
Contraindications to vasoconstrictors in dentistry: Part III

Pharmacologic interactions

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This article discusses the relative contraindications to the use of vasoconstrictor in patients currently medicated with tricyclic antidepressants, monoamine oxidase inhibitors, phenothiazines and β -blockers. It reviews drug interactions and emphasizes potential detrimental systemic effects that epinephrine contained in local anesthetics can have when administered concomitantly with these drugs. Finally, special considerations are expressed concerning patients who abuse illicit drugs such as cocaine.

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The first two articles of this series reviewed and discussed the "absolute" contraindications to the use of vasoconstrictors in dentistry. This third and last part deals with their "relative" contraindications, which by definition do not preclude their use but dictate the exercise of great caution. The focus here is on the potential drug interactions that may take place between vasoconstrictors injected with local anesthetic and exogenously administered adrenergic drugs. It emphasizes once more the importance of careful assessment of the general health and drug intake including illicit drugs. When treating any patient taking medication, dentists should be aware of the potential medical complications and always use the least concentrated solution of vasoconstrictor that allows for deep anesthesia during a sufficient period of time. As a routine procedure, the local anesthetic solution should always be injected slowly with frequent aspiration to minimize the potential hazard of an accidental intravascular injection.

RELATIVE CONTRAINDICATIONS

Tricyclic antidepressants

The tricyclic antidepressants (TCAs) are drugs widely used today in the treatment of major depres-

sion. Their efficacy in alleviating depression is well established, but TCAs are also extremely effective in the treatment of certain chronic pain states including orofacial pain disorders.^{1, 2} The TCAs act on the central nervous system by blocking the reuptake and thus the physiologic inactivation of certain neurotransmitters at the neuroeffector junction³ (Fig. 1).

Among the drug interactions involving the TCAs, dentists should be mostly concerned with the potential enhancement of the cardiovascular effects associated with exogenously administered catecholamines. In normotensive subjects pretreated for 4 days with protriptyline, 20 mg three times daily, Svedmyr⁴ observed an important increase in the systolic and diastolic blood pressure after the intravenous infusion of very small doses of norepinephrine (0.022 $\mu\text{g}/\text{kg}/\text{min}$). As for epinephrine infusion, similar hemodynamic changes were observed but at a dosage three times greater (0.067 $\mu\text{g}/\text{kg}/\text{min}$). Other investigators^{5, 6} have also substantiated these findings. It is clear from the results of these studies that the vasoconstrictor effects of norepinephrine, epinephrine, and presumably levonordefrin are seriously potentiated by TCAs. Although this enhancement is fivefold to tenfold for norepinephrine and levonordefrin, it is not as dramatic for epinephrine and phenylephrine (twofold to threefold) enhancement at concentration currently used in local anesthetic solutions.⁷ The powerful interactions between adrenergic drugs and the biogenic amines accumulated at the neuroeffector syn-

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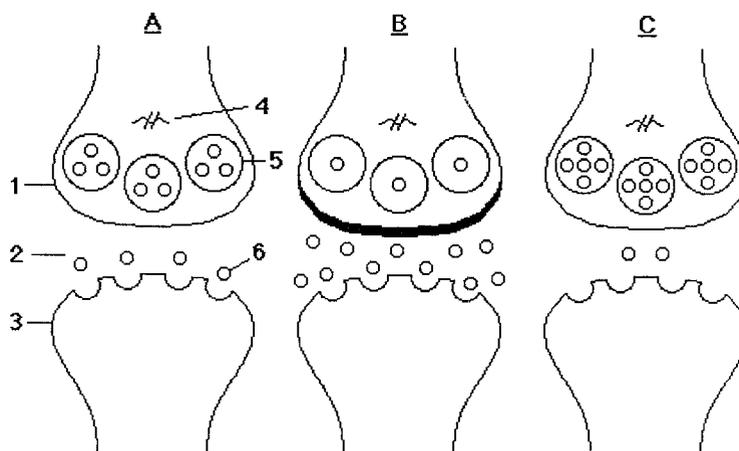


Fig. 1. Action of TCAs and MAOIs. 1, Presynaptic neuron; 2, synaptic cleft; 3, postsynaptic neuron; 4, monoamine oxidase; 5, terminal vesicles and neurotransmitters; 6, neurotransmitters. A, Normal synaptic junction. B, junction in patient receiving tricyclic drugs. C, Junction in patient receiving MAOI.

apse have led to serious medical complications. Series of severe hypertensive crises, one of which resulted in the death of a patient, were reported by Boakes et al.⁸ after the injection of small quantity of local anesthetic containing norepinephrine 1:25,000 in patients treated with TCAs. Although such complications are not frequent, it should emphasize once more the importance of assessing the current drug intake and being aware of the potential drug interactions.

As several investigators pointed out,⁹⁻¹³ patients currently taking TCAs may have numerous electrocardiographic changes. TCAs have the property of lengthening the conduction time (PR, QRS, or QT intervals) and inducing various anomalies of repolarization characterized by flattening of the P wave and the appearance of the U wave. Although infrequent at low dosages, such changes have been observed at therapeutic doses in otherwise healthy persons beside their depressive state.¹⁰ These phenomena can be more consistent and significant as the plasma concentration of TCAs increases or in patients with preexisting cardiac disease.¹³ Interestingly, TCAs possess antiarrhythmic properties but in overdose they become arrhythmogenic, exposing the patient to reentry arrhythmias and circus rhythms.¹⁰⁻¹³ On the basis of these reports, concomitant administration of adrenergic drugs and TCAs has the potential to provoke serious arrhythmias. The cardiotoxicity of TCAs is furthermore reflected by the report of sudden death of cardiac patients treated with amitriptyline and imipramine.¹⁴

Sufficient evidence exists to consider the use of local anesthetic with norepinephrine or levonordefrin dangerous in patients taking TCAs. Even though the

potentiation of the pressor effect of epinephrine is two to three times less than that reported for norepinephrine or levonordefrin, the possibility of potential untoward reactions should be taken into consideration. In that respect, Yagiela et al.⁶ recommend reducing to 0.05 mg (5.4 ml local anesthetic with epinephrine 1:100,000) the maximum amount of epinephrine that patients receiving TCAs should receive in any given session. Until more data are available, this recommendation seems reasonable and appropriate. We must reemphasize, however, the pitfall of false security when one relies on a maximum recommended dose of vasoconstrictor. We believe dentists should always administer the lowest dose of vasoconstrictor compatible with effective pain control of sufficient duration. In addition, local anesthetic should be injected slowly with careful aspiration to avoid inadvertent intravascular injection.

Monoamine oxidase inhibitors

The monoamine oxidase inhibitors (MAOIs) are another group of psychotropic drugs primarily used in the treatment of major depression, certain phobic-anxiety states and obsessive-compulsive disorders. Their action is targeted at organ systems regulated by the sympathomimetic amines and 5-hydroxytryptamine. They can potentiate the effects of biogenic amines in the central nervous system by inhibiting their breakdown by the monoamine oxidase enzyme at the presynaptic neuron level³ (Fig. 1). Thus traditionally, local anesthetics with vasoconstrictor have been contraindicated for patients receiving MAOIs because the possibility of serious potentiation of exogenously administered catecholamines could

eventually lead to hypertensive crisis. This recommendation no longer seems to be substantiated in light of more recent work.

In an animal study Yagiela et al.⁶ did not observe any significant interaction between epinephrine, norepinephrine, levonordefrin, and MAO. Only phenylephrine, which is metabolized by monoamine oxidase, is likely to be potentiated severalfold by MAOIs.⁷ We now recognize that the risk of hypertensive crisis attributed to vasoconstrictors in local anesthetic has been overestimated for patients taking MAOIs. In fact, the metabolic degradation of exogenous catecholamines is largely regulated by the enzyme catechol-*O*-methyltransferase and by neuronal reuptake. Undoubtedly the cardiovascular effect of a variety of sympathomimetic amines can be enhanced by MAOIs; however, these drugs are much less effective in potentiating or prolonging the action of exogenous catecholamines. Despite the fact that previous findings have not been confirmed in any human study, there seems to be no restriction from a theoretical basis to use local anesthetic with vasoconstrictor other than phenylephrine in patients currently treated with MAOIs.

Phenothiazines

The phenothiazines are a class of psychotropic drugs primarily employed in the treatment of serious psychotic disorders. In addition, many drugs in this group have useful antihistaminic properties and the ability to potentiate sedatives and analgesics. Orthostatic hypotension is the most common cardiovascular side effect reported with the phenothiazines. It is brought about through a powerful α -adrenergic receptor blockade in the peripheral vasculature and inhibition of centrally mediated pressor reflexes, which are not exclusive to chlorpromazine as initially thought.³ Consequently this suppresses the vasoconstricting effect of epinephrine and unmasks its usually weak vasodilatory effect. Although the epinephrine content of a single dental cartridge of local anesthetic is small, accidental intravascular injection could potentially worsen the hypotension frequently associated with the phenothiazines through an unbalanced stimulation of vascular β -receptors. The risk of a serious complication is probably remote because no such case has yet been reported in the dental literature. On the other hand, certain hypotensive episodes might have been falsely attributed to vasovagal reactions when small amounts of local anesthetic with epinephrine were inadvertently injected into the bloodstream of patients taking phenothiazine drugs.

Thioridazine (Mellaril) and other phenothiazines can also induce repolarization abnormalities resem-

bling those produced by quinidine. These drugs have been shown to decrease conduction velocity and facilitate reentry phenomena.^{3,10,15} We cannot predict the clinical significance of these changes nor the possible effect adrenergic drugs may have in such instances. The chances of a worsening of the conduction anomalies after an accidental intravascular injection of local anesthetic with vasoconstrictor must be considered. In fact, cases of major and even fatal arrhythmias have been reported in patients without previous heart disease who were receiving usual therapeutic doses of thioridazine or chlorpromazine.¹⁵⁻¹⁸

Until more data are available to strengthen or refute our concern about potential untoward effects regarding the use of vasoconstrictors in patients treated with phenothiazine drugs, dentists should be prudent and administer the smallest amount of anesthetic solution with vasoconstrictor required to obtain deep anesthesia of adequate duration.

β -Blockers

β -Blocking agents are usually prescribed for their antihypertensive, antiarrhythmic, and antianginal effects. They are used less frequently for the treatment of vascular headaches and certain forms of involuntary tremors. β -blockers are either cardioselective or nonselective depending on their affinity to preferentially inhibit β_1 cardiac receptors or block simultaneously β_2 peripheral receptors (Table I). There is a wide diversity of β -blocking compounds, the prototype being propranolol (Inderal).

Epinephrine is known to have at least two distinct pharmacologic actions on the cardiovascular system. It causes vasoconstriction of arterial vessels in many organs through α -adrenergic stimulation and vasodilation of arterioles in skeletal muscles through β_2 -adrenergic stimulation. In addition, epinephrine stimulates β_1 -adrenergic receptors in the heart, resulting in tachycardia. The concurrent administration of vasoconstrictor in patients treated with nonselective β -blockers raises the likelihood of a serious elevation of the blood pressure brought about by an unopposed α -adrenergic stimulation caused by the blockade of β_2 peripheral receptors.^{19,20} When this occurs it is usually followed by a secondary reflex bradycardia mediated by vagally innervated aortic arch and carotid baroreceptors. Although no such complication has been reported after dental local anesthesia, several case reports have been published in the medical literature.²¹⁻²³ Foster and Aston²³ observed a dramatic increase in blood pressure and severe bradycardia after the injection of local anesthetic with epinephrine in six patients undergoing eyelid plasty and currently taking propranolol, a nonselective β -blocker. The reactions occurred within few minutes with a quantity

of epinephrine ranging from 0.04 to 0.32 mg, thus equivalent to the injection of 4 to 32 ml of local anesthetic with epinephrine 1:100,000.

β -Adrenergic blockade may also influence catecholamine kinetics and contribute to amplify the physiologic activity of exogenously administered epinephrine. Studies have revealed that β -adrenergic blockade reduces the clearance of intravenously infused epinephrine,^{24, 25} raising the possibility that the clearance of endogenous epinephrine might also be affected. It has also been reported that the kinetics of epinephrine varies according to the type of β -blocker administered. Hjemdahl et al.²⁵ observed no differential effect on the clearance of epinephrine and norepinephrine by the cardioselective β -blocker metoprolol. However, impairment of epinephrine kinetics was greater than that of norepinephrine by the nonselective β -blocker propranolol. In addition, compared with placebo the increase in plasma epinephrine level after propranolol infusion was greater than during metoprolol blockade. Although the clinical significance of a sustained elevation of plasma epinephrine concentration by beta blockade has not been fully investigated, we must acknowledge the possibility of untoward cardiovascular effects triggered by exogenously administered epinephrine. On the other hand, recent studies have shown that cardioselective β -blockers interfere very little with the normal hemodynamic reactions to epinephrine infusion.^{26, 27}

From all the data available, no relevant evidence precludes the use of local anesthetic with vasoconstrictor for patients treated with cardioselective β -blockers. However, the risk of a potential complication exists for patients taking nonselective β -blocking agents. Until more data are available, we believe dentists should be cautious and avoid the administration of local anesthetic with vasoconstrictor in patients currently taking nonselective β -blockers. In a recent warning to otolaryngologists Brummet²⁸ suggested discontinuing the medication for at least 3 days before using local anesthetic with vasoconstrictor. Because of reports of serious worsening of the preexistent cardiac disease and sudden death after abrupt cessation of chronic β -blocker therapy,^{29, 30} this should be done only with the consent of the prescribing physician. If the medication cannot be discontinued or changed, a local anesthetic without vasoconstrictor should then be used to prevent any potential drug interaction.

Cocaine abuse

Use of illicit drugs reached a dramatic level in people of all ages, races, and socioeconomic levels during the 1980s.³¹⁻³⁵ Once thought to be benign and nonad-

Table I. β -Blocker compounds

<i>Nonselective β-blockers (β_1 and β_2 adrenoceptors)</i>	<i>Cardioselective β-blockers (β_1 adrenoceptors)</i>
Propranolol (Inderal)	Metoprolol (Lopressor)
Nadolol (Corgard)	Atenolol (Tenormin)
Timolol (Blockadren, Timolate, Timoptic, Timoptol)	Acebutolol (Sectral)
Pindolol (Visken)	Betaxolol (Kerlone)
Alprenolol (Aptine)	
Labetalol (Trandate, Normodyne)	
Oxprenolol (Trasicor)	
Sotalol (Sotacort)	
Carteolol (Cartrol)	
Penbutolol (Levatol)	

dicting, cocaine is now recognized as one of the most dangerous illicit drugs in common use.³⁶ Cocaine is an alkaloid that has the quality of being both a local anesthetic and a sympathomimetic agent with powerful central nervous system effects. It was once used extensively as a local anesthetic in ophthalmology, otolaryngology, and dentistry. Besides its striking systemic effect on the central and sympathetic nervous systems, it has profound effects on the cardiovascular system.

Cocaine is a sympathomimetic agent that stimulates norepinephrine release and inhibits its reuptake in adrenergic nerve terminals.³⁷⁻³⁹ This action gives rise to a state of catecholamine hypersensitivity and increases the adrenergic response in susceptible organs. Through its action on endogenous catecholamine balance, in sufficient doses cocaine may induce a sympathetically mediated tachycardia and hypertension, resulting in greater cardiac workload and oxygen requirements.^{40, 41} Such sympathetic activity may decrease coronary artery perfusion and lead to significant ischemia, ventricular arrhythmia, angina, and myocardial infarction. Indeed, adverse cardiovascular effects related to cocaine use have been extensively reported and well documented by several authors.⁴²⁻⁵⁰ Although the specific sequence of events that leads to sudden death is poorly understood and might be amplified by chemical adulterants of street cocaine preparation,^{31, 34, 50} an overdose has toxic effects on the central nervous system and the heart muscle.

Undoubtedly cocaine users are at prime risk for all sorts of unpredictable cardiovascular complications. This risk is even greater if local anesthetic with epinephrine is inadvertently injected into their vascular system while the drug is still active. Peak blood levels

of cocaine are reached within 30 minutes and usually disappear after 2 hours.⁵¹ However, when the intranasal route of administration is used, blood release is slowed down and as a consequence the effect may be prolonged for as long as 4 to 6 hours.^{32, 51} Because of the potential medical risk they represent for dentists, precautions should be taken to identify any illicit drug users, especially those using cocaine and derivative substances such as crack. These patients are walking time bombs if they have used the drug the same day they have their dental appointment. Dentists should educate them on the medical risks and never inject local anesthetic with epinephrine or use epinephrine-impregnated retraction cords unless they declare that they have not used the drug within the past 24 hours. As a minimal precaution, when a dentist is suspicious about a patient's statement, dental treatments should be postponed to a later day.

CONCLUSION

During the past few decades the advance of medicine has contributed significantly to increase life expectancy. More people with chronic diseases are visiting their dentists. Although we have always been concerned with medically compromised patients, more attention is given to certain disease states, especially when local anesthetic with vasoconstrictor is being used. Most of the published guidelines and recommendations are directed to patients with cardiovascular diseases. Dentists should know about both the noncardiac conditions where the use of vasoconstrictors is contraindicated and the different drugs that could interact with these substances. A thorough understanding of the pharmacologic interactions between exogenously administered adrenergic drugs and vasoconstrictors used in dentistry is a prerequisite to prevent untoward reactions in patients taking psychotropic drugs or nonselective beta blockers, or in users of illicit drugs such as cocaine.

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