can be precipitated by exogenously administered sympathomimetic amines. In thyroid storm hypertension, delirium and eventually vasomotor collapse can result. The mortality rate associated with this acute crisis can be as high as 70%.13

Drug Interactions

Inhalation Anesthetics

Occasionally dental procedures are performed under general anesthesia with inhalation agents. In these cases, the anesthetic/vasoconstrictor solution is often used for control of hemostasis rather than anesthesia. Some general anesthetics sensitize the myocardium to the direct myocardial effects of sym-
pathomimetic amines including epinephrine. Halothane is the most important of the commonly used inhalation agents, as it possesses the lowest arrhythmogenic threshold for epinephrine. Enflurane and isoflurane have a minimal effect on myocardial sensitivity to sympathomimetics. One study has shown that three times as much epinephrine is required to produce premature ventricular contractions with enflurane and isoflurane than with halothane. Also of significance is the fact, noted by several investigators, that epinephrine-halothane induced arrhythmias are more likely to be longer duration and more numerous than those occurring with enflurane or isoflurane. Controversy exists over the recommended maximum dose of epinephrine for a patient anesthetized with halothane with the maximum dose ranging from 0.1 mg in ten minutes to 0.3 mg in sixty minutes. 

Epinephrine impregnated retraction cord utilized in restorative dentistry to minimize bleeding during impression making has been observed to provoke cardiac dysrhythmias during halothane anesthesia. A recent fatality was reported that resulted from combined use of halothane and gingival retraction cord impregnated with 8% racemic epinephrine. This type of retraction cord is hazardous with the use of halothane anesthesia as the solution of 8% racemic epinephrine used to impregnate the cord has 40 times the concentration of L-epinephrine found in 1 ml of 1:1000 solution. Each inch of this retraction cord contains 0.44 to 0.61 mg of racemic epinephrine. Racemic epinephrine, a mixture of the two optical isomers of epinephrine, has 50% of the biological activity of L-epinephrine. An inch of cord contains the equivalent of 0.22 to 0.30 mg of L-epinephrine. This is approximately equal to the amount of epinephrine contained in twelve cartridges of dental anesthetic with 1:100,000 epinephrine. The oral mucosa provides a relatively rapid route for systemic absorption of drugs as evidenced with the use of nitroglycerin tablets sublingually. When the gingival retraction cord is placed in the traumatized or inflamed gingival sulcus of a patient under halothane anesthesia, the patient is at high risk to develop dysrhythmias as a result of rapid systemic absorption. The cardiovascularly compromised patient is at an even greater risk. When the anesthetist is unaware of the presence of epinephrine in the retraction cord, adverse reactions may occur.

Antidepressants

Two classes of antidepressant drugs, tricyclic agents and monoamine oxidase (MAO) inhibitors, are used throughout the United States. The tricyclics are the most commonly employed of the two agents. It was previously thought that MAO inhibitors potentiated the direct acting sympathomimetic amines, producing vasopressor responses; however, MAO inhibitors do not potentiate exogenously administered epinephrine. Exogenously administered catecholamines are inactivated primarily by catechol-o-methyl transferase. Inhibiting monoamine oxidase has little effect on the degradation of epinephrine. Human trials and a recent dog model study have failed to show any interactions between epinephrine and MAO inhibitors.

Some controversy exists regarding the interaction between tricyclic antidepressants and epinephrine in local anesthetics for dentistry. Tricyclic antidepressants prevent neuronal uptake of catecholamines at the adrenergic nerve terminals. This results in a higher concentration of catecholamines present at the sympathetic neuroeffector junction. With the use of adrenergic vasoconstrictors in local anesthetics, one would expect potentiation of vasoconstrictor effects and cardiac stimulation. Cawson et al., in a review of the literature and data from the British Registrar General's Office, concludes that there is no clinical evidence of significant interactions between tricyclic antidepressants and local anesthetics containing epinephrine. However, Jastak and Yagiela interpreted the experimental data of Boakess and concluded there was a two- to four-fold potentiation of epinephrine by tricyclics in the study. A recent study by Yagiela et al., using dog models showed that the cardiopulmonary response was not greatly affected with doses of epinephrine in the 0.33-0.67 mg/kg range. This represents 1-2 car- pules of 2% lidocaine with 1:100,000 epinephrine in a 55 kg patient injected intravascularly. At a level of 2.5 mcg/kg epinephrine, a statistically significant increase in arterial blood pressure was noted. Person and Siwers conclude from their study of twenty-one patients receiving anti-depressant medication, who were administered lidocaine with epinephrine for dental treatment, that epinephrine is contraindicated for these individuals. As Yagiela et al., proposed, from reviewing the literature and their own studies, a maximum limit of 0.05 mg of epinephrine (equivalent to three cartridges of 1:100,000 epinephrine) would be a reasonable limit.

The beta blocking agents commonly used in the treatment of hypertension may interact with epinephrine to enhance its vasopressor action. As the beta blocker inhibits vasodilatation of skeletal muscle, the reflex vasodilation that normally would occur in response to the alpha stimulating effects of epinephrine does not take place. Blood pressure often rises significantly as a result. Those patients being treated with beta blockers are the same portion of the population that can least afford the potential pressor effects.

Phenothiazines

This class of drug is used largely for its anti-emetic, tranquilizing and anti-psychotic effects. Alvarez and Frank have reported that the phenothiazines have been incriminated in the production of electrocardiographic repolarization abnormalities and sudden
The repolarization abnormalities are characterized by alteration in configuration, voltage, or polarity of T-waves unassociated with changes in mean electrical QRS axis, QRS voltage or configuration, or the ST segment. However, there is little evidence of the clinical significance of these T-wave changes.46

The use of local anesthetics with vasoconstrictors in patients taking phenothiazines has also been admonished in the past. Common to phenothiazine toxicity is the presence of arterial hypotension caused by the blockade of alpha adrenergic receptors in the peripheral vasculature. Treatment of such hypotension with epinephrine may have disastrous results as each vasoconstricting (alpha adrenergic) property of the epinephrine is partially blocked by the phenothiazine, but the vasodilating effect remains the same leading to worsening hypotension. However, patients with acute overdosages of phenothiazines are rarely encountered in practice.

Yagiela et al. showed no significant interaction between chlorpromazine and epinephrine.36 This observation combined with the fact that dentists and physicians have been administering local anesthetics with vasoconstrictors to patients on phenothiazines without incident for years, seems to indicate that judicious use of vasoconstrictors is unlikely to have deleterious effects in the phenothiazine treated patient.

Cardiovascular Response to Vasoconstrictors

There has long been debate regarding the safety of using epinephrine as a vasoconstrictor with local anesthetics, especially in patients with cardiovascular disease. The use of epinephrine has been criticized for the possibility systemic absorption, intravenous injection, drug interaction and resulting adverse cardiovascular effects. Several studies have attempted to measure plasma catecholamine levels after intraoral injections of local anesthetic solutions containing epinephrine, and correlate these levels with hemodynamic responses.22,46 Three studies found that after injections of 1.8 ml of 2% lidocaine with 1:100,000 epinephrine there was a two to three fold rise in plasma catecholamine levels over baseline levels without a significant hemodynamic response.42,43,46 These studies utilized young, healthy patients and a small dosage of epinephrine (18 mcg). Two other studies found that intraoral injections of local anesthetics containing epinephrine resulted in increased circulating epinephrine levels associated with cardiovascular changes.44,46

It is important to note that in each of those studies, a relatively small dosage of epinephrine containing local anesthetic was administered. Cioffi et al.,45 Chernow et al.,42 and Tolas et al.43 used 18 mcg; while Dionne et al.46 and Goldstein et al.46 used 54 mcg. All were administered via standard intraoral injections using either inferior alveolar nerve blocks or posterior superior alveolar nerve blocks. Significant increases in plasma epinephrine levels, five times the baseline levels, were measured (Figure 1). This indicates that there is a large amount of systemic absorption of vasoconstrictor, even with amounts less than 10% the maximum dosage of epinephrine, 0.4 mg, which is recommended by the New York Heart Association.47 There was no significant cardiovascular response to plasma epinephrine levels of two to three times baseline levels in three of the studies cited.42,43,46 However, Dionne et al. reported increases in heart rate and systolic blood pressure at epinephrine levels five times the baseline. In this study, resting plasma epinephrine levels were found to be 34 ± 31 pg/ml. The plasma epinephrine threshold for increase in heart rate is reported to be 50 - 100 pg/ml.48 The threshold level for increases in systolic blood pressure is 75 - 125 pg/ml, while 150 - 200 pg/ml results in decreases in diastolic blood pressure.49 Post-anesthetic levels reported by Dionne et al.46 ranged from 106 ± 70 to 302 ± 142 pg/ml, which, taken with the observation of Clutter et al.,46 provides an explanation for the physiologic changes seen following the administration of local anesthetic containing epinephrine. It appears that these levels could be exceeded, if only one-third the maximum recommended dose of epinephrine is injected via standard intraoral blocks.

The amount of administrated epinephrine that reaches the general circulation after local anesthesia for dentistry has been hypothesized to be less than the amount of epinephrine endogenously released in response to the pain and stress of inadequate anes-
Psychogenic stress may also play a role in the release of endogenous catecholamines. In physiologic response to stimulation and stress, the increase in plasma epinephrine is accompanied by a comparable increase in plasma norepinephrine concentration. By measuring concomitant plasma norepinephrine levels in two studies and by using lidocaine without epinephrine as a control in another, it was determined that this hypothesis is without support. A fifth study, in which epinephrine and norepinephrine levels were measured after retrobulbar blocks with 2% lidocaine containing 1:200,000 epinephrine, showed a significant increase in plasma epinephrine compared to control values, while norepinephrine levels increased in only two of 17 patients. Again, the significant change in epinephrine concentration probably originated from exogenous epinephrine rather than the stress response.

The vast majority of studies that measure plasma epinephrine levels and hemodynamic responses to intracranial injections of local anesthetic with epinephrine, utilize healthy, young, ASA I patients and small amounts of vasoconstrictor. Patients with cardiovascular disease are often treated with drugs that may alter the synthesis, storage, biotransformation, and release of catecholamines. They are at risk, not only for an adverse response to epinephrine, but for drug interactions. Tolas et al., Chernow et al. and Cioffi et al. studying the hemodynamic response to local anesthetics containing epinephrine in dental patients, found minimal changes in heart rate associated with elevated plasma epinephrine levels.

Dionne et al., Clutter et al. and Goldstein et al. found cardiovascular responses to plasma epinephrine levels easily obtained with minimal dosage of epinephrine from dental injections. One should not conclude that the results seen with low doses of epinephrine in healthy subjects can be applied toward patients with cardiovascular disease or the general population as a whole.

**Periodontal Ligament Injections**

In recent years, the periodontal ligament (PDL) injection and pistol grip anesthetic syringes have become more popular. The pistol grip syringes are capable of delivering the anesthetic under high pressure. Previous studies by Smith and Walton indicated that the PDL injection is essentially an intra-osseous injection. Lilenthal demonstrated that intra-osseous injection of vasoactive agents (i.e., epinephrine) has a measurable effect on blood pressure and pulse rate in humans. A more recent dog study by Smith and Pashley showed that PDL injection of 2% lidocaine with 1:100,000 epinephrine caused decreases in blood pressure and increases in heart rate. There was no difference in results between solutions injected intravenously and those injected in the PDL. The high pressures in the PDL developed during these types of injections may force solutions into capillaries and venules so rapidly that they mimic an intravascular injection.

Rawson and Orr recently studied the spread of solution during PDL injections. Using fresh, unembalmed cadavers and injecting reagent grade mercury via the Lignajet syringe (Healthco Inc., Boston, Massachusetts) for PDL injection, they found universal entrance into the vascular tree rather than simple diffusion into the alveolar tissue. Further investigation of blood levels of intraligamentary injected anesthetic agents and vasoconstrictors is needed to further assess possible systemic implications.

**Selecting the Optimal Concentration of Vasoconstrictor**

As discussed earlier, vasoconstrictors are added to dental local anesthetic solutions to provide a longer duration of anesthesia, to reduce systemic toxicity of the local anesthetic, to enhance the depth of anesthesia and to provide hemostasis at the surgical site. In determining the concentration of vasoconstrictor to use, the ideal concentration is that which achieves the above mentioned characteristics, while least affecting the physiology of the patient.

The most commonly used dental local anesthetic today is 2% lidocaine with 1:100,000 epinephrine. Evidence points to an optimal epinephrine concentration of 1:200,000 in dental local anesthetics; yet the only solutions presently marketed in U.S. dental cartridges with 1:200,000 epinephrine are bupivacaine and prilocaine.

Keesling and Hinds studied the depth and duration of lidocaine anesthesia with varying concentrations of epinephrine. Their double blind study concluded that 1:250,000 epinephrine was as effective as 1:50,000 epinephrine in prolonging the duration and maintaining the depth of anesthesia. Gargarosa and Halik in a double blind study compared: 1) speed of onset, 2) efficacy of anesthesia, 3) duration of anesthesia, 4) degree of hemostasis, and 5) toxic symptoms. The conclusion reached in this study was that solutions of 1:300,000 epinephrine were as satisfactory as solutions of 1:100,000 epinephrine with lidocaine. Tullar and Roberts concluded that no clinical advantage is gained with 1:100,000 versus 1:300,000 epinephrine. Kennedy et al., in another study, corroborate the above conclusion that increasing the amount of epinephrine above 1:200,000 does not increase the duration of the anesthetic block.

Fink et al., however, used the infraorbital nerve of rats in their animal model and found a dose related prolongation of lidocaine levels. This study questions whether the maximal effect is produced with 1:200,000 epinephrine concentration. It is not evident whether this represents a difference due to the animal model used or a different effect of epinephrine on tissue blood flow versus tissue anesthetic levels.
Several studies have also measured the concentration of epinephrine providing optimal vasoconstriction. Mulroy and Halcomb recently used an animal model and measured cutaneous blood flow in skin wheals with varying concentrations of epinephrine with 1% lidocaine. They found that there was no measurable difference in cutaneous blood flow among solutions containing 1:50,000; 1:100,000; and 1:200,000 epinephrine. Bulrow and Bastron also compared hemostasis with varying concentrations of epinephrine and found 1:200,000 to be as effective as 1:100,000. Their data confirms the indirect evidence of Dhuner and Lewis, and Braid and Scott demonstrating a 1:200,000 concentration of epinephrine as the optimal dose.

In using a local anesthetic with high epinephrine concentration for hemostasis during oral and periodontal surgery, the possibility of post-operative blood loss via a rebound effect should be noted. In a study of third molar extractions, the frequency of post-op bleeding was high in the vasoconstrictor group, whereas no post-op hemorrhage was seen in the control group where no vasoconstrictor was employed. Studies of blood loss during full mouth odontectomy also showed significant post-op blood loss associated with epinephrine use. The post-op blood loss was found to be unrelated to the intraoperative blood loss. The rebound effect exhibited with epinephrine in these studies seems to be a reactive hyperemia that ensues when the vasoconstrictor wears off. The cause of the hyperemia is most likely to be local tissue ischemia and acidosis that result from the vasoconstriction of the vessels.

A recent animal study by Yagiela revealed that lidocaine was significantly more toxic intravenously than by internal carotid artery injection and that epinephrine potentiated the intravascular toxicity of lidocaine. Although the mechanism of the increased toxicity was not determined, it was postulated that epinephrine could alter the distribution of lidocaine by its effects on the cardiovascular system, or the drug interaction directly results in enhanced CNS and cardiovascular toxicity. This would suggest that a smaller concentration of epinephrine be used when possible.

**Clinical Application**

From the data presented, it seems a decrease in the concentration of epinephrine used with lidocaine would not significantly change the efficacy of the local anesthetic solution. There appears to be general agreement that 2% lidocaine with 1:200,000 epinephrine should be used whenever possible, especially in mandibular injections, as this would afford a greater margin of safety for the patient without sacrificing satisfactory quality and duration of anesthesia. This is especially true in the use of halothane with local anesthetics containing epinephrine, as well as in patients with cardiovascular disease. Although

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>2% lidocaine with 1:100,000 epinephrine cost comparison: dental cartridge vs use of multiple dose vial with epinephrine added</th>
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<tbody>
<tr>
<td>Volume</td>
<td>Dental Cartridge and Needle</td>
</tr>
<tr>
<td>1.8 ml</td>
<td>$.139</td>
</tr>
<tr>
<td>3.6 ml</td>
<td>$.224</td>
</tr>
<tr>
<td>5.4 ml</td>
<td>$.309</td>
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<tr>
<td>7.2 ml</td>
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These costs presume that one needle or needle/syringe will be used per given volume. The above costs were determined using the following: $.085 per 1.8 cc dental cartridge (carpule) of 2% lidocaine with 1:100,000 epinephrine. $0.23 per ml using 50 ml multiple dose vial of 2% lidocaine with epinephrine added for 1:100,000 epinephrine. $.054 per 25 gauge 1½" (long) dental needle $.14 per 3 ml syringe with 25 gauge 1½" needle

Cawson points out that there are few reported drug interactions and fatalities resulting from local anesthetics containing epinephrine, the principle of using the lowest dosage of drug to produce the desired action while minimally affecting the physiology of the patient should be applied. The 1:100,000 epinephrine concentration has been said to provide a cushion for the rapid breakdown of epinephrine in dental cartridges exposed to light or heat. With minimal effort and significant cost savings, clinicians can make up local anesthetic solutions with varying concentrations of vasoconstrictor that will not require increased vasoconstrictor concentrations due to potential breakdown during storage. In addition, these solutions will not require a preservative, which effectively removes the component of local anesthetic solutions to which patients are most often sensitive.

As an example, using current prices, the cost of mixing 2% lidocaine with epinephrine in a 1:200,000 concentration can result in savings of approximately five cents per patient, assuming an average of 5.4 cc or 3 cartridges used per patient. (Table 2.) Multiplied over the number of patients treated per year, a significant savings may be realized.

**References**


