Basic and Clinical Pharmacology of Autonomic Drugs

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Autonomic drugs are used clinically to either imitate or inhibit the normal functions of the sympathetic and parasympathetic nervous systems. A large number of additional drug classes also interact with these systems to produce a stunning number of possible side effects. This article reviews the basic function of the autonomic nervous system and the various drug classes that act within these neural synapses.

Key Words: Autonomic drugs; Sympathomimetics; Adrenergic agonists; Adrenergic antagonists; Cholinergic drugs; Anticholinergic drugs.

The extent to which autonomic pharmacology impacts clinical practice is often unappreciated. Drugs that imitate and inhibit autonomic nerves are used extensively in medicine for managing cardiovascular, respiratory, urinary tract, and gastrointestinal disorders. In dental practice, the use of autonomic drugs is more limited, but sympathomimetics are used extensively as vasoconstrictors to potentiate local anesthetics, and the cholinergic agonists and antagonists are used to influence salivation. Equally important, however, is that side effects and interactions associated with many drug classes can be attributed to autonomic mechanisms. For these reasons, and the occasional need to manage medical urgencies, the dental provider should remain familiar with principles of autonomic pharmacology.

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

To understand autonomic pharmacology, one does not require knowledge of precise anatomical components nor distributions. Regardless of their classification,

efferent neurons are strikingly similar in performance. At the most simplistic level, neurons conduct electrical impulses (action potentials) that initiate the release of neurotransmitters from storage vesicles located in their terminal endings. Following their release, neurotransmitters bind with receptors on the membranes of effector cells and initiate the effect credited to the specific innervation. Acetylcholine and norepinephrine are the principal neurotransmitters that initiate parasympathetic and sympathetic effects on target tissues. To be even more precise, however, cholinergic and adrenergic receptors are what actually generate the biochemical events leading to the clinical effect; the neurotransmitter merely “activates the switch.” This process can be imitated or inhibited by drugs that act as agonists and antagonists for these receptors. The general pattern of distribution for peripheral efferent neurons is illustrated in Figure 1.

Influences of autonomic innervations germane to clinical practice are summarized in Table 1. In most cases, both divisions innervate each target tissue, but 2 exceptions are notable: sympathetics have minimal influence on salivation, and there is no parasympathetic innervation to blood vessels. Sympathetic innervations stimulate the cardiovascular system, inhibit gastrointestinal and urinary tracts, and dilate pupils and bronchioles. Parasympathetic innervations produce the opposite effects.

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Figure 1. Origin and distribution of somatic and autonomic nerves.^{1,2} Somatic (voluntary) neurons exit all levels of the brain and spinal cord (CNS). They release acetylcholine (ACh) to activate nicotinic receptors (N_m) on skeletal muscle. Preganglionic parasympathetic neurons exit the brain and sacral spinal cord, where they synapse with ganglia near or within smooth muscle and heart. Here ACh is released and activates nicotinic receptors (N_n) on postganglionic neurons. These neurons also release ACh to activate muscarinic receptors (M) on the target tissues. Preganglionic sympathetic neurons exit the thoracic and lumbar levels (thoracolumbar) of the spinal cord and synapse with ganglia near the cord and, like the preganglionic parasympathetic fibers, release ACh to activate N_n receptors on postganglionic neurons. The most abundant of these distribute to smooth muscle and heart where they release norepinephrine (NE) to activate alpha and beta receptors (α , β). The adrenal medulla is functionally a postganglionic neuron that secretes mostly epinephrine (~80% epinephrine and 20% norepinephrine), which arrives at the target tissues via the circulation. Also noteworthy is that some postganglionic sympathetic fibers distribute to sweat glands and release ACh where it activates muscarinic receptors (M).

CHOLINERGIC AND ANTICHOLINERGIC DRUGS

Cholinergic and anticholinergic are adjectives for drugs that resemble acetylcholine in structure and target the postganglionic parasympathetic synapse illustrated in Figure 1. In most cases they have specificity for muscarinic rather than nicotinic cholinergic receptors and are more precisely described as muscarinic and antimuscarinic. They generally have no influence on skeletal muscle or autonomic ganglia. Drugs having specificity for nicotinic subtypes of cholinergic receptors

Table 1. Autonomic Control of Selected Target Tissues^{1,2}

Target	Sympathetic Effect	Parasympathetic Effect
Pupil (via iris)	Mydriasis	Miosis
Gastrointestinal and urinary motility	Inhibitory	Excitatory
Bronchioles	Dilation	Constriction
Heart	Excitatory	Inhibitory
Vasculature	Dilation/constriction	Insignificant
Oral/airway secretions	Insignificant	Stimulation

Figure 2. Postganglionic parasympathetic synapse. A nerve impulse triggers release of acetylcholine (ACh), which subsequently binds to muscarinic receptors and initiates the parasympathetic response. Acetylcholine unbound in the synapse is hydrolyzed instantaneously by the enzyme acetylcholinesterase (AChE) to acetate (A) and choline (Ch). Muscarinic receptors (M) are also located on the nerve endings themselves and are referred to as prejunctional receptors. When activated by ACh, further release of the neurotransmitter is inhibited, providing a so-called negative-feedback loop.

(N_m and N_n) are more conventionally regarded as neuromuscular or ganglionic agents and are an entirely separate topic for discussion. A more detailed explanation of the postganglionic parasympathetic synapse is illustrated in Figure 2.

Cholinergic Drugs

Cholinergic drugs have limited use in dental practice. Medically they are used most often for urinary retention or topically for their miotic effect in glaucoma, eg, pilocarpine (Pilocar). Pilocarpine is an agonist at muscarinic receptors and can also be used to promote salivation for the treatment of xerostomia in patients with radiation induced salivary dysfunction.³ Pilocarpine is marketed for this indication as Salagen in 10-mg tablets administered 3 times daily. Side effects of pilocarpine may include any of the parasympathetic effects listed in Table 1. Obviously, it should be avoided in patients with respiratory disease or those prone to bradycardia. Researchers have established that muscarinic receptors exist as 5 subtypes designated M_{1-5} . The M_1 subtype is found in brain, autonomic ganglia, and presynaptic neuronal endings, whereas the M_2 subtype is most prevalent in the heart, and the M_3 subtype more prevalent in glands. The M_4 and M_5 subtypes are largely confined to the central nervous system (CNS).^{1,4} This knowledge has allowed further research and development of more selective cholinergic drugs. Cevimeline (Evoxac) is a cholinergic agonist having greater selectivity for the M_3 receptor and is Food and Drug Administration–approved for xerostomia at dosages of 30 mg 3 times daily.

Table 2. Comparisons of Anticholinergic Drugs*^{5,6}

<i>Drug</i>	<i>Adult Dose (IV)</i>	<i>Duration</i>	<i>CNS</i>	<i>Heart</i>	<i>Secretions</i>
Atropine	0.5 mg†	15–30 min	+	+++	++
Scopolamine	0.3 mg	30–60 min	+++	0, +	+++
Glycopyrrolate	0.2 mg	2–4 h	0	++	+++

* CNS indicates central nervous system; 0 to +++, relative activity at selected target site.

† For bradycardias up to 2–3 mg may be required.

Cholinergic effects can also be produced indirectly by drugs that inhibit the enzyme acetylcholinesterase. These drugs are neither agonists nor antagonists because they do not bind to receptors. Instead, they increase the amount of acetylcholine within all cholinergic synapses, and effects are actually attributed to the neurotransmitter itself. This action results in a much greater compilation of effects, because acetylcholine has activity at all cholinergic receptors, including those on skeletal muscle and throughout the brain. Cholinesterase inhibitors are used to stimulate skeletal muscle in patients with myasthenia gravis, eg, pyridostigmine (Mestinon), and for reversal of neuromuscular blockade, eg, neostigmine (Prostigmin). Patients suffering from Alzheimer dementia have diminished cholinergic transmission within the cortical brain region, and cholinesterase inhibitors such as donepezil (Aricept) have provided modest benefit. When used for this purpose, cholinesterase inhibitors produce many parasympathetic side effects that may require use of selective muscarinic antagonists, addressed in the next section.

Anticholinergic Drugs

Anticholinergic drugs act as antagonists at muscarinic receptors, thereby inhibiting parasympathetic influences. Precise affinity for specific muscarinic receptor subtypes has not been fully confirmed, but empirically they differ somewhat in their activity at various targets.^{4–7} (See Table 2.) It must be appreciated that cholinergic synapses are abundant throughout the brain, where their influences are largely excitatory. Therefore, cholinergic antagonists can produce sedation and antiemetic influences, but may also worsen symptoms of dementias.

Atropine is the drug of choice for managing symptomatic episodes of bradycardia that may accompany syncopal episodes or deep sedation and general anesthesia. At low doses, eg, <0.5 mg, atropine may produce paradoxical slowing of heart rate. Putative explanations for this include a transient agonist action on cardiac muscarinic receptors, or blockade of presynaptic muscarinic receptors, allowing further release of acetylcholine from the nerve endings.^{4–7} Therefore, it is wise to avoid doses of atropine below 0.5 mg when managing bradycardias.

Anticholinergic drugs may also be used as antisialagogues to improve conditions during tedious dental procedures. Scopolamine is very effective in this regard, but its sedative and psychotomimetic effects may be troubling at times, especially in geriatric patients. Glycopyrrolate (Robinul) is a quaternary, water-soluble compound, which limits its distribution to brain. As an antisialagogue, it is preferred over atropine and scopolamine, because it effectively inhibits salivation while producing less change in heart rate and no CNS influences. In cases where intravenous access is not in place, it is effective following sublingual injection, but onset may require up to 5 minutes. It is also available in tablets for oral administration.

In addition to conventional anticholinergic drugs, the dental provider should be familiar with a variety of additional drug classes having significant anticholinergic actions. (See Table 3.) For example, many antihistamines and psychotropics have substantial anticholinergic activity. These medications are not only prescribed medically, but are also included in a variety of sedation and anesthesia regimens used in dental practice. Various medical conditions may indicate, or more importantly contraindicate, the use of these agents.

Table 3. Exemplary Products Having Significant Anticholinergic Actions

<i>Antihistamines</i>	<i>Tricyclic Antidepressants</i>	<i>Antipsychotics</i>
Diphenhydramine (Benadryl)	Imipramine (Tofranil)	Chlorpromazine (Thorazine)
Hydroxyzine (Vistaril)	Amitriptyline (Elavil)	Thioridazine (Mellaril)
Promethazine (Phenergan)	Doxepin (Sinequan)	Fluphenazine (Prolixin)
	Nortriptyline (Pamelor)	Haloperidol (Haldol)
	Desipramine (Norpramin)	Thiothixene (Navane)
		Olanzapine (Zyprexa)

Figure 3. The adrenergic synapse. The nerve impulse releases norepinephrine (NE), which binds to specific adrenergic receptors on the cell membranes of target tissue (α_1 , β_1 , β_2). The neuronal endings contain α_2 prejunctional receptors. When activated by NE, further release of the neurotransmitter is inhibited. Adrenergic ligands also arrive at the synapse via the circulatory system. These include epinephrine (E) and norepinephrine (NE) secreted by the adrenal medulla or adrenergic drugs (D). The termination of norepinephrine (NE) is due primarily to reuptake into the nerve ending. Epinephrine (E) from the adrenal medulla and adrenergic drugs (D) are metabolized by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) in local tissues or the liver following absorption. (See text for further explanation.)

Parkinson disease is an extrapyramidal disorder credited to a degeneration of dopamine neurons within the basal ganglia. This leads to an imbalance in neural traffic expressed as excessive cholinergic along with diminished dopaminergic neurotransmission. In addition to dopamine agonists, anticholinergic drugs are used in the management of this disorder. Diphenhydramine (Benadryl) has significant anticholinergic properties in addition to its antihistaminic action. For this reason it has been included in anesthetic regimens to prevent or manage acute parkinsonian and other extrapyramidal episodes such as akathisia.⁸ Promethazine (Phenergan) also possesses significant antihistaminic and anticholinergic actions, but it should be avoided in such patients because it also possesses modest but significant dopaminergic blocking activity.

All drugs having anticholinergic action should be avoided if possible in patients troubled with constipation or urinary retention. Also, they should be avoided in patients with Alzheimer disease and other dementias. The pathogenesis of dementia is poorly defined but

Figure 4. Catecholamine synthesis. The molecular structure of catecholamines includes a catechol and an amine. During their termination, each of these moieties is a target for a specific enzyme, ie, catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO). Catecholamine synthesis proceeds in a stepwise fashion, each step driven by a specific enzyme leading to a molecular change indicated by the asterisks. In the adrenal medulla the final step in the pathway results in the synthesis of epinephrine. Sympathetic neurons do not contain the methylating enzyme and therefore cannot synthesize epinephrine. All 3 neurotransmitters are found throughout the brain, but neurons within the basal ganglia release dopamine because they lack dopamine hydroxylase.

includes defective cholinergic transmission. Drugs currently approved for managing this disorder resemble physostigmine in action and act to elevate CNS levels of acetylcholine. Obviously, anticholinergic drugs can not only worsen mentation in these patients but counter the beneficial effect of their medication. For inhibiting secretions, glycopyrrolate is acceptable because it does not distribute to brain.

ADRENERGIC AGONISTS AND ANTAGONISTS

The term adrenergic is an adjective used to describe ligands and processes that resemble adrenalin, ie, epinephrine. Postganglionic sympathetic neurons release norepinephrine that activates adrenergic receptors on the target cell and initiates the sympathetic effects listed in Table 1. Within the CNS, however, epinephrine, norepinephrine, and dopamine all function as adrenergic neurotransmitters. Furthermore, the adrenal medulla secretes all 3 of these transmitters as so-called neurohormones. The sympathetic adrenergic synapse is the focus of our discussion and is illustrated in Figure 3.

Adrenergic compounds are synthesized within the adrenal medulla and neuronal endings commencing with tyrosine, which is sequentially converted to dopamine, norepinephrine, or epinephrine, depending on the

Table 4. Selected Target Tissues and Adrenergic Receptors

Target	Receptor	Response Mediated
Heart	Beta-1	Increased rate, contractility, and atrioventricular conduction
Bronchioles	Beta-2	Bronchodilation
Systemic vessels	Beta-2	Vasodilation
	Alpha-1	Vasoconstriction
Submucosal vessels	Alpha-1	Vasoconstriction
Neuronal endings	Alpha-2	Inhibit neurotransmitter release

presence or absence of specific converting enzymes. In the case of postganglionic sympathetic neurons, norepinephrine is the final product synthesized. (See Figure 4.) They are classified chemically as catecholamines because their molecular structure includes an amine and a catechol. Each of these components is a substrate for a specific enzyme that contributes to termination: monoamine oxidase (MAO) acts on the amine and catechol-O-methyltransferase (COMT) acts on the catechol portion of the molecule. These concepts will be important in appreciating the elimination of adrenergic drugs and the actions of several classes of drugs prescribed for CNS disorders.

Adrenergic neurotransmitters and drugs may bind to any of several adrenergic receptor subtypes. Whereas most tissues contain a mixture of receptor subtypes, one or two are predominant and mediate the conventional effect attributed to sympathetic innervation of the tissue. The principal adrenergic receptors, along with their locations and functions, are summarized in Table 4. A thorough understanding of these receptors is essential for the proper use of adrenergic drugs.

Termination of adrenergic neurotransmitters is a more complex process than the simple hydrolysis described for acetylcholine. A reasonable understanding is essential in order to avoid common misconceptions regarding adrenergic drug termination and drug interactions. Following receptor activation, adrenergic ligands are quickly removed from the synapse by 2 principal methods: neuronal reuptake and metabolism by COMT and MAO.^{1,2} (See Figure 3.)

Whereas neuronal reuptake is the most significant process by which endogenous neurotransmitters are terminated, hepatic clearance is the principal pathway for termination of adrenal products and exogenously administered adrenergic drugs. Those having a catecholamine structure are primarily inactivated by COMT, whereas most noncatecholamines are metabolized by MAO. Termination by COMT is a very rapid process and accounts for the very short elimination half-life of catecholamines, generally 1–3 minutes. Epinephrine

and levonordefrin, the principal vasopressors used with local anesthetics, are both catecholamines. Their principal method of termination is hepatic biotransformation, with COMT acting as the primary enzyme; MAO has little significance. For this reason, antidepressants that inhibit this enzyme (MAO inhibitors) do not limit their metabolism. Misconceptions regarding this interaction were likely conceived long ago when the metabolic disposition of adrenergic drugs was less understood. The interaction is a concern only for those adrenergic drugs having a noncatecholamine structure.

Tricyclic antidepressants, such as those listed in Table 3, act by inhibiting neuronal reuptake. The molecular structure of levonordefrin (but not epinephrine) closely resembles that of norepinephrine, the principal endogenous adrenergic neurotransmitter. For this reason, neuronal uptake may account for a small portion of levonordefrin clearance, and therefore, in high enough doses, it could possibly be potentiated by tricyclic antidepressants. It has been suggested that mepivacaine solutions containing levonordefrin should be used cautiously in such patients.^{9,10} Solutions containing epinephrine are a wiser choice, but these too must nevertheless be used cautiously for the following reason. Tricyclic antidepressants not only elevate norepinephrine levels, but also produce anticholinergic effects. Both of these actions contribute to their arrhythmogenic potential, and this can enhance similar influences associated with adrenergic drugs. The newest generation of antidepressants, eg, fluoxetine (Prozac), selectively inhibits serotonin reuptake and is not a concern for either of these vasopressors.

Adrenergic Agonists

In manners analogous to those for the cholinergic system described previously, sympathetic effects can be imitated or inhibited by drugs acting respectively as agonists or antagonists on adrenergic receptors. The former produce effects that are sympathomimetic and the latter produce sympatholytic effects.

When administering an adrenergic drug, the dentist should know its molecular classification (catechol or noncatechol) and the specific receptors it activates. The molecular classification will predict the enzyme primarily responsible for inactivation, and therefore enables one to predict its duration of systemic effects and assess any potential for interactions with drugs that inhibit COMT or MAO. Knowledge regarding the drug's receptor activity will enable the clinician to predict systemic influences following its absorption. Information regard-

Table 5. Selected Adrenergic Agonists and Antagonists^{*11,12}

	Receptor Affinity				
Drug	Alpha	Beta-1	Beta-2	Indication	Preparations/Administration
Agonists					
Epinephrine	+++	+++	+++	With local anesthesia	1 : 100,000 and 1 : 200,000 concentrations for blocks and infiltrations (1 : 50,000 for local infiltrations)
				Anaphylaxis or bronchospasm	1 : 1000 (1 mg/mL)/0.3 mg (0.3 mL) IM
				Cardiac arrest	1 : 10,000 (0.1 mg/mL)/0.1 mg (1 mL) IV
Levonordefrin	+++	+++	0, +	With local anesthesia	1 : 10,000 (0.1 mg/mL)/1 mg (10 mL) IV
Ephedrine	++	+++	++	Hypotension	1 : 20,000 concentration for blocks and infiltrations
					50 mg/mL/25 mg (0.5 mL) IM or submucosal or titrate 10 mg (0.2 mL) IV q 3–5 min
Phenylephrine	+++	0	0	Hypotension	10 mg/mL: (dilute to 0.1 mg/mL)/titrate 0.1 mg (1 mL) IV q 3–5 min
				Decongestion	Use 1% nose drops or spray
Albuterol	0	0,+	+++	Bronchospasm	Inhaler; 2–3 puffs
Antagonists					
Labetalol	–	---	---	Hypertension	5 mg/mL/titrate 10–20 mg (2–4 mL) IV q 5 min (300 mg maximum)
Esmolol	0	---	0	Sinus tachycardia	10 mg/mL/titrate 20 mg (2 mL) IV q 3 min

* + designates relative potency as agonist and – designates relative potency as antagonist.

ing those agents of particular interest in dental practice is summarized in Table 5.

Epinephrine. Epinephrine is combined with local anesthetics to provide constriction of submucosal vessels that contain only alpha receptors. This action delays

Figure 5. Cardiovascular effects of epinephrine and phenylephrine. Epinephrine increases heart rate (HR) by activating beta-1 receptors in the sinoatrial node, the heart's normal pacemaker. It also activates beta-1 receptors on myocardial cells, increasing their contractility and increasing systolic blood pressure (SBP). However, at low doses such as those provided in local anesthetic formulations, it activates beta-2 receptors on systemic arteries, producing vasodilation. This decline in arterial resistance produces a reduction in diastolic pressure (DBP). The sum of these effects results in little change of mean arterial pressure (MAP). In contrast, phenylephrine activates only alpha receptors, increasing arterial resistance and diastolic pressure. Systolic pressure also rises as the heart compensates for this increase in resistance by increasing its contractility and venoconstriction increases venous return (preload). The net effect is an increase in mean arterial pressure, which is sensed in baroreceptors, and a reflex slowing of heart rate supervenes. (Adapted from Westfall et al.¹¹)

absorption of the local anesthetic and provides hemostasis locally at the site of injection. The use of epinephrine and levonordefrin for this purpose has been reviewed previously.¹³ As epinephrine is absorbed from the site of injection, systemic cardiovascular effects will begin to appear and can be attributed to activation of all 3 classes of adrenergic receptors.^{1,2,11}

- Heart rate increases because of activation of beta-1 receptors on the sinoatrial node.
- Systolic blood pressure increases for 2 reasons: (a) activation of beta-1 receptors on ventricular myocardial cells increases force of contraction and (b) activation of alpha receptors on veins produces venoconstriction and subsequent increase in venous return and stroke output. (Veins contain only alpha receptors.)
- Diastolic pressure declines because of activation of beta-2 receptors on systemic arteries leading to dilation. Although these vessels contain both alpha and beta-2 receptors, the latter predominate. This is particularly true for arterial supply to skeletal muscle, which serves to improve blood flow.
- Mean arterial pressure changes little because the increase in systolic pressure is largely offset by the decline in diastolic pressure.

The conventional view that epinephrine is a vasoconstrictor must be clarified. Although this is certainly true for submucosal vessels, doses ranging from 0.5 to 1.5 mg subcutaneous or 10–30 mcg/min intravenous infusion produce vasodilation of systemic arteries¹¹ (see

Figure 5). In contrast, following high doses of epinephrine such as 1-mg intravenous boluses administered for cardiac arrest, the alpha receptor actions of epinephrine on systemic arteries begin to appear and diastolic pressure will increase.

Epinephrine is indicated for a variety of medical emergencies, including anaphylactoid reactions and cardiac arrest, and as an alternative to selective beta-2 agonists for managing acute episodes of bronchospasm. During anaphylactoid reactions, several classes of inflammatory mediators are synthesized and released. These can produce bronchospasm and generalized vasodilation, which accounts for a drop in peripheral vascular resistance, venous capacitance, and laryngeal edema. There are no specific antagonists for all of these mediators. Fluid challenge and epinephrine's actions at both alpha and beta receptors are required to physiologically reverse the syndrome.^{14,15} The conventional dose is 0.3 mg IM using 0.3 mL of a 1 : 1000 concentration. For extremely severe cases 0.1 mg may be administered IV using 1 mL of a 1 : 10,000 concentration. A similar protocol can be used for life-threatening asthmatic attacks if a patient is noncompliant with a selective beta-2 inhaler or it proves ineffective.

Epinephrine has a lengthy record of use in cardiac arrest, but the basis for its benefit is frequently misunderstood. Many think that stimulation of cardiac beta receptors accounts for its benefit, but this thinking is flawed. Long ago Yakaitis et al¹⁶ demonstrated that isoproterenol, a pure beta agonist, was ineffective whereas methoxamine, a pure alpha agonist, demonstrated efficacy comparable to that for epinephrine. These and subsequent findings have established the consensus that epinephrine in 1-mg doses produces an alpha receptor-mediated increase in systemic vascular resistance that improves coronary perfusion during cardiac arrest. This improvement increases cardiac responsiveness to defibrillation.¹⁷

Ephedrine. Ephedrine has direct actions on alpha, beta-1, and beta-2 receptors qualitatively similar to those observed for epinephrine, but it is much less potent. Unlike epinephrine, ephedrine also acts indirectly by displacing norepinephrine from storage vesicles, and this is the basis for its being contraindicated in patients receiving MAO inhibitors. These antidepressants elevate intraneuronal stores of norepinephrine by inhibiting their oxidation by intraneuronal MAO. Release of neurotransmitter triggered by indirect acting agents such as ephedrine or amphetamines introduces a significant risk for exaggerated sympathomimetic events.^{11,12}

Ephedrine is an excellent agent for managing hypotensive episodes that occur in outpatient dental practice. Such events are rarely cardiogenic or hypovolemic, requiring more powerful agents such as epinephrine or

dopamine recommended in advanced life support courses. Rather, they follow profound vasovagal responses or centrally mediated sympathetic depression from anesthetics and other CNS depressants. In such cases, ephedrine's indirect action is particularly attractive. Furthermore, its direct vasoconstrictive action is more venous than arterial and nicely complements fluid challenge in elevating central venous return and subsequent cardiac output.¹⁸ Using a tuberculin syringe, a standard 50 mg/mL ampule or vial can be used to administer 0.2 mL (10 mg) intravenous increments every 3–5 minutes until pressure and perfusion are acceptable. Alternatively, 0.5 mL (25 mg) can be injected intramuscularly or submucosally and repeated in 5 minutes if necessary. Unlike catecholamines, which have a short duration (5–10 minutes), ephedrine's effect will generally persist for 60–90 minutes.

Phenylephrine. Phenylephrine is an alpha adrenergic agonist that is useful for treating hypotension when tachycardia is present or when any increase in heart rate should be avoided, such as in a patient with significant coronary artery disease. Phenylephrine produces venoconstriction, improving preload and systolic pressure, and produces arterial constriction, which increases diastolic pressure. The elevation in mean arterial pressure generally triggers a baroreceptor-mediated reduction in heart rate.^{11,12,18} (See Figure 5.) Phenylephrine is typically administered by continuous intravenous infusion, but in the office setting it may be administered in 0.1-mg IV increments, but this requires a double-dilution technique. A standard 1% or 10 mg/mL concentration is diluted with normal saline in a 10-mL syringe providing 1 mg/mL. Nine milliliters is then discarded and the remaining 1 mL (1 mg) is again diluted to 10 mL, providing 0.1 mg/mL for incremental dosing.

Congestion that follows surgical involvement of the maxillary sinus may indicate the use of phenylephrine as a decongestant. Alpha receptor agonists shrink sinus membranes by inducing vasoconstriction within the inflamed mucosa. For this purpose, 1% phenylephrine (Neo-Synephrine) drops or spray can be suggested and is available without prescription. There is no data supporting its routine use as prophylaxis prior to sinus surgery.

Albuterol. Intramuscular administration of epinephrine (0.3 mg) is acceptable treatment for acute bronchospasm that may follow aspiration or an acute asthmatic reaction, but aerosolized adrenergic preparations have equivalent efficacy and fewer side effects.^{11,12} Albuterol (Proventil, Ventolin) is a selective beta-2 agonist and is preferred for initial treatment. Terbutaline is the only selective beta-2 agonist available for parenteral use as an alternative to epinephrine. It is available in 1 mg/mL single-dose vials and should be administered as 0.25 mg subcutaneously.

Clonidine. Clonidine (Catapres) is a selective alpha-2 receptor agonist. Activation of prejunctional alpha-2 receptors inhibits release of norepinephrine (see Figure 3) and their activation within the CNS inhibits sympathetic outflow. Together these actions lead to a reduction in blood pressure, which accounts for its primary use in hypertension. However, following intravenous administration there is a transient rise in blood pressure, because both alpha-1 and alpha-2 receptors found in vascular smooth muscle mediate vasoconstriction before sympatholytic influences manifest. This early response is generally not observed following oral administration.¹¹ However, abrupt withdrawal from chronic use may result in rebound hypertension, and it should not be withheld perioperatively.⁶

Clonidine has many additional influences whose mechanisms are not fully understood. Clonidine is an imidazoline derivative and binds to various subtypes of imidazoline receptors throughout the brain. These actions, along with alpha-2 receptor activation, likely contribute to its constellation of effects.^{6,11} It has gained considerable popularity not only as an analgesic adjunct and sedative, but for management of substance abuse, menopausal hot flashes, restless leg syndrome, and several psychiatric disorders. Clonidine, as well as newer selective alpha-2 agonists such as dexmedetomidine, is receiving considerable attention for procedural sedation.^{19,20} This use, along with additional novel agents, will be the topic of a future continuing education article in this journal.

Adrenergic Antagonists

Antagonists are available for each of the adrenergic receptor subtypes. Their pharmacodynamic profile is logically the converse of those described for the adrenergic agonists. They have no indications in dental practice other than possible management of acute symptomatic elevations in heart rate or blood pressure. In these cases, however, drug administration is rarely required, provided treatment is interrupted and the patient is allowed to calm.²¹

Esmolol (Brevibloc) is a short-acting (elimination half-life ~9 minutes), selective beta-1 antagonist useful in managing symptomatic atrial tachycardias. It is available in 10 mg/mL multidose vials and can be administered in 20-mg intravenous increments every 3 minutes. Before administering any beta blocker, hypotension and hypoxemia must be ruled out as possible causes for reflex tachycardia. Labetalol (Trandate and Normodyne) is a nonselective alpha and beta blocker with a ratio of alpha : beta blockade of ~1 : 5. Labetalol lowers blood

pressure by blocking the alpha-1 receptors in vascular smooth muscle and the beta-1 receptors in the heart. Labetalol is available in 5 mg/mL multidose vials and can be administered in 5–20-mg intravenous increments every 5 minutes while taking care not to inadvertently produce hypotension, which can be more threatening than hypertension. When administered in this manner, labetalol is generally safe with minimal adverse reactions.²²

The use of esmolol and labetalol should be limited to those having advanced training and requires careful electrocardiographic and blood pressure monitoring to guide incremental administration. They should be avoided in patients with severe heart failure or atrioventricular block. Selective beta-1 blockers such as esmolol may lose their specificity at higher doses and block beta-2 receptors on bronchial smooth muscle. Therefore, both agents should be used with extreme caution if at all in patients having a history of asthma or chronic obstructive pulmonary disease to avoid the possibility of bronchospasm.

Adrenergic blocking agents are frequently prescribed for cardiovascular disorders and offer potential for drug interactions with vasopressors included in local anesthetic formulations. For example, one should anticipate that the hemostasis and prolonged local anesthetic duration attributed to epinephrine and levonordefrin will be diminished by alpha blockers such as prazosin (Mini-press) and the magnitude of their cardiac stimulation attenuated in patients medicated with selective beta-1 blockers such as atenolol (Tenormin).

Patients who are medicated with nonselective beta blockers present a significant concern. Although beta blockers are prescribed for their action in blocking cardiac beta-1 receptors, nonselective agents also block beta-2 receptors. As described earlier, low doses of epinephrine, such as those contained in local anesthetic solutions, mediate a beta-2 (vasodilation) influence on systemic vasculature. When patients are taking nonselective blockers, epinephrine's activity on systemic arteries will shift to alpha receptors, and this may result in an acute elevation in blood pressure due to intense arterial constriction without compensatory beta-2 vasodilation. Typically, a reflex slowing of heart rate accompanies this sudden elevation. Acute hypertensive episodes attributed to this interaction have been well documented in the medical literature.^{23–25} It has also been reported following administration of mepivacaine with levonordefrin.²⁶ The interaction is unlikely with selective beta-1 antagonists because, at conventional doses, they have little or no affinity for vascular beta-2 receptors. Some beta blockers are not pure antagonists, but have weak agonist activity. This property is described as intrinsic sympathomimetic activity. The potential for

Table 6. Exemplary Beta Blockers and Suggestions for Avoiding Vasopressor Interactions*

Nonselective Beta Blockers: Major Concern for Interaction	Selective Beta Blockers: Little Concern for Interaction	ISA Beta Blockers: Unknown Potential for Interaction
Propranolol (Inderal) Nadolol (Corgard) Timolol (Blocadren) Carvedilol (Coreg) Options for Patient Management	Atenolol (Tenormin) Metoprolol (Toprol XL) Acebutolol (Sectral) Betaxolol (Kerlone)	Carteolol (Cartrol) Penbutolol (Levatol) Pindolol (Visken)
Option	Protocol	
1	If hemostasis is not essential, consider using local anesthetic without vasopressor.	
2	Administer 1–2 cartridges (~20–40 mcg if 1 : 100,000 concentration) and reassess blood pressure and pulse in 3–5 min. Repeat protocol for additional cartridges.	

* ISA indicates intrinsic sympathomimetic activity.

this class of beta blocker to interact with vasopressors is unknown. Beta blockers of concern and options for use of vasopressors are summarized in Table 6.

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CONTINUING EDUCATION QUESTIONS

1. In general, anticholinergic drugs should be avoided in patients suffering which of the following?
 - A. Alzheimer dementia
 - B. Asthma
 - C. Bradycardias
 - D. Parkinson disease
2. Which of the following is the principal characteristic that distinguishes glycopyrrolate from atropine?
 - A. It is more selective in blocking M1 receptor subtypes
 - B. It lacks central nervous system effects
 - C. It is more effective for increasing heart rate
 - D. It is more effective for managing xerostomia
3. Which of the following most accurately reflects the cardiovascular influences of epinephrine following administration of doses typically contained in local anesthetic formulations?
 - (1) increases systolic pressure
 - (2) decreases diastolic pressure
 - (3) increases heart rate
 - A. 1 and 2
 - B. 1 and 3
 - C. 2 and 3
 - D. 1, 2, and 3
4. In which of the following manners does ephedrine differ from epinephrine?
 - (1) It is not metabolized by COMT
 - (2) It stimulates release of norepinephrine
 - (3) It does not directly activate alpha and beta receptors
 - A. 1 and 2
 - B. 1 and 3
 - C. 2 and 3
 - D. 1, 2, and 3