

# ADVERSE DRUG INTERACTIONS IN DENTAL PRACTICE: INTERACTIONS ASSOCIATED WITH VASOCONSTRICTORS

## PART V OF A SERIES

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### ABSTRACT

**Background.** Adrenergic vasoconstrictors are commonly used by dentists to enhance the pain-relieving action of local anesthetics and to control local bleeding. Although normally considered safe for these applications, vasoconstrictors can participate in drug interactions that potentially are harmful to patients.

**Methods.** The faculty of a March 1998 symposium entitled "Adverse Drug Interactions in Dentistry: Separating the Myths From the Facts" extensively reviewed the literature on drug interactions. They then established a significance rating of alleged adverse drug interactions pertaining to dentistry, based on the quality of documentation and severity of effect. The author of this article focused on the adrenergic vasoconstrictors epinephrine and levonordefrin.

**Results.** Vasoconstrictor drug interactions involving tricyclic antidepressants, nonselective  $\beta$ -adrenergic blocking drugs, certain general anesthetics and cocaine are well-documented in both humans and animals as having the potential for causing serious morbidity or death. Evidence for adverse interac-

tions involving adrenergic neuronal blocking drugs, drugs with  $\alpha$ -adrenergic blocking activity, local anesthetics and thyroid hormones is much less compelling, suggesting for the most part that clinically significant reactions may occur only when both the vasoconstrictor and the interacting drug are used in excessive doses. In the case of monoamine oxidase inhibitors, there is no credible evidence of a significant interaction with epinephrine or levonordefrin.

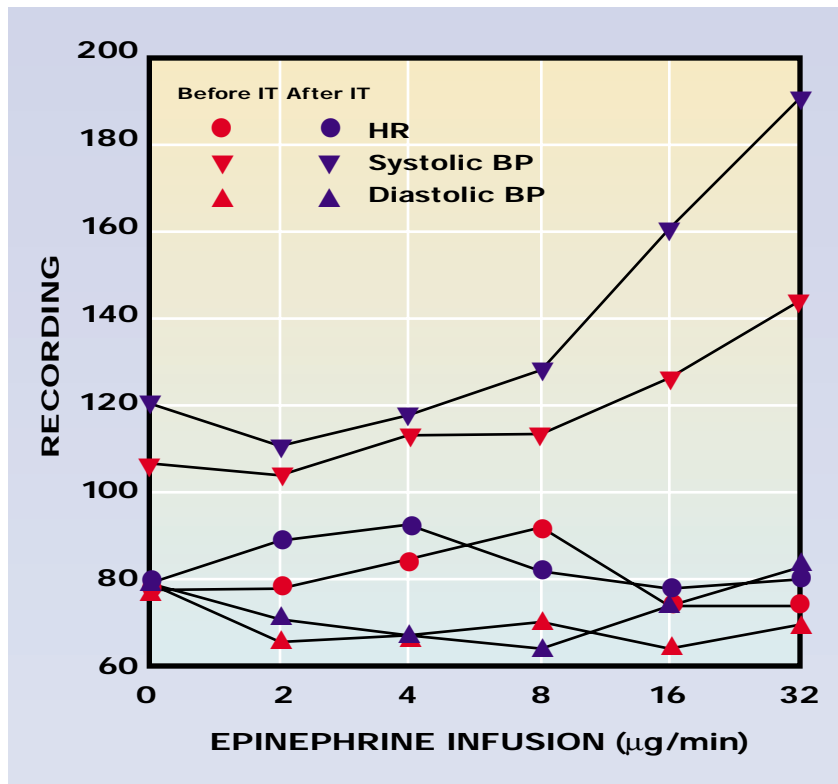
**Conclusions.** Potentially serious adverse drug interactions involving adrenergic vasoconstrictors can occur in dental practice. In most circumstances, careful administration of small doses of vasoconstrictors and avoidance of gingival retraction cord containing epinephrine, coupled with monitoring of vital signs, will permit these drugs to be used with no risk or only minimally increased risk. Only in the case of cocaine intoxication must adrenergic vasoconstrictors be avoided completely.

**Clinical Implications.** For optimal patient safety, dentists must recognize potential drug interactions involving adrenergic vasoconstrictors and modify their use of these agents accordingly.

**A**drenergic vasoconstrictors are among the most commonly administered therapeutic agents in dentistry. They also participate in more drug interactions than do any other dental drugs. Epinephrine (Adrenalin, Parke-Davis) and related sympathomimetic amines are routinely injected in combination with local anesthetics for pain relief and, less frequently, are used alone in gingival retraction cord and in topical or injectable solutions for hemorrhage control.

The ability of vasoconstrictors to retard the systemic absorption of injected local anesthetic agents such as lidocaine (Xylocaine, Astra) is the basis for their widespread use.<sup>1,2</sup> This beneficial drug interaction frequently increases the duration of local anesthesia and even the incidence of successful nerve blockade.<sup>3,4</sup> It also may result in lower plasma concentrations of the local anesthetic.<sup>5</sup>

Although adrenergic vasoconstrictors normally cause no untoward effects when used for dental



**Figure 1. Cardiovascular response to epinephrine infusion in a healthy man before and after five days of imipramine therapy, or IT (25 milligrams three times per day). Based on data from Boakes and colleagues.<sup>7</sup> HR: Heart rate (in beats per minute); BP: blood pressure (in millimeters of mercury); µg: micrograms; min: minute.**

procedures, they have the potential to do so. Local reactions may include tissue ischemia and necrosis. Systemically, epinephrinelike drugs can cause a number of cardiovascular disturbances, from changes in arterial blood pressure to cardiac palpitation and dysrhythmias. While most systemic reactions are short-lived, because of the rapid inactivation of the vasoconstrictor once it is absorbed into the circulation, permanent injury or even death may follow drug-induced ventricular fibrillation, myocardial infarction or cerebrovascular accidents. Factors that increase the likelihood of such adverse events include patient intolerance, acute overdosage, rapid entry of vasoconstrictor into the bloodstream and spe-

cific drug interactions.

This article reviews drug interactions known or suspected to involve adrenergic vasoconstrictors used in dentistry. Knowledge of these interactions, and of any medications the patient may be taking, is essential for the delivery of optimal patient care.

**TRICYCLIC ANTIDEPRESSANTS**

Tricyclic antidepressants, such as imipramine (Tofranil, Geigy), amitriptyline (Elavil, Zeneca) and doxepin (Sinequan, Roerig), were the first drugs (in the early 1960s) to gain widespread use for the treatment of depression. Although they have been largely replaced in recent years by safer alternatives, such as the serotonin-selective reuptake

inhibitors fluoxetine (Prozac, Dista) and paroxetine (Paxil, SmithKline Beecham), tricyclics are still used in patients intolerant of or unresponsive to the newer drugs. They are also prescribed for the treatment of severe anxiety disorders, neuropathic pain, nocturnal enuresis and attention deficit hyperactivity disorder.

The tricyclic antidepressants block the active reuptake of biogenic amine neurotransmitters by nerve terminals from which they were released. The net effect is a potentiation of the action of the affected neurotransmitters. Adrenergic vasoconstrictors are subject to the same uptake process—and, therefore, to the same potentiation by tricyclics—once they reach adrenergic receptors in close association with sympathetic neurons. Tricyclic antidepressants also block muscarinic and  $\alpha_1$ -adrenergic receptors and directly depress the myocardium. These actions can additionally modify cardiovascular responses to the vasoconstrictors.

Various experimental studies in humans and animals have consistently revealed a significant interaction between tricyclic antidepressants and adrenergic vasoconstrictors.<sup>6,9</sup> For example, Figure 1 illustrates the potentiation of the effects of epinephrine infused intravenously in one of four healthy volunteers studied by Boakes and colleagues<sup>7</sup> before and after the administration of imipramine. The most obvious change was the dramatic increase in systolic blood pressure at the higher infusion rates. However, the researchers also noted that each subject they studied experienced an interaction-induced dysrhythmia: sinus dysrhythmia in three subjects, multiple ectopic

beats in the fourth.

The potentiation of epinephrine by imipramine and related tricyclic antidepressants administered acutely is about threefold. Greater potentiations, six- to eightfold, occur with norepinephrine (Levophed, Sanofi Winthrop), which is no longer used in the United States as a vasoconstrictor in local anesthetics, and levonordefrin, which is the vasoconstrictor in local anesthetic solutions that contain mepivacaine (such as Polocaine with levonordefrin, Astra).

How often, or even if, this potentiation results in clinically significant adverse events is subject to debate. Boakes and colleagues<sup>10</sup> reviewed 15 reports of adverse reactions to local anesthetics with norepinephrine as the vasoconstrictor. Five of these cases involved patients taking tricyclic antidepressants.

Persson and Siwers<sup>11</sup> prospectively studied the effects of one to three cartridges of 2 percent lidocaine with 1:80,000 epinephrine in 21 patients taking tricyclic antidepressants. One patient receiving a total of 45 micrograms of epinephrine (the amount of epinephrine in 2.5 cartridges of a 1:100,000 solution) experienced a headache and a concomitant increase in systolic blood pressure that peaked at 45 millimeters of mercury over baseline four minutes after injection. It should be noted that this patient was also taking a low dosage of propranolol (discussed below). Cawson and colleagues<sup>12</sup> reviewed available evidence in 1983 and concluded that there was "no clinical evidence of significant interactions between tricyclic antidepressants and dental local anesthetics containing adrenaline."

Several factors probably contribute to the discrepancy be-

TABLE 1

THE DRUG INTERACTION SIGNIFICANCE RATING SCALE.*		
SIGNIFICANCE RATING	SEVERITY RATING	DOCUMENTATION RATING
1	Major	Established, probable or suspected
2	Moderate	Established, probable or suspected
3	Minor	Established, probable or suspected
4	Major or moderate	Possible
5	Minor All	Possible Unlikely

\* This rating scale was described in depth in the first article in this series.<sup>16</sup>

tween the clear experimental proof of a tricyclic-epinephrine interaction and the paucity of clinical reports verifying it in dentistry.

■ First, epinephrine produces both vasoconstrictive effects, mediated by  $\alpha$ -adrenergic receptors, and vasodilative effects, mediated by  $\beta_2$ -adrenergic receptors. For dosages normally used in dental practice, even a threefold potentiation will result in modest changes in blood pressure, because these opposing receptor influences tend to counterbalance each other.

■ Second, the cardiovascular status of dental patients is rarely monitored. Thus, changes in heart rate or rhythm may go unnoticed or, if obvious to the patient, be misdiagnosed as anxiety responses or hypersensitivity reactions.

■ Third, several interactions have been identified but not published on the assumption that the interaction was firmly established (J. Yagiela, D.D.S., Ph.D., unpublished data, 1980; J. Giovannitti, D.D.S., written communication, 1990).

■ Fourth, experimental studies have relied on the short-term

administration of tricyclic agents. As argued by Brown and Lewis<sup>13</sup> and supported by laboratory studies,<sup>14,15</sup> long-term administration of these agents may result in desensitization to adrenergic vasoconstrictors and a diminution of the drug interaction.

A cautious but prudent approach to the patient taking a tricyclic antidepressant is to assume the existence of a fully active drug interaction. Given that assumption, levonordefrin should not be used, because an accidental intravascular injection of a single cartridge of 2 percent mepivacaine with 1:20,000 levonordefrin conceivably could result in acute hypertension and cardiac dysrhythmias.<sup>8</sup>

Similarly, certain brands of gingival retraction cord contain large amounts of epinephrine, and the possibility of rapid drug absorption by abraded crevicular tissue proscribes their use. In the case of epinephrine in local anesthetic solutions, injecting no more than a 1:100,000 concentration in a dosage no more than one-third the normal maximum for a given patient should preclude any problem that could arise from a tricyclic drug inter-

TABLE 2

ADVERSE DRUG INTERACTIONS IN DENTISTRY: VASOCONSTRICTORS.

POSSIBLE DRUG INTERACTION	CUMULATIVE RATING*	MECHANISM AND CLINICAL PRESENTATION
Vasoconstrictor with tricyclic antidepressant (levonordefrin with imipramine)	1	Sympathomimetic effects may be enhanced. Epinephrine should be used cautiously; use of levonordefrin should be avoided.
Vasoconstrictor with nonselective $\beta$ -adrenoceptor antagonist (epinephrine with propranolol)	1	Hypertensive and/or cardiac reactions are possible. Vasoconstrictor should be used cautiously; blood pressure and heart rate should be monitored.
Vasoconstrictor with general anesthetic (epinephrine with halothane)	1	Increased possibility of cardiac arrhythmias exists with some general anesthetics. Consultation with anesthesiologist is recommended.
Vasoconstrictor with cocaine (epinephrine with cocaine)	1	Arrhythmias and hypertensive responses possible. Concurrent use should be avoided.
Vasoconstrictor with antipsychotic or other $\alpha$ -adrenoceptor blocker (epinephrine with chlorpromazine)	4	Hypotension resulting from overdose of antipsychotic agent may be worsened. Vasoconstrictor should be used cautiously.
Vasoconstrictor with adrenergic neuronal blocker (levonordefrin with guanadrel)	4	Sympathomimetic effects may be enhanced. Vasoconstrictor should be used cautiously.
Vasoconstrictor with local anesthetic (lidocaine with epinephrine)	4	Multiple effects on systemic toxicity, which may be self-limiting.
Vasoconstrictor with thyroid hormone (epinephrine with thyroxine)	4	Summation of effects possible when thyroid hormones are used in excess. Vasoconstrictor should be used cautiously if signs of hyperthyroidism are present.
Vasoconstrictor with monoamine oxidase inhibitor (epinephrine with phenelzine)	5	No substantial evidence of an interaction.

\* This rating system was described previously.<sup>16</sup> See Table 1.

action. Additional injections then may be safely given 30 minutes later.

According to the rating scale adopted by Moore and colleagues<sup>16</sup> for this series of articles (Table 1), the tricyclic-vasoconstrictor interaction rates a 1 (Table 2) because it is "established" and is "potentially life-threatening or capable of causing permanent injury."

**$\beta$ -ADRENERGIC ANTAGONISTS**

$\beta$ -adrenergic receptor antagonists (otherwise known as

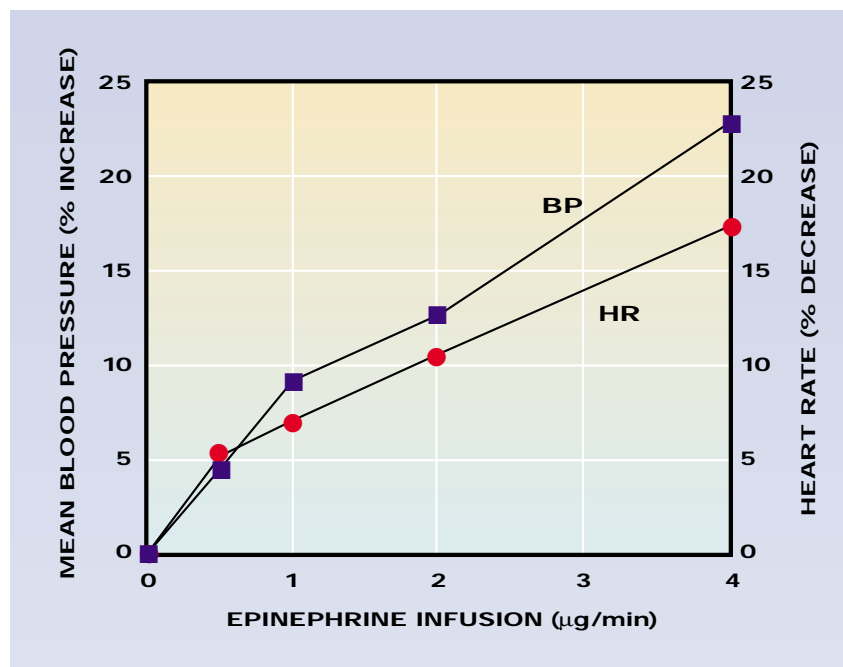
$\beta$ -adrenoceptor blockers or, more simply,  $\beta$ -blockers) are prescribed for a variety of conditions: acute panic symptoms, angina pectoris, cardiac dysrhythmias, essential tremors, glaucoma, hypertension, hyperthyroidism, hypertrophic subaortic stenosis, migraine headache, myocardial infarction and pheochromocytoma. They act by competitively blocking the stimulation of  $\beta$  receptors by endogenous catecholamines such as epinephrine and norepinephrine. They also block  $\beta$ -receptor activation by exogenously adminis-

tered adrenergic drugs.  $\beta$ -blockers can be categorized by their specificity of action: propranolol (Inderal, Wyeth-Ayerst) and nadolol (Corgard, Bristol-Myers) are examples of nonselective  $\beta$ -blockers, which block both  $\beta_1$  and  $\beta_2$  receptors; atenolol (Tenormin, ICI Pharma) and metoprolol (Lopressor, Geigy) represent drugs with  $\beta_1$ -selective antagonistic effects.

Although the ability of  $\beta$ -blockers to counter the cardiac effects of adrenergic drugs has been known for more than four decades, it became widely ap-

preciated only in the 1970s that propranolol qualitatively changes physiologic responses to epinephrine. By blocking vasodilating  $\beta_2$  receptors in the blood vessels of skeletal muscle and other tissues, propranolol causes epinephrine to act vascularly as a pure  $\alpha$ -adrenergic stimulant.<sup>17-19</sup> Peripheral resistance, which normally falls after moderate doses of epinephrine are administered, rises and thus induces a dose-dependent increase in blood pressure and a reflex slowing of the heart (Figure 2).<sup>17</sup> Selective  $\beta_1$ -blockers such as metoprolol are incapable of creating this effect.<sup>17-19</sup> However, both types of  $\beta$ -blockers decrease clearance of epinephrine and norepinephrine from the bloodstream.<sup>18</sup> This effect may partially explain the modestly increased pressor responsiveness to norepinephrine caused by these agents.<sup>20</sup>

Interactions between nonselective  $\beta$ -blockers and epinephrine, as used in local anesthetic solutions, have been shown to occur regularly in medicine and dentistry.<sup>21-23</sup> Although local anesthetics with epinephrine injected into skin generally produce mild interactions,<sup>21</sup> intravenous infusion of as little as 15  $\mu\text{g}$  epinephrine (equivalent to  $\frac{1}{100,000}$  epinephrine) results in pronounced, if transient, bradycardia (mean heart rate  $\pm$  standard deviation:  $38 \pm 8$  beats per minute).<sup>23</sup> Adverse responses, including cardiac arrest occurring after facial injection of the equivalent of two cartridges of 2 percent lidocaine with 1:50,000 epinephrine, also document the clinical relevance of the interaction between nonselective  $\beta$ -



**Figure 2.** Mean changes in heart rate, or HR, in beats per minute, and mean arterial blood pressure, or BP (in millimeters of mercury), during low-dose epinephrine infusion in hypertensive patients ( $n = 5$ ) taking an average daily dose of 208 milligrams of propranolol. Based on data from Houben and colleagues.<sup>17</sup>  $\mu\text{g}$ : micrograms; min: minute.

blockers and epinephrine.<sup>24,25</sup> Finally, one case report links levonordefrin with hypertension caused by a propranolol interaction.<sup>26</sup>

Given the potential danger of this interaction and the strong documentation of its existence, it richly deserves a "1" rating (Table 2). Epinephrine or levonordefrin may be used in patients taking nonselective  $\beta$ -adrenergic antagonists; however, the initial dose should be kept to a minimum, such as one-half of a dental cartridge with 1:100,000 epinephrine, and injected carefully to avoid intravascular administration. Monitoring the patient's vital signs before injection and five minutes afterward will dictate further administration. If there is no change in cardiovascular status, additional cartridges can be injected individually at five-minute intervals with continual

monitoring. As with the tricyclic antidepressants, neither the 1:50,000 epinephrine formulation nor epinephrine-containing retraction cord should be used in a patient who is taking a nonselective  $\beta$ -antagonist.

#### GENERAL ANESTHETICS

Certain general anesthetics are known to potentiate the dysrhythmogenic effect of epinephrine and, presumably, of levonordefrin and other adrenergic agents. Of the inhalation anesthetics currently in use, halothane (Fluothane, Wyeth-Ayerst) is the most problematic in this regard. In 1962, Katz and colleagues<sup>27</sup> argued that epinephrine could be injected safely for hemostasis in patients anesthetized with halothane so long as the dose in adults did not exceed 10 milliliters of a 1:100,000 solution (or 1  $\mu\text{g}/\text{kilogram}$ ) over a



10-minute period. Subsequent work by Johnston and colleagues<sup>28</sup> demonstrated that the minimum dysrhythmic dose of epinephrine injected into the submucosa of the mouth and/or nose was about 2 µg/kg for halothane, 3.5 µg/kg for enflurane (Ethrane, Anaquest) and 5.5 µg/kg for isoflurane (Forane, Anaquest). When 0.5 percent lidocaine was injected with 1:200,000 epinephrine, the minimum dysrhythmic dose during halothane anesthesia increased to 3 µg/kg because of the lidocaine's cardioprotective effect.

Thiopental (Pentothal, Abbott Laboratories), an ultra-short-acting barbiturate, also is capable of enhancing the dysrhythmogenic potential of adrenergic drugs. This fact was not appreciated in previous studies involving halothane,<sup>27,28</sup> as thiopental often was used for induction of anesthesia, and has led to the revised dosage guideline of 1 µg/kg epinephrine if halothane is used with thiopental and 2 µg/kg epinephrine if it is used alone.<sup>29</sup>

Although the mechanism by which general anesthetics augment the dysrhythmic actions of adrenergic agents is unknown, it appears to involve the simultaneous stimulation of both  $\alpha_1$  and  $\beta$  receptors.<sup>30,31</sup> Epinephrine and levonordefrin each are capable of activating both receptor types and eliciting dysrhythmias during general anesthesia. However, phenylephrine (Neo-Synephrine, Sanofi-Winthrop), a selective  $\alpha_1$  agonist, and isoproterenol (Isuprel, Sanofi-Winthrop), a  $\beta$  agonist, similarly disrupt the cardiac rhythm only if given together.

As shown in Table 2, this "established" interaction warrants a 1 rating. The dentist treating

a patient who has received general anesthesia should inform the anesthesiologist of the need to administer a vasoconstrictor and then follow the dosage limits that are recommended. A reported death under halothane anesthesia caused by epinephrine in gingival retraction cord<sup>32</sup> reinforces the general prohibition against using concentrated forms of epinephrine when there is a significant potential for drug interactions.

#### COCAINE

Introduced into Western medicine in 1884 as the first local anesthetic, cocaine was mixed with epinephrine in 1903 to improve its clinical efficacy. By 1924, several dozen deaths led to the abandonment of cocaine with epinephrine as an injectable anesthetic.<sup>33</sup> Cocaine remains a useful drug for topical anesthesia of mucous membranes and still is commonly mixed with epinephrine for application in nasal surgery. Of course, illicit consumption constitutes by far the greatest use of cocaine.

Cocaine possesses a complex pharmacology. As a local anesthetic, it blocks nerve conduction similarly to lidocaine. As a stimulant, it prevents the active reuptake of norepinephrine, dopamine and 5-hydroxytryptamine by presynaptic nerve terminals. This tricyclic antidepressantlike action potentiates the effects of adrenergic vasoconstrictors. There also is evidence that cocaine may enhance adrenergic neurotransmitter release and intensify postsynaptic responses to epinephrinelike drugs. Blockade of cardiac muscarinic receptors and central alteration of autonomic nervous system activity

may additionally contribute to exaggerated responses to injected vasoconstrictors.

Animal experiments and human reports have clearly demonstrated the potential for adverse drug interactions between adrenergic vasoconstrictors and cocaine.<sup>34</sup> In one well-documented case, a healthy young man given topical cocaine for nasal surgery developed angina and suffered a heart attack after injection of lidocaine with epinephrine.<sup>35</sup> Deaths in dentistry and medicine also are alleged to have been caused by this drug combination.<sup>36</sup> Animal studies indicate that normal responsiveness to vasoconstrictors, as with tricyclic antidepressants, may return during continuous exposure to cocaine.<sup>37</sup> Even so, a 1 rating for this interaction (Table 2) is justified because of its potential lethality and the fact that most cocaine abusers take the drug on an intermittent basis.

A unique problem regarding cocaine is that the patient may not report its use. Therefore, the dentist must be suspicious when confronted with a patient showing signs of potential cocaine abuse, such as agitation, tremor, sympathetic arousal and dysrhythmias. Damage to the nasal septum or skin lesions on the forearms may indicate, respectively, the "snorting" or injection of cocaine. Because cocaine itself may cause sudden death as a result of cardiac arrest, myocardial infarction or stroke, no elective dental treatment is advisable while the patient is under its influence. In all cases, vasoconstrictors should be withheld for at least 24 hours after cocaine exposure to allow for elimination of the drug and its active metabolites.<sup>38</sup>

### ANTIPSYCHOTIC AGENTS AND OTHER $\alpha$ -ADRENERGIC BLOCKERS

Antipsychotic drugs, such as chlorpromazine (Thorazine, SmithKline Beecham), thioridazine (Mellaril, Novartis) and risperidone (Risperdal, Janssen), have as a side effect the ability to block  $\alpha$ -adrenergic receptors and cause orthostatic hypotension. Drugs specifically developed for their  $\alpha$ -adrenergic blocking activity, such as prazosin (Minipress, Pfizer) and phenoxybenzamine (Dibenzylamine, SmithKline Beecham), of course share this hypotensive property. When chlorpromazine is given in overdose sufficient to produce frank hypotension, a resuscitative dose of epinephrine will reduce the blood pressure further because only the vasodilative ( $\beta_2$ -adrenergic) action of epinephrine can occur.<sup>8</sup> However, no interaction has been demonstrated with levonordefrin or doses of epinephrine normally injected in dentistry, and there are no clinical case reports of significant adverse interactions between vasoconstrictors used in local anesthetics and these drugs.

Thioridazine and several other antipsychotics also may impair cardiac conduction and promote tachydysrhythmias.<sup>39</sup> It has been conjectured that the added cardiac effects of a vasoconstrictor might precipitate an adverse event.<sup>38</sup> Once again, there are no such instances on record that pertain to the dental setting.

A rating of 4 reflects the limited evidence of this drug interaction. With proper care to avoid intravascular injection, vasoconstrictors may be used without special reservation in patients who are taking antipsychotic or other drugs with

$\alpha$ -adrenergic blocking activity, so long as the patient has not been rendered acutely hypotensive by the medication.

### ADRENERGIC NEURONAL BLOCKERS

Guanethidine (Ismelin, Geigy) and guanadrel (Hylorel, Fisons) are examples of drugs that inhibit the release of norepinephrine from sympathetic nerve terminals. When used long-term in the management of essential hypertension, postsynaptic adrenergic receptors may be up-regulated by the body in an attempt to restore normal neurotransmission.<sup>40</sup> An increase in receptor number and/or sensitivity should result in greater responsiveness to adrenergic vasoconstrictors. The neuronal blockers also may augment the effect of epinephrine-like drugs by a competitive inhibition of the neuronal reuptake transport system.

Perhaps because of their infrequent use, adrenergic neuronal blocking drugs have never been reported to be associated with clinically evident drug interactions involving adrenergic vasoconstrictors. A 4 rating is assigned to reflect the "possible" nature of the reaction, but clinicians are advised to follow the same recommendations described previously for the tricyclic antidepressants.

### LOCAL ANESTHETICS

Adverse interactions between adrenergic vasoconstrictors and local anesthetics are rarely considered. Nevertheless, animal experiments and limited human data suggest that they may occur.

Studies in rodents document that adrenergic vasoconstrictors can exert two opposite effects on

the pharmacokinetics of local anesthetics.<sup>41-43</sup> In addition to the previously mentioned reduction in the rate of systemic absorption, epinephrine-like drugs may increase the entry of local anesthetics into the brain.<sup>41</sup>

When the anesthetic solution is injected into tissues, the opposing effects of epinephrine tend to counteract each other. However, with intravascular injection, only the detrimental effect can occur, resulting in increased local anesthetic toxicity.<sup>42,43</sup> No corroborating data from studies in larger animals or humans have been reported.

Lidocaine similarly exerts two effects on epinephrine toxicity. The vasodilatory effect of lidocaine significantly increases the vasoconstrictor's rate of absorption. Dose-dependent adverse systemic effects of epinephrine, therefore, should be potentiated. However, lidocaine also protects the heart against epinephrine-induced rhythm disturbances.<sup>28</sup>

The essential lack of human data regarding these interactions dictates a 4 rating for these possible moderate reactions (Table 2).

Lastly, local anesthetics injected into peripheral tissues are selectively toxic to skeletal muscle. The damage is greatly increased when the local anesthetic is administered with a vasoconstrictor, and multiple injections of the combination in rats can result in permanent scarring.<sup>44</sup> Humans appear to be similarly susceptible to the myotoxic effect of local anesthetics.<sup>45</sup> Were this interaction included in Table 2 (it was excluded because of its localized effect), it would have been assigned a 3 rating as a probable

interaction of minor severity.

### THYROID HORMONES

Hyperthyroidism, whether the result of disease or of the inappropriate use of thyroxine (Synthroid, Boots) or another thyroid hormone preparation, can cause a number of cardiovascular changes reminiscent of epinephrine overdosage: tachycardia and other dysrhythmias, a widening of the pulse width, increased cardiac output and myocardial ischemia. For many years, it was believed that thyroid hormone and epinephrine interacted synergistically to create these effects.<sup>46</sup> Nevertheless, evidence has accumulated over the last three decades to show that hemodynamic responses to epinephrine and norepinephrine are not significantly altered in the patient with hyperthyroidism.

Aoki and colleagues<sup>47</sup> evaluated responses to intravenous epinephrine and norepinephrine in subjects before and after they became hyperthyroid as a result of the administration of liothyronine (Cytomel, SmithKline Beecham) and in spontaneously hyperthyroid patients before and after they were rendered euthyroid with radioactive iodine.<sup>48</sup> No clinically significant changes in cardiovascular responsiveness to adrenergic vasoconstrictors were noted. Subsequent studies have confirmed and extended these findings by demonstrating no altered responses to epinephrinelike drugs in patients with hypothyroidism.<sup>49,50</sup> Although a cardiovascular interaction between epinephrine and thyroxine would be potentially serious, the lack of documentation of its existence causes it to be assigned a rating of 4.

Even so, a subset of patients with excessive amounts of thyroid hormone in the circulation will have developed cardiac abnormalities as a result of the chronic overstimulation of myocardial metabolism.<sup>51</sup> Thus, it is appropriate to use adrenergic vasoconstrictors cautiously in patients with evidence of excessive thyroid stimulation.

### MONOAMINE OXIDASE INHIBITORS

The monoamine oxidase, or MAO, inhibitors comprise the antidepressants isocarboxazid (Marplan, Hoffman-LaRoche), phenelzine (Nardil, Parke-Davis) and tranylcypromine (Parnate, SmithKline Beecham), the antimicrobial agent furazolidone (Furoxone, Norwich Eaton) and the antiparkinson drug selegiline (Eldepryl, Somerset). As a group, the MAO inhibitors have been implicated in a number of potentially life-threatening interactions with various adrenergic amines. Two actions of the MAO inhibitors account for these interactions:

- the inhibitors prevent the metabolism of drugs normally metabolized by MAO;
- the inhibitors block the intraneuronal breakdown of norepinephrine in sympathetic nerves by MAO, increasing the pool of neurotransmitter capable of being released by indirect-acting adrenergic drugs such as amphetamine, pseudoephedrine (commonly found in nasal decongestants) and tyramine (an amino acid present in various food products).

However, there is no credible evidence of a clinically significant interaction involving epinephrine or levonordefrin as used in dentistry. These direct-

acting, exogenously administered vasoconstrictors are preferentially inactivated by the enzyme catechol *O*-methyltransferase. Repeated studies with these drugs in humans<sup>7,52</sup> and animals<sup>8,9,53</sup> consistently have shown no significant interaction attributable to inhibition of MAO. The continued listing of this interaction in the package insert for local anesthetics with vasoconstrictors is simply a testament to the bureaucracy of the U.S. Food and Drug Administration.

### CONCLUSION

The adrenergic vasoconstrictors epinephrine and levonordefrin may participate in a variety of adverse drug interactions, the most important of which involve tricyclic antidepressants, nonselective  $\beta$ -adrenergic blocking drugs, certain general anesthetics and cocaine. With few exceptions, the appropriate selection of a vasoconstrictor and its dosage and avoidance of gingival retraction cord containing epinephrine, coupled with careful drug administration and patient monitoring, will allow the clinician to provide necessary dental care with little or no increased risk of adverse outcome. ■

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The drugs listed by brand name in this article are given as examples only. Their listing does not imply any endorsement.

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