The issue concerning how much and under what circumstances epinephrine vasoconstriction within dental local anesthesia is appropriate has been strenuously debated over the last 50 years. Because relevant human and animal studies are difficult to perform, there are, at present, insufficient data to answer many of our questions. Many of the previous conclusions regarding safety and efficacy were based upon incomplete understanding, bias, and limited scientific and clinical data. Well designed controlled, randomized, and blinded studies are the gold standard with regard to determining pharmacotherapeutic efficacy and safety.

With regard to epinephrine vasoconstriction, many opinions concerning this issue neglect our current understanding of physiology and pharmacology as well as the results of scientific clinical studies. Previous misunderstanding has been woven into much of our current clinical practice and as such reappraisal is warranted, because medical comprehension of the dynamics of physiology and pharmacology have recently undergone dramatic changes.

Issues regarding these medications remain and include: 1) the advantages of combining vasoconstriction with local anesthesia, 2) the physiologic workings of the adrenergic nervous system, 3) toxicity issues of vasoconstrictors, 4) insignificant changes in mean arterial (MAP) blood pressure with relatively small amounts of epinephrine, 5) receptor dynamics, 6) drug-drug interactions, and 7) vasoconstrictor issues with regard to the dental treatment of patients with severe cardiac disease.

**THE RATIONALE FOR COMBINATION OF VASOCONSTRICTOR WITH LOCAL ANESTHETICS**

The presence of epinephrine and other vasoconstrictors in local anesthetic solutions is beneficial with regard to duration, depth of anesthesia, blood loss, and the reduction of systemic local anesthesia toxicity. Local anesthetic clinical efficacy is dependent upon the action of the vasoconstrictor. Dental treatment with insufficient vasoconstriction within the local anesthetic formulation may lead to less than adequate pain control and thus increased levels of endogenous catecholamines and particularly norepinephrine (NE). Pain control was significantly impaired in those patients receiving the local anesthetic without the vasoconstrictor as compared to those patients receiving the local anesthetic with vasoconstrictor. Ineffective pain control increases patient health outcomes risk. NE (either parental or endogenous) increases blood pressure and has other cardiotoxic effects.

Local alpha-adrenergic agonist action resulting in vasoconstriction at the injection site, in addition to increased depth and duration of anesthesia, may be important in limiting the systemic dose of the local anesthetic. In a randomized, double-blind, parallel-group, and crossover study evaluating the removal of impacted third molars, Knoll-Kohler and Fortsch demonstrated that systemic NE levels as a measure of stress were significantly elevated with 4% articaine with 1:200,000 epinephrine as compared to 4% articaine with 1:100,000 epinephrine. According to Knoll-Kohler and Fortsch and Knoll-Kohler and Fortsch and Knoll-Kohler et al (also a randomized, double-blind, parallel-group and crossover study), the combination...
of epinephrine and local anesthetic is especially important in patients suffering from cardiovascular diseases, because only in the combination of epinephrine with the local anesthetic in an appropriate concentration is there a sufficient guarantee of depth and duration of pulpal and surgical anesthesia and thus the avoidance of patient pain/stress (which increases sympathetic drive) and the ill effects of excess endogenous NE.

THE ADRENERGIC SYSTEM

This system is composed of both beta and alpha receptors and various subtypes including beta 1 and beta 2, along with alpha 1 and alpha 2 receptors. The beta 1 receptors increase heart rate, and the beta 2 receptors increase vasodilation of the pulmonary vascular beds. The actions of the beta-adrenergic system are mainly systemic whereas the actions of the alpha-adrenergic system are mainly peripheral with some systemic action. Stimulation of the alpha receptors increases vasoconstriction mainly of local peripheral circulation, though with limited systemic activity. Therefore, beta 1 stimulation tends to cause an increase in blood pressure and beta 2 stimulation tends to decrease blood pressure. Systemic alpha stimulation tends to increase blood pressure but not dramatically.

The actions of the 2 catecholamines are different. NE stimulates the beta 1--adrenergic receptors preferentially, with very little beta 2 activity, therefore causing an increase in blood pressure when utilized as a local anesthetic vasoconstrictor. However, because epinephrine has both beta 1 and beta 2 activity, it does not tend to dynamically increase blood pressure owing in part to beta 2 vasodilation.

Furthermore, the hemodynamic alterations seen with elevated serum epinephrine are usually very short in duration owing to the very short plasma half-life of epinephrine, which is approximately less than 1 minute. Pharmacotherapeutic administered epinephrine is eliminated from the blood stream in approximately 10 minutes or less owing to breakdown by catechol-O-methyl transferase (COMT) in the blood, liver, lungs, and other tissues. The sympathetic nervous system transmits the body’s response to pain. Under stimulation, NE is released from the sympathetic nerve terminals, and the target immune cells express adrenoreceptors. Through stimulation of these receptors, locally released NE, or circulating catecholamines such as epinephrine, affects circulation and modulates cytokine production and the functional activity of different lymphoid cells. Essentially, sympathetic drive (pain) primarily results in the release of NE and secondarily epinephrine. The systemic alpha-adrenergic effects upon blood pressure are limited. Both NE and epinephrine are alpha-adrenergic agonists. The alpha-adrenergic agonist effect is vasoconstriction, which aids the analgesic effects at the peripheral injection site but has limited systemic effects upon blood pressure. For example, the drug prazosin, an alpha-adrenergic antagonist (specifically, an alpha 1 antagonist), is also utilized as an antihypertensive drug. But the antihypertensive effects of prazosin are limited and effective only for minimal to moderate hypertension. Prazosin’s actions account for either minimal or at best a moderate decrease (approximately 10-12 mm Hg) in blood pressure.

TOXICITY OF NOREPINEPHRINE AND EPINEPHRINE (AND OTHER VASOCONSTRICTORS)

Local anesthetic formulations utilizing NE as the vasoconstrictor resulted in numerous adverse patient consequences within the context of standard dental treatment. Furthermore, NE vasoconstriction may result in rebound bradycardia secondary to the initial hypertension. Therefore, NE was removed as a vasoconstrictor from most formulations. Furthermore, Niwa et al concluded that epinephrine activates left ventricular diastolic function compared to NE, which impairs left ventricular diastolic function. However, concerns regarding problematic catecholamine (NE)-induced hypertension have persisted. Levonordefrin is similar to NE in action but with somewhat less alpha 1 potency and slightly more beta 2 potency. In order to simplify this issue, Table I is provided.

Table I shows that epinephrine is approximately 4 times more potent with respect to alpha (peripheral vasoconstrictor) action compared to NE and considerably more potent compared to levonordefrin and phenylephrine. Vasoconstrictor concentrations are titrated to approximately the same alpha-adrenergic activity for many commercial formulations with regard to epinephrine 1:100,000, NE 1:30,000, and levonordefrin 1:20,000. Also, epinephrine has considerably greater beta 2 activity compared to other vasoconstrictors.

INSIGNIFICANT CHANGES IN MEAN ARTERIAL BLOOD PRESSURE (MAP)

Multiple studies with regard to local anesthesia and epinephrine combinations have confirmed that even though blood pressure and heart rate may have changed significantly, the hemodynamic response as defined by the mean arterial blood pressure (MAP) is unchanged. The MAP is defined as the average pressure throughout the pressure-pulse cycle and often calculated as the addition of the systolic and diastolic divided by 2. In evaluating the relationship between systemic resistance, blood flow, and pressure, it is the...
MAP that is important and not the diastolic or systolic blood pressure values.

Repeated studies have failed to determine deleterious effects of local anesthetic formulations with epinephrine included in dental patients with hypertension or cardiovascular disease.10,19,22-29 The dose limit of exogenous epinephrine on patients with cardiovascular disease was previously set at 200 µg.30 This allows for 11 cartridges of 1.8 mL lidocaine with 1:100,000 epinephrine, which is relatively close to the maximum allowable dose in a 70-kg (160-lb) adult of 13.9 cartridges of 2% lidocaine with 1:100,000 epinephrine.31 Local anesthetics have a relatively narrow therapeutic window and therefore overdoses of these drugs have been reported, although usually in children and with local anesthetic formulations in greater than the 2% concentrations utilized for lidocaine (and without epinephrine).31,32

In a study of normotensive (n = 39) and hypertensive (n = 36) groups undergoing injection and extraction procedures, comparing 2% lidocaine with and without 1:100,000 epinephrine, Meyer27 reported that in both groups the changes of blood pressure and heart rate were similar. On the other hand, the vasoactive concentration of NE (between 1:20,000 and 1:30,000) produced a significant rise in blood pressure and decrease in heart rate and Meyer27 concluded that NE as a vasoconstrictor is contraindicated in hypertensive dental patients.

Epinephrine usually increases heart rate, stroke volume, systolic blood pressure, myocardial oxygen consumption, and cardiac automaticity but reduces diastolic blood pressure.31 Therefore, the mean arterial pressure is relatively unchanged.

RECEPTOR DYNAMICS

There is a tendency of receptor-based systems, including the adrenergic system, for a negative feedback loop. The basics of this type of system is that when receptors are exposed to large amounts of an agonist (ligand), the receptors will down-regulate. This phenomenon produces the effect of accommodation and it will take greater and greater amounts of the ligand/agonist to produce the same biologic effect (eg, opioid addiction). Conversely, when the receptor is not exposed to the ligand/agonist for a significant period of time, the receptor system will up-regulate and lesser amounts of the ligand/agonist will cause a greater biologic effect.33,34

For instance, patients with the medical condition of pheochromocytoma produce excess amounts of catecholamines. Therefore, individuals with this condition have down-regulated adrenergic receptors and small amounts (<200 µg epinephrine) of catecholamines will have very little effect on these individuals.35,36

\[
\begin{array}{|c|c|c|c|}
\hline
\text{Vasoconstrictor} & \text{Beta 1 selectivity, %} & \text{Beta 2 selectivity, %} & \text{Relative alpha potency, %} \\
\hline
\text{Epinephrine} & 50 & 50 & 100 \\
\text{Norepinephrine} & 85 & 15 & 25 \\
\text{Levonorephrine} & 75 & 25 & 15 \\
\text{Phenylephrine} & 95 & 5 & 5 \\
\hline
\end{array}
\]

Modified from Henslee et al, 1987.21

DRUG-DRUG INTERACTIONS

In reviewing the literature regarding drug-drug interactions related to epinephrine and local anesthesia, the case report literature is exceedingly sparse. Those few documented cases may well be idiosyncratic.37,39 In the last several years, at least 2 articles have addressed the specific drug-drug interactions related to epinephrine in local anesthetic formulations.40,41

A possible drug-drug interaction related to local anesthetic formulations and tricyclic antidepressants (TCAs) was presented.40,41 Both articles quoted essentially the same references42-45 to support their particular viewpoints with regard to this interaction between the vasoconstrictor epinephrine local anesthesia formulation and TCAs. The support for this point of view appears to be questionable, which a review of the same literature demonstrates.46-48 Boakes et al42 in 1972 reported several adverse reactions to 2% lidocaine combined with 1:25,000 NE (11 patients) and combined 1% procaine and 2% butanilicaine with 1:25,000 NE (1 patient). These adverse reactions appeared to be hypertensive crises secondary to the NE vasoconstrictor. Of these 12 patients, 1 of them was concomitantly taking a TCA, 1 may have been, and 1 was taking a TCA along with chlor Diazepoxide, amantadine, and cyclophosphamide. The patient who was taking the TCA had a severe headache after the injection and vomited. Her blood pressure increased to 140/90 and returned to her normal pressure values of 120/75 the next day. Her symptoms were tame when compared to some of the other adverse events after injections with local anesthetic and NE-containing formulations reported by patients not concomitantly using a TCA.16-18

Three studies43-45 regarding the potential interaction of TCAs and hypertension were noted. None of the 3 was blinded or randomized or utilized appropriate statistical analysis. Two of the studies33,44 used only 4 healthy male volunteers and the other35 utilized only 4 dogs in the evaluation of a TCA and epinephrine interaction. Interestingly, with regard to a study by Yagiela et al,35 there were no significant changes noted in the MAP for the dogs retested with lidocaine combined with epinephrine in the pretreated desipramine dogs (although significant differences were noted with
the vasoconstrictors NE and levonordefrin). Nevertheless, they noted that the interaction between vasoconstrictors and TCAs (without distinguishing between NE and epinephrine) deserves special comment because it has “firm experimental verification,” to quote Boakes et al.43 and Svedmyr.44

Furthermore, studies of the biochemical mechanism of action of antidepressant drugs show that virtually all of these drugs (monoamine oxidase (MAO) inhibitors, selective serotonin reuptake inhibitors, and TCAs) along with electroconvulsive shock therapy, regardless of acute biochemical effects, result in the down-regulation of CNS beta-adrenergic receptors in a time course that parallels the onset of the antidepressant action. This drug-induced down-regulation takes between 2 and 3 weeks from TCA administration.49-53 Therefore, a beta-receptor agonist (epinephrine, NE) should have more effect when given to a patient (or animal) who had taken a TCA for less than 3 weeks compared to subjects taking a TCA more than 3 weeks. There is a presumption that adrenergic down-regulation also occurs in the periphery, but cardiac effects are centrally mediated. The reader may note that in all the above studies by Boakes et al.,43 Svedmyr,44 and Yagiela et al.,45 the TCAs were given for only 5 days, 4 days, or acutely, respectively. Therefore, such down-regulation would not have had time to occur and any such down-regulation could result in the disappearance of any potential interaction related to beta-adrenergic activity. The 3 studies demonstrated a possible drug-drug action in TCA-naive subjects rather than in adrenergic receptor down-regulated clinical subjects. Yagiela40 argued that because beta blockers do not influence depression the concept of the down-regulation of beta-adrenergic receptors as a factor within the drug-drug interaction between TCAs and epinephrine was undermined. But that point is irrelevant because the drug consequence of beta-adrenergic down-regulation remains whether or not the down-regulation is essential to the drug action of antidepression. With regard to epinephrine local anesthetic formulations and any potential drug-drug interaction with TCAs, a rational objective view does not support such a drug-drug interaction.

Furthermore, the possibility of an interaction between MAO inhibitors and local anesthetics with or without epinephrine was disputed by Yagiela for the purported rationale that exogenously administered vasoconstrictors are preferentially inactivated by the enzyme COMT and that the literature does not support such a drug interaction.45,55 However, this same rationale should also apply to any drug-drug interaction between exogenous epinephrine and TCAs.

Further supporting evidence for the lack of an interaction between epinephrine and TCAs is the total absence of case reports within the English-language scientific literature. This lack of case reports is striking in populations which have used both epinephrine and local anesthesia formulations and TCAs in millions of patients over 30 years.

Other drug-drug interactions with epinephrine local anesthetic formulation also are debatable. For instance, within the literature, there were very few reported cases of an interaction between a nonselective beta blocker and a local anesthetic combined with a vasoconstrictor. Mito and Yagiela reported 1 dental case with propranolol and levonordefrin (a vasoconstrictor similar to NE—see Table 1). Within the medical literature, a reported hypertensive crisis case report involving propranolol and epinephrine occurred in an emergency room environment with higher doses of epinephrine (1:1,000 concentration) than normally utilized within a dental clinic environment. Furthermore, Foster and Aston in regard to plastic surgery reported 6 cases. However, all of these cases demonstrated other possible polypharmacy interactions. All the reported Foster and Aston cases were noted for antihistamines including 4 cases with hydroxyzine, 1 with lorazepam, and 1 with combined hydroxyzine and lorazepam. Therefore, the potential beta blocker and local anesthetic with vasoconstrictor interaction may be possible but extremely unlikely and perhaps related to a vasoconstrictor other than epinephrine. Several studies with regard to nonselective beta blockers and local anesthetic vasoconstrictor formulations have demonstrated such an interaction which results in increased duration of action of local anesthesia.50-62 There is also a theoretical increased risk of local anesthetic toxicity because beta blockers (and also cimetidine) can retard the hepatic oxidation of the local anesthetic by inhibiting hepatic enzyme activity (by approximately 40%). But, this noted drug-drug interaction involves only the local anesthetic and not epinephrine. There is a striking paucity of such case reports regarding these 2 widely utilized pharmaceuticals.

Yagiela also proposed an interaction between epinephrine local anesthetic formulations and both cocaine and general anesthetics. Cocaine and antidepressants block reuptake of NE into nerve terminals, which increases NE activity. However, the inclusion of the vasoconstrictor epinephrine into such drug interactions is problematic. Cocaine is a local anesthetic with a known cardiovascular toxicity. All other local anesthetics possess a similar toxicity profile. The addition of any 2 drugs with similar toxicity profiles (typically drugs within the same drug category) is known as additive toxicity and can contribute to drug-drug interactions. With or without epinephrine, adding a known local anesthetic to the circulation of a patient using cocaine...
may result in additive toxicity. It is true that cocaine may block reuptake of NE and that epinephrine could add to sympathetic drive, but this is a relatively minor issue compared to additive toxicity. Of course, the vasoconstrictor properties of cocaine and epinephrine are a good reason to avoid a combination of the 2 along with regard to additive toxicity. Interestingly, blood pressure values actually descend in cocaine-abusing patients (not acutely using cocaine) during extraction procedures using epinephrine and lidocaine and with regard to local anesthetic and epinephrine epidurals and childbirth.

Furthermore, additive toxicity between anesthetics, such as local and general anesthetics, is also an expected additive drug-drug interaction. Ganzberg noted that both epinephrine and levonordrin (vasoconstrictors with local anesthetic formulations) should be administered carefully and in small quantities to patients under halothane general anesthesia to avoid unwanted dysrhythmias. By the same rationale, there is potential concern with the administration of more than 1 μg/kg of epinephrine (70 μg or a little less than 4 anesthetic cartridges of 1:100,000 epinephrine in a 160-lb patient) to patients undergoing halothane, enflurane, or isoflurane general anesthesia.

As previously noted, the principle drug action of a vasoconstrictor, alpha 1—receptor agonism, results in vasoconstriction at the local anesthetic injection site and may actually aid in decreasing the rate of systemic absorption of the local anesthetic and therefore limit local anesthetic toxicity and drug-drug interactions.

**VASOCONSTRICTOR ISSUES WITH REGARD TO THE DENTAL TREATMENT OF PATIENTS WITH SEVERE CARDIAC DISEASE**

As noted by Little et al, the critical question is, how does a patient with hypertension or other cardiovascular disease react to these dose challenges of epinephrine (or other vasoconstrictors)? This question was addressed empirically in 1955 by the New York Heart Association, which recommended that a maximum of 0.2 mg of epinephrine (<11 cartridges of 1:100,000 epinephrine) be used at 1 session in dental patients with heart disease. In 1964, a Working Conference of the American Dental Association and the American Heart Association concluded, “Concentrations of vasoconstrictors normally used in dental local anesthetic solutions are not contraindicated in patients with cardiovascular disease when administered carefully and with preliminary aspiration.” Contrary to these recommendations, Abraham-Inpijn et al. found that patients with hypertension undergoing dental extractions had a greater increase in blood pressure than did patients thought to be normotensive after injection of 2% lidocaine with 1:80,000 epinephrine. In addition, 7.5% of the patients with hypertension developed significant arrhythmias. However, in a similar study, Meyer compared the response of patients who were normotensive and hypertensive to lidocaine plain, with 1:100,000 epinephrine, and with 1:20,000 NE during extractions, and no significant differences were noted in heart rate or blood pressure between plain lidocaine and lidocaine with epinephrine. However, lidocaine with NE produced a significant increase in blood pressure and a decreased heart rate when compared to plain lidocaine. Another study of dental patients undergoing surgery found no difference in the blood pressure of patients with hypertension who received 2% lidocaine with 1:80,000 epinephrine. A study evaluating epinephrine infusion as a stress test for 39 patients suspected of having coronary artery disease involved a series of increasing levels of epinephrine from 2.1 to 21 μg per minute injected intravenously over 30 minutes (21 μg is slightly greater than the 18 μg in 1 cartridge of 1:100,000 epinephrine). Of the 24 patients subsequently found not to have coronary artery disease, none developed electrocardiographic changes, and none had symptoms over the course of 30 minutes. Of the 15 patients diagnosed with coronary artery disease, however, 7 developed significant arrhythmias, 7 had chest pain, and 4 had shortness of breath or other symptoms. In spite of the symptoms and hemodynamic changes, no test had to be terminated and all symptoms subsided after the test without sequelae. A recent article noted increased heart rate in heart transplant dental patients (but no increase in blood pressure) with the use of epinephrine as a vasoconstrictor. Furthermore, Niwa et al demonstrated that infiltration anesthesia with 3.6 mL 1:80,000 epinephrine (45 μg epinephrine) and lidocaine can be carried out safely on patients with an exercise capacity of more than 4 metabolic equivalents (the approximate equivalent to the workload of walking 4.8 km/h, doing light yard work, or painting). In another study utilizing 10 healthy human subjects and pulsed Doppler echocardiography of mitral valve inflow, Niwa et al compared the effects of infiltration injection of 3.6 mL 2% lidocaine with either 1:80,000 (45 μg) epinephrine or 1:25 NE (144 μg) and concluded that epinephrine activates left ventricular diastolic function and in contrast NE impairs it. In yet another study, Niwa et al evaluated 27 patients with cardiovascular disease with impedance cardiography to determine hemodynamic responses to an injection of 1.8 mL 2% lidocaine with 1:80,000 epinephrine. The conclusion was that lidocaine-epinephrine was safe and had few, if any, hemodynamic consequences in patients with cardiovascular disease.

From the preceding studies, 2 to 3 cartridges of 2% lidocaine with 1:100,000 epinephrine (36 to 54 μg of
epinephrine) appears to be tolerated in most patients with hypertension or other cardiovascular disease, and the benefits of the vasoconstrictor appear to outweigh potential disadvantages or risks.  

DISCUSSION

The focus of this article is to discuss the relative safety of epinephrine and local anesthetic formulations with respect to hypertension. Many of the quoted studies supporting the safety and efficacy of epinephrine and local anesthetic formulations are not perfect. However, several of these studies regarding local anesthesia and epinephrine combinations are documented with prospective, blinded, randomized, human, clinical trials. Furthermore, several other clinical human studies support the safety of epinephrine as a local anesthetic vasoconstrictor.

A recent review on this subject by Bader et al1 reported that adverse outcomes among hypertensive dental patients are infrequent and that risk indicators reflect only minimal change, and replicating existing studies is not an efficient method of furthering our knowledge of the risks for adverse cardiovascular outcomes associated with dental treatment and local anesthesia. Bader et al1 proposed a prospective long-term protocol documenting pre-existing cardiovascular diagnoses and medications and evaluating the outcomes of dental treatment. Certainly, there is no argument regarding the advantages of a prospective study. However, to be truly helpful in determining the advantages of various local anesthetic formulations in defined cardiovascular patient populations, it will be necessary to complete prospective, randomized, blinded, controlled studies utilizing comparison between differing local anesthetic formulations in specific patient populations. Furthermore, it would be extremely helpful to determine the dose-response curves regarding the toxicity profiles of these medications on hypertensive patient populations. Such studies would be exceedingly valuable but expensive, potentially dangerous, and labor intensive.

In conclusion, the issues relating to local anesthesia and epinephrine vasoconstrictor safety are relatively simple. Firstly, there is a relative absence of case reports noting adverse consequences related to the administration of formulations of epinephrine and local anesthesia when used appropriately on dental patient populations. Secondly, clinical studies have repeatedly demonstrated the effectiveness and safety of these formulations on dental patient populations. Thirdly, we must continue to scientifically evaluate the efficacy and safety of these drugs and to objectively define our treatment protocols based upon scientific evidence.

REFERENCES


41. Svedmyr N. The influence of a tricyclic antidepressant agent (protryptyline) on some of the circulatory effects of noradrenaline and adrenaline in man. Life Sci 1965;7:77-84.


Reprint requests:
Dr R. S. Brown
Howard University College of Dentistry
600 W Street NW
Washington, DC 20059
rbrown@howard.edu