Mechanisms of Adrenergic Receptor Activation

Overview of the Adrenergic Agonists

Chemical Classification: Catecholamines Versus Noncatecholamines

Receptor Specificity

Therapeutic Applications and Adverse Effects of Adrenergic Receptor Activation

Clinical Consequences of \( \alpha_1 \) Activation

Clinical Consequences of \( \alpha_2 \) Activation

Clinical Consequences of \( \beta_1 \) Activation

Clinical Consequences of \( \beta_2 \) Activation

Clinical Consequences of Dopamine Receptor Activation

Multiple Receptor Activation: Treatment of Anaphylactic Shock

Properties of Representative Adrenergic Agonists

Epinephrine

Norepinephrine

Isoproterenol

Dopamine

Dobutamine

Phenylephrine

Albuterol

Discussion of Adrenergic Agonists in Other Chapters

By definition, adrenergic agonists produce their effects by activating adrenergic receptors. Since the sympathetic nervous system acts through these same receptors, responses to adrenergic agonists and responses to stimulation of the sympathetic nervous system are very similar. Because of this similarity, adrenergic agonists are often referred to as sympathomimetics. Adrenergic agonists have a broad spectrum of indications, ranging from heart failure to asthma to preterm labor.

Learning about adrenergic agonists can be a challenge. To facilitate the process, our approach to these drugs has four stages. We begin with the general mechanisms by which drugs can activate adrenergic receptors. Next we establish an overview of the major adrenergic agonists, focusing on their receptor specificity and chemical classification. After that, we address the adrenergic receptors themselves; for each receptor type—\( \alpha_1 \), \( \alpha_2 \), \( \beta_1 \), \( \beta_2 \), and dopamine—we discuss the beneficial and harmful effects that can result from receptor activation. Finally, we integrate all of this information by discussing the characteristic properties of representative sympathomimetic drugs.

Please note that this chapter is intended only as an introduction to the adrenergic agonists. Our objective here is to discuss the basic properties of the sympathomimetic drugs and establish an overview of their applications and adverse effects. In later chapters, we will discuss the clinical applications of these agents in greater depth.

MECHANISMS OF ADRENERGIC RECEPTOR ACTIVATION

Drugs can activate adrenergic receptors by four basic mechanisms: (1) direct receptor binding, (2) promotion of norepinephrine (NE) release, (3) blockade of NE reuptake, and (4) inhibition of NE inactivation. Note that only the first mechanism is direct. With the other three, receptor activation occurs by an indirect process. Examples of drugs that act by these four mechanisms are presented in Table 17–1.

**Direct Receptor Binding.** Direct interaction with receptors is the most common mechanism by which drugs activate peripheral adrenergic receptors. The direct-acting receptor stimulants produce their effects by binding to adrenergic receptors and mimicking the actions of natural transmitters (NE, epinephrine, dopamine). In this chapter, all of the drugs discussed activate receptors directly.

**Promotion of NE Release.** By acting on terminals of sympathetic nerves to cause NE release, drugs can bring about activation of adrenergic receptors. Amphetamines act by this mechanism.

**Inhibition of NE Reuptake.** Recall that reuptake of NE into terminals of sympathetic nerves is the major mechanism for terminating adrenergic transmission. By blocking NE

<table>
<thead>
<tr>
<th>Mechanism of Stimulation</th>
<th>Examples</th>
</tr>
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<tbody>
<tr>
<td>Direct Mechanism</td>
<td></td>
</tr>
<tr>
<td>Receptor activation through direct binding</td>
<td>Dopamine, Epinephrine, Isoproterenol</td>
</tr>
<tr>
<td>Indirect Mechanisms</td>
<td></td>
</tr>
<tr>
<td>Promotion of NE release</td>
<td>Amphetamine</td>
</tr>
<tr>
<td>Inhibition of NE reuptake</td>
<td>Cocaine, Tricyclic antidepressants</td>
</tr>
<tr>
<td>Inhibition of MAO</td>
<td>MAO inhibitors</td>
</tr>
</tbody>
</table>

MAO = monoamine oxidase, NE = norepinephrine.
reuptake, drugs can cause NE to accumulate within the synap tic gap, and can thereby increase receptor activation. Agents that act by this mechanism include cocaine and the tricyclic antidepressants (eg, imipramine).

**Inhibition of NE Inactivation.** As discussed in Chapter 13, some of the NE in terminals of adrenergic neurons is subject to inactivation by monoamine oxidase (MAO). Hence, drugs that inhibit MAO can increase the amount of NE available for release, and can thereby enhance receptor activation. (It should be noted that, in addition to being present in sympathetic nerves, MAO is present in the liver and the intestinal wall. The significance of MAO at these other sites is considered later in the chapter.)

In this chapter, which is dedicated to *peripherally* acting sympathomimetics, all of the drugs discussed act exclusively by *direct* receptor activation.

Most of the indirect-acting adrenergic agonists are used for their ability to activate adrenergic receptors in the central nervous system (CNS)—not for their effects in the periphery. The indirect-acting sympathomimetics (eg, amphetamine, cocaine) are mentioned here to emphasize that, although these agents are employed for effects on the brain, they can and will cause activation of adrenergic receptors in the periphery. Peripheral activation is responsible for certain toxicities of these drugs (eg, cardiac dysrhythmias, hypertension).

**OVERVIEW OF THE ADRENERGIC AGONISTS**

**Chemical Classification: Catecholamines Versus Noncatecholamines**

The adrenergic agonists fall into two major chemical classes: catecholamines and noncatecholamines. As discussed below, the catecholamines and noncatecholamines differ in three important respects: (1) oral usability, (2) duration of action, and (3) the ability to act in the CNS. Accordingly, if we know to which category a particular adrenergic agonist belongs, we will know three of its prominent features.

**Catecholamines**

The catecholamines are so named because they contain a *catechol* group and an *amine* group. A catechol group is simply a benzene ring that has hydroxyl groups on two adjacent carbons (Fig. 17–1). The amine component of the catecholamines is *ethylamine*. Structural formulas for each of the major catecholamines—epinephrine, norepinephrine, isoproterenol, dopamine, and dobutamine—are presented in Figure 17–1. Because of their chemistry, all catecholamines have three properties in common: (1) they cannot be used orally, (2) they have a brief duration of action, and (3) they cannot cross the blood-brain barrier. The actions of two enzymes—*monoamine oxidase* and *catechol-O-methyltransferase* (COMT)—explain why the catecholamines have short half-lives and cannot be used orally. MAO and COMT are located in the liver and in the intestinal wall. Both enzymes are very active and quickly destroy catecholamines administered by any route. Because these enzymes are located in the liver and intestinal wall, catecholamines that are administered orally become inactivated before they can reach the systemic circulation. Hence, catecholamines are ineffective if given by mouth. Because of rapid inactivation by MAO and COMT, three catecholamines—norepinephrine, dopamine, and dobutamine—are effective only if administered by continuous infusion. Administration by other parenteral routes (eg, subQ, IM) will not yield adequate blood levels, owing to rapid hepatic inactivation.

Catecholamines are polar molecules, and hence cannot cross the blood-brain barrier. (Recall from Chapter 4 that polar compounds penetrate membranes poorly.) The polar nature of the catecholamines is due to the hydroxyl groups on the catechol portion of the molecule. Because they cannot cross the blood-brain barrier, catecholamines have minimal effects on the CNS.

Be aware that catecholamine-containing solutions, which are colorless when first prepared, turn pink or brown over time. This pigmentation is caused by oxidation of the catecholamine molecule. As a rule, catecholamine solutions should be discarded as soon as discoloration develops. The only exception is dobutamine, which can be used up to 24 hours after the solution was made, even if discoloration appears.

**Noncatecholamines**

The noncatecholamines have ethylamine in their structure (see Fig. 17–1), but do not contain the catechol moiety that characterizes the catecholamines. In this chapter, we discuss two noncatecholamines: albuterol and phenylephrine.

The noncatecholamines differ from the catecholamines in three important respects. First, because they lack a catechol group, noncatecholamines are not substrates for COMT and are metabolized slowly by MAO. As a result, the half-lives of noncatecholamines are much longer than those of catecholamines. Second, because they do not undergo rapid degradation by MAO and COMT, noncatecholamines can be given orally, whereas catecholamines cannot. Third, noncatecholamines are considerably less polar than catecholamines, and hence are more able to cross the blood-brain barrier.

**Receptor Specificity**

To understand the actions of individual adrenergic agonists, we need to know their receptor specificity. Since the sympathomimetic drugs differ widely with respect to the receptors they can activate, learning the receptor specificity of these drugs will take some effort.

Variability in receptor specificity among the adrenergic agonists can be illustrated with three drugs: albuterol, isoproterenol, and epinephrine. Albuterol is highly selective, acting at beta₂ receptors only. Isoproterenol is less selective, acting at beta₁ receptors and beta₂ receptors. Epinephrine is less selective yet, acting at all four adrenergic receptor subtypes: alpha₁, alpha₂, beta₁, and beta₂.

The receptor specificities of the major adrenergic agonists are summarized in Table 17–2. In the upper part of the table, receptor specificity is presented in tabular form. In the lower part, the same information is presented schematically. By learning (memorizing) the content of Table 17–2, you will be well on your way toward understanding the pharmacology of the sympathomimetic drugs.

Please note that the concept of receptor specificity is relative, not absolute. The ability of a drug to selectively activate...
certain receptors to the exclusion of others depends on the dosage: at low doses, selectivity is maximal; as dosage increases, selectivity declines. For example, when albuterol is administered in low to moderate doses, the drug is highly selective for beta₂-adrenergic receptors. However, if the dosage is high, albuterol will activate beta₁ receptors as well. The information on receptor specificity in Table 17–2 refers to usual therapeutic doses. So-called selective agents will activate additional adrenergic receptors if the dosage is abnormally high.

**Figure 17–1** Structures of representative catecholamines and noncatecholamines.

*Catecholamines*: Note that all of the catecholamines share the same basic chemical formula. Because of their biochemical properties, the catecholamines cannot be used orally, cannot cross the blood-brain barrier, and have short half-lives (owing to rapid inactivation by MAO and COMT).

*Noncatecholamines*: Although structurally similar to catecholamines, noncatecholamines differ from catecholamines in three important ways: they can be used orally; they can cross the blood-brain barrier; and, because they are not rapidly metabolized by MAO or COMT, they have much longer half-lives.

**THERAPEUTIC APPLICATIONS AND ADVERSE EFFECTS OF ADRENERGIC RECEPTOR ACTIVATION**

In this section we discuss the responses—both therapeutic and adverse—that can be elicited with sympathomimetic drugs. Since many adrenergic agonists activate more than one type of receptor (see Table 17–2), it could be quite confusing if we were to talk about the effects of the sympathomimetics...
while employing specific drugs as examples. Consequently, rather than attempting to structure this presentation around representative drugs, we discuss the actions of the adrenergic agonists one receptor at a time. Our discussion begins with alpha₁ receptors, and then moves to alpha₂ receptors, beta₁ receptors, beta₂ receptors, and finally dopamine receptors. For each receptor type, we discuss both the therapeutic and adverse responses that can result from receptor activation.

To understand the effects of any specific adrenergic agonist, all you need is two types of information: (1) the identity of the receptors at which the drug acts and (2) the effects produced by activating those receptors. Combining these two types of information will reveal a profile of drug action. This is the same approach to understanding neuropharmacologic agents that we discussed in Chapter 12.

Before you go deeper into this chapter, I encourage you (strongly advise you) to review Table 13–3 now, at least be prepared to refer back to it as we discuss the consequences of receptor activation.

### Clinical Consequences of Alpha₁ Activation

In this section we discuss the therapeutic and adverse effects that can result from activation of alpha₁-adrenergic receptors. As shown in Table 17–2, drugs capable of activating alpha₁ receptors include epinephrine, NE, phenylephrine, and dopamine.

### Therapeutic Applications of Alpha₁ Activation

Activation of alpha₁ receptors elicits two responses that can be of therapeutic use: (1) vasoconstriction (in blood vessels of the skin, viscera, and mucous membranes); and (2) mydriasis. Of the two, vasoconstriction is the one for which alpha₁ agonists are used most often. Using these drugs for mydriasis is rare.

#### Hemostasis

Hemostasis is defined as the arrest of bleeding, which alpha₁ agonists accomplish through vasoconstriction. Alpha₁ stimulants are given to stop bleeding primarily in the skin and mucous membranes. Epinephrine, applied topically, is the alpha₁ agonist used most for this purpose.

#### Nasal Decongestion

Nasal congestion results from dilatation and engorgement of blood vessels in the nasal mucosa. Drugs can relieve congestion by causing alpha₁-mediated vasoconstriction. Specific alpha₁-activating agents employed as nasal decongestants include phenylephrine (applied topically) and pseudoephedrine (taken orally).

#### Adjunct to Local Anesthesia

Alpha₁ agonists are frequently combined with local anesthetics to delay anesthetic absorption. The mechanism is alpha₁-mediated vasoconstriction, which reduces blood flow to the site of anesthetic administration. Why delay anesthetic absorption? Because doing so prolongs anesthesia, allows a reduction in anesthetic dosage, and reduces the systemic effects that a local anesthetic might produce. The drug used most frequently to delay anesthetic absorption is epinephrine.

#### Elevation of Blood Pressure

Because of their ability to cause vasoconstriction, alpha₁ agonists can elevate blood pressure in hypotensive patients. Please note, however, that alpha₁ agonists are not the primary therapy for hypotension. Rather, they are reserved for situations in which fluid replacement and other measures have failed to restore blood pressure to a satisfactory level.

#### Mydriasis

Activation of alpha₁ receptors on the radial muscle of the iris causes mydriasis (dilation of the pupil), which can facilitate eye examinations and ocular surgery. Note that producing mydriasis is the only clinical use of alpha₁ activation that is not based on vasoconstriction.

### Adverse Effects of Alpha₁ Activation

All of the adverse effects caused by alpha₁ activation result directly or indirectly from vasoconstriction.

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**TABLE 17–2 Receptor Specificity of Representative Adrenergic Agonists**

<table>
<thead>
<tr>
<th>Catecholamines</th>
<th>Noncatecholamines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Receptors Activated</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>α₁, α₂, β₁, β₂</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>α₁, α₂, β₁</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>β₁, β₂</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>β₁</td>
</tr>
<tr>
<td>Dopamine*</td>
<td>α₁, β₁, dopamine</td>
</tr>
</tbody>
</table>

α = alpha, β = beta.

*Receptor activation by dopamine is dose dependent.

†This chart represents in graphic form the same information on receptor specificity given above. Arrows indicate the range of receptors that the drugs can activate (at usual therapeutic doses).
**Hypertension.** Alpha₁ agonists can produce hypertension by causing widespread vasoconstriction. Severe hypertension is most likely with parenteral dosing. Accordingly, when alpha₁ agonists are given parenterally, cardiovascular status must be monitored continuously. Never leave the patient unattended.

**Necrosis.** If the IV line employed to administer an alpha₁ agonist becomes extravasated, local seepage of the drug may result in necrosis (tissue death). The cause is lack of blood flow secondary to intense local vasoconstriction. If extravasation occurs, the area should be infiltrated with an alpha₂-blocking agent (eg, phentolamine), which will counteract alpha₁-mediated vasoconstriction, and thereby help minimize injury.

**Bradycardia.** Alpha₁ agonists can cause reflex slowing of the heart. The mechanism is this: Alpha₁-mediated vasoconstriction elevates blood pressure, which triggers the baroreceptor reflex, causing heart rate to decline. In patients with marginal cardiac reserve, the decrease in cardiac output may compromise tissue perfusion.

**Clinical Consequences of Alpha₂ Activation**

As discussed in Chapter 13, alpha₂ receptors in the periphery are located presynaptically, and their activation inhibits NE release. Several adrenergic agonists (eg, epinephrine, NE) are capable of causing alpha₂ activation. However, their ability to activate alpha₂ receptors in the periphery has little clinical significance. There are no therapeutic applications related to activation of peripheral alpha₂ receptors. Furthermore, activation of these receptors rarely causes significant adverse effects.

In contrast to alpha₁ receptors in the periphery, alpha₂ receptors in the CNS are of great clinical significance. By activating central alpha₂ receptors, we can produce two useful effects: (1) reduction of sympathetic outflow to the heart and blood vessels and (2) relief of severe pain. The central alpha₂ agonists used for effects on the heart and blood vessels, and the agents used to relieve pain, are discussed in Chapters 19 and 28, respectively.

**Clinical Consequences of Beta₁ Activation**

All of the clinically relevant responses to activation of beta₁ receptors result from activating beta₁ receptors in the heart; activation of renal beta₁ receptors is not associated with either beneficial or adverse effects. As indicated in Table 17–2, beta₁ receptors can be activated by epinephrine, NE, isoproterenol, dopamine, and dobutamine.

**Therapeutic Applications of Beta₁ Activation**

- **Heart Failure.** Heart failure is characterized by a reduction in the force of myocardial contraction, resulting in insufficient cardiac output. Because activation of beta₁ receptors in the heart has a positive inotropic effect (ie, increases the force of contraction), drugs that activate these receptors can improve cardiac performance.

- **Shock.** This condition is characterized by profound hypotension and greatly reduced tissue perfusion. The primary goal of treatment is to maintain blood flow to vital organs. By increasing heart rate and force of contraction, beta₁ stimulants can increase cardiac output and can thereby improve tissue perfusion.

**Clinical Consequences of Beta₂ Activation**

**Clinical Consequences of Beta₂ Activation**

**Therapeutic Applications of Beta₂ Activation**

Therapeutic applications of beta₂ activation are limited to the lungs and the uterus. Drugs used for their beta₂-activating ability include epinephrine, isoproterenol, and albuterol.

**Asthma.** Asthma is a chronic condition characterized by inflammation and bronchoconstriction occurring in response to a variety of stimuli. During a severe attack, the airflow reduction can be life threatening. Since drugs that activate beta₂ receptors in the lungs promote bronchodilation, these drugs can help relieve or prevent asthma attacks.

For therapy of asthma, adrenergic agonists that are selective for beta₂ receptors (eg, albuterol) are preferred to less selective agents (eg, isoproterenol). This is especially true for patients who also suffer from angina pectoris or tachycardia. Why? Because drugs that can activate beta₁ receptors would aggravate these cardiac disorders.

Most beta₂ agonists used to treat asthma are administered by inhalation. This route is desirable in that it helps minimize adverse systemic effects. It should be noted, however, that inhalation does not guarantee safety: Serious systemic toxic-
ity can result from overdosing with inhaled sympathomimetics. Accordingly, patients must be warned against inhaling too much drug.

**Delay of Preterm Labor.** Activation of beta₂ receptors in the uterus relaxes uterine smooth muscle. This action can be exploited to delay preterm labor.

**Adverse Effects of Beta₂ Activation**

**Hyperglycemia.** The most important adverse response to beta₂ activation is hyperglycemia (elevation of blood glucose). The mechanism is activation of beta₂ receptors in the liver and skeletal muscles, which promotes breakdown of glycogen into glucose. As a rule, beta₂ agonists cause hyperglycemia only in patients with diabetes; in patients with normal pancreatic function, insulin release will maintain blood glucose at an appropriate level. If hyperglycemia develops in the diabetic patient, insulin dosage should be increased.

**Tremor.** Tremor is the most common side effect of beta₂ agonists. It occurs because activation of beta₂ receptors in skeletal muscle enhances contraction. Tremor generally fades over time and can be minimized by initiating therapy at low doses.

**Clinical Consequences of Dopamine Receptor Activation**

Activation of peripheral dopamine receptors causes dilation of the renal vasculature. This effect is exploited in the treatment of shock: by dilating renal blood vessels, we can improve renal perfusion and can thereby reduce the risk of renal failure. Dopamine itself is the only drug available that can activate dopamine receptors. It should be noted that, when dopamine is given to treat shock, the drug also enhances cardiac performance (because it activates beta₁ receptors in the heart).

**Multiple Receptor Activation: Treatment of Anaphylactic Shock**

**Pathophysiology of Anaphylaxis.** Anaphylactic shock is a manifestation of severe allergy. The reaction is characterized by hypotension (from widespread vasodilation), bronchoconstriction, and edema of the glottis. Although histamine contributes to these responses, symptoms are due largely to release of other mediators (eg, leukotrienes). Anaphylaxis can be triggered by a variety of substances, including bee venom, wasp venom, latex rubber, certain foods (eg, peanuts, shellfish), and certain drugs (eg, penicillins).

**Treatment.** Epinephrine, injected IM, is the treatment of choice for anaphylactic shock. Benefits derive from activating three types of adrenergic receptors: alpha₁, beta₂, and beta₁. By activating these receptors, epinephrine can reverse the most severe manifestations of the anaphylactic reaction. Activation of beta₂ receptors increases cardiac output, thereby helping elevate blood pressure. Blood pressure is also increased because epinephrine promotes alpha₁-mediated vasoconstriction. In addition to increasing blood pressure, vasoconstriction helps suppress glottal edema. By activating beta₂ receptors, epinephrine can counteract bronchoconstriction. Individuals who are prone to severe allergic responses should carry an epinephrine auto-injector (eg, Epipen) at all times (Box 17–1). Antihistamines are not especially useful against anaphylaxis because histamine is only a minor contributor to the reaction.

**PROPERTIES OF REPRESENTATIVE ADRENERGIC AGONISTS**

Our aim in this section is to establish an overview of the adrenergic agonists. The information is presented in the form of “drug digests” that highlight characteristic features of representative sympathomimetic agents.

As noted, there are two keys to understanding individual adrenergic agonists: (1) knowledge of the receptors that the drug can activate and (2) knowledge of the therapeutic and adverse effects that receptor activation can elicit. By integrating these two types of information, you can easily predict the spectrum of effects that a particular drug can produce.

Unfortunately, knowing the effects that a drug is capable of producing does not always indicate how that drug is actually used in a clinical setting. Why? Because some adrenergic agonists are not used for all the effects they can produce. Norepinephrine, for example, can activate alpha₁ receptors and can therefore produce mydriasis. However, although NE can produce mydriasis, the drug is not actually used for this purpose. Similarly, although isoproterenol is capable of producing uterine relaxation (through beta₂ activation), isoproterenol is not employed clinically for this effect. Because receptor specificity is not always a predictor of the therapeutic applications of a particular adrenergic agonist, for each of the drugs discussed below, approved clinical applications are indicated.

**Epinephrine**

- **Receptor specificity:** alpha₁, alpha₂, beta₁, beta₂
- **Chemical classification:** catecholamine

Epinephrine [Adrenalin, others] was among the first adrenergic agonists employed clinically and can be considered the prototype of the sympathomimetic drugs. Because of its prototypic status, epinephrine is discussed in detail.

**Therapeutic Uses**

Epinephrine can activate all four subtypes of adrenergic receptors. As a consequence, the drug can produce a broad spectrum of beneficial sympathomimetic effects:

- Because it can cause alpha₁-mediated vasoconstriction, epinephrine is used to (1) delay absorption of local anesthetics, (2) control superficial bleeding, and (3) elevate blood pressure. In the past, epinephrine-induced vasoconstriction was also used for nasal decongestion.
- Activation of alpha₁ receptors on the iris can be used to produce mydriasis during ophthalmologic procedures.*
- Because it can activate beta₁ receptors, epinephrine is used to (1) overcome AV heart block and (2) restore cardiac function in patients experiencing cardiac arrest caused by asystole.
- Activation of beta₂ receptors in the lung promotes bronchodilation, which can be useful in patients with asthma (although other drugs are preferred).
- Because it can activate a combination of alpha and beta receptors, epinephrine is the treatment of choice for anaphylactic shock.

*Epinephrine for ophthalmic use is no longer available in the United States.
The EpiPen is an epinephrine auto-injector, one of three brands available in the United States.* The device is indicated for emergency treatment of anaphylaxis, a life-threatening allergic reaction caused by severe hypersensitivity to insect venoms (eg, from bees, wasps, fire ants), certain foods (eg, peanuts, walnuts, shellfish), and certain drugs (especially penicillins). Every year, anaphylaxis kills about 6000 Americans: 125 who have food allergies, between 40 and 400 who have venom allergies, and over 5400 who have penicillin allergy. Could most of these deaths be avoided? Yes—through immediate injection of epinephrine. Unfortunately, many of the people at risk don’t carry an epinephrine injector, and many of those who do aren’t sure how to use it. So listen up: By encouraging highly allergic clients to carry an EpiPen, and by teaching them when and how to use it, you could well save someone’s life.

EpiPen Description and Dosage
The EpiPen auto-injector is a single-use delivery device, featuring a spring-activated needle, designed for IM injection of epinephrine. Two strengths are available. The larger one, sold as EpiPen, delivers a 0.3-mg dose (for individuals weighing 66 pounds or more). The smaller one, sold as EpiPen Jr, delivers a 0.15-mg dose (for individuals between 33 and 66 pounds). If one injection fails to completely reverse symptoms, a second injection (using a second EpiPen) may be given. The EpiPen is available only by prescription.

EpiPen Storage and Replacement
Epinephrine is sensitive to extreme heat and light, and hence the EpiPen should be stored at room temperature in a dark place. The factory-issue storage tube provides additional protection from UV light. Refrigeration can compromise the injection mechanism, and should be avoided. If the epinephrine solution turns brown, if a precipitate forms, or if the expiration date has passed, the unit should be replaced. (The distributor offers a free service to remind patients when their EpiPen is about to expire.)

Who Should Carry an EpiPen and When Should They Use It?
Anyone who has experienced a severe, systemic allergic reaction should always carry at least one epinephrine auto-injector! Anaphylaxis can develop within minutes after allergen exposure. To prevent a full-blown reaction, epinephrine should be injected as soon as early symptoms appear (eg, swelling, shortness of breath). People who do not carry an EpiPen, and hence must wait for an emergency response team, greatly increase their risk of death.

What’s the Self-Injection Procedure?
The EpiPen auto-injector is a tubular device with three prominent external features: a black tip (the needle comes out through this end), a clear window (for examining the epinephrine solution), and a gray cap (which prevents activation until being removed).

Injections are made into the outer thigh as follows:
1. Form a fist around the unit with the black tip pointing down.
2. With the free hand, pull off the gray activation cap.
3. Jab the device firmly into the outer thigh, at an angle perpendicular to the thigh, and hold it there for 10 seconds. (The injection may be made directly through clothing.)
4. Remove the unit and massage the area for 10 seconds to facilitate absorption.

To ensure the injection was made, examine the used EpiPen: If the needle is projecting through the black tip, the procedure was a success; if the needle is not projecting, jab the device in again. Note: The EpiPen contains 2 mL of epinephrine solution, but only 0.3 mL is actually injected. Hence, even after a successful injection, the device will not be empty.

What Should Be Done After the Injection?
Following epinephrine injection, it is important to get immediate medical attention. Why? Because (1) the effects of epinephrine begin to fade in 10 to 20 minutes and (2) anaphylactic reactions can be biphasic and prolonged. Accordingly, to ensure a good outcome, hospitalization (up to 6 hours) is recommended. Hospital staff should be informed that epinephrine has been injected, and should be shown the used EpiPen (to confirm the dosage). Prednisone may be given to manage delayed or persistent symptoms.

Does IM Epinephrine Have Side Effects?
Of course. The injection itself may cause discomfort, and the epinephrine may cause tachycardia, palpitations, and a feeling of nervousness. The drug may also cause sweating, dizziness, headache, nausea, and vomiting.

*In addition to the EpiPen, two other epinephrine auto-injectors—Adrenaclick and Twinject—are now available. The Adrenaclick injector is nearly identical to the EpiPen. Twinject differs from the other two products in that it can deliver two separate doses. The first dose is injected automatically, just as with EpiPen and Adrenaclick. The second dose, if needed, is injected manually.
Pharmacokinetics

**Absorption.** Epinephrine may be administered topically or by injection. The drug cannot be given orally because, as discussed, epinephrine and other catecholamines undergo destruction by MAO and COMT before reaching the systemic circulation. Following subQ injection, absorption is slow owing to epinephrine-induced local vasoconstriction. Absorption is more rapid following IM injection.

**Inactivation.** Epinephrine has a short half-life because of two processes: enzymatic inactivation and uptake into adrenergic nerves. The enzymes that inactivate epinephrine and other catecholamines are MAO and COMT.

**Adverse Effects**

Because it can activate the four major adrenergic receptor subtypes, epinephrine can produce multiple adverse effects.

- **Hypertensive Crisis.** Vasoconstriction secondary to excessive alpha, activation can produce a dramatic increase in blood pressure. Cerebral hemorrhage can occur. Because of the potential for severe hypertension, patients receiving parenteral epinephrine must undergo continuous cardiovascular monitoring.

- **Dysrhythmias.** Excessive activation of beta, receptors in the heart can produce dysrhythmias. Because of their sensitivity to catecholamines, hyperthyroid patients are at high risk for epinephrine-induced dysrhythmias.

- **Angina Pectoris.** By activating beta, receptors in the heart, epinephrine can increase cardiac work and oxygen demand. If the increase in oxygen demand is big enough, an anginal attack may ensue. Causing angina is especially likely in patients with coronary atherosclerosis.

- **Necrosis Following Extravasation.** If an IV line containing epinephrine becomes extravasated, the resultant localized vasoconstriction may result in necrosis. Because of this possibility, patients receiving IV epinephrine should be monitored closely. If extravasation occurs, injury can be minimized by local injection of phenolamine, an alpha-adrenergic antagonist.

- **Hyperglycemia.** In diabetic patients, epinephrine can cause hyperglycemia. How? By causing breakdown of glycogen secondary to activation of beta, receptors in liver and skeletal muscle. If hyperglycemia develops, insulin dosage should be increased.

**Drug Interactions**

- **MAO Inhibitors.** As their name implies, MAO inhibitors suppress the activity of MAO. These drugs are used primarily to treat depression (see Chapter 32). Because MAO is one of the enzymes that inactivate epinephrine and other catecholamines, inhibition of MAO will prolong and intensify epinephrine’s effects. As a rule, patients receiving an MAO inhibitor should not receive epinephrine.

- **Tricyclic Antidepressants.** Tricyclic antidepressants block the uptake of catecholamines into adrenergic neurons. Since neuronal uptake is one mechanism by which the actions of norepinephrine and other catecholamines are terminated, blocking uptake can intensify and prolong epinephrine’s effects. Accordingly, patients receiving a tricyclic antidepressant may require a reduction in epinephrine dosage.

- **General Anesthetics.** Several inhalation anesthetics render the myocardium hypersensitive to activation by beta, agonists. When the heart is in this hypersensitive state, exposure to epinephrine and other beta, agonists can cause tachydyssrhythmias.

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**TABLE 17-3 Epinephrine Solutions: Concentrations for Different Routes of Administration**

<table>
<thead>
<tr>
<th>Concentration of Epinephrine Solution</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1% (1:100)</td>
<td>Oral inhalation</td>
</tr>
<tr>
<td>0.1% (1:1000)</td>
<td>Subcutaneous Intramuscular Intraspinal</td>
</tr>
<tr>
<td>0.01% (1:10,000)</td>
<td>Intravenous Intracardiac</td>
</tr>
<tr>
<td>0.001% (1:100,000)</td>
<td>In combination with local anesthetics</td>
</tr>
</tbody>
</table>

**Alpha-Adrenergic Blocking Agents.** Drugs that block alpha-adrenergic receptors can prevent receptor activation by epinephrine. Alpha blockers (eg, phentolamine) can be used to treat toxicity (eg, local vasoconstriction) caused by excessive epinephrine-induced alpha activation.

**Beta-Adrenergic Blocking Agents.** Drugs that block beta-adrenergic receptors can prevent receptor activation by epinephrine. Beta-blocking agents (eg, propranolol) can reduce adverse effects (eg, dysrhythmias, anginal pain) caused by epinephrine and other beta, agonists.

**Preparations, Dosage, and Administration**

Epinephrine [Adrenalin, EpiPen, Primatene Mist, others] is supplied in solution for administration by several routes: IV, IM, subQ, intracardiac, intraspinal, inhalation, and topical. As indicated in Table 17–3, the strength of the epinephrine solution employed depends on the route of administration. Note that solutions intended for intravenous administration are less concentrated than solutions intended for administration by most other routes. Why? Because intravenous administration of a concentrated epinephrine solution can produce potentially fatal reactions (severe dysrhythmias and hypertension). Therefore, before you give epinephrine IV, check to ensure that the concentration is appropriate! Aspirate prior to IM or subQ injection to avoid inadvertent injection into a vein.

Patients receiving IV epinephrine should be monitored constantly. They should be observed for signs of excessive cardiovascular activation (eg, tachydysrhythmias, hypertension) and for possible extravasation of the IV line. If systemic toxicity develops, epinephrine should be discontinued; if indicated, an alpha-adrenergic blocker, a beta-adrenergic blocker, or both should be given to suppress symptoms. If an epinephrine-containing IV line becomes extravasated, administration should be discontinued and the region of extravasation infiltrated with an alpha-adrenergic blocker.

Treatment of anaphylaxis using an epinephrine auto-injector [EpiPen, Twinject, Adrenaclick] is discussed in Box 17–1.

**Norepinephrine**

- **Receptor specificity:** alpha, alpha, beta,
- **Chemical classification:** catecholamine

Norepinephrine [Levophed] is similar to epinephrine in several respects. With regard to receptor specificity, NE differs from epinephrine only in that NE does not activate beta, receptors. Accordingly, NE can elicit all of the responses that epinephrine can, except those that are beta, mediated. Because NE is a catecholamine, the drug is subject to rapid inactivation by MAO and COMT.
Adrenergic agonists

Isoproterenol
- **Receptor specificity:** beta_1 and beta_2
- **Chemical classification:** catecholamine

Isoproterenol (formerly available as Isuprel) differs significantly from NE and epinephrine in that isoproterenol acts only at beta-adrenergic receptors. Isoproterenol was the first beta-selective agent employed clinically and will serve as our prototype of the beta-selective adrenergic agonists.

Therapeutic Uses
- **Cardiovascular.** By activating beta_2 receptors in the heart, isoproterenol can benefit patients with cardiovascular disorders. Specifically, it can help overcome AV heart block, restart the heart following cardiac arrest, and increase cardiac output during shock.
- **Bronchospasm.** Although isoproterenol is no longer used for asthma, it is used to treat bronchospasm during anesthesia. Benefits derive from activating beta_2 receptors in the lung.
- **Asthma.** By activating beta_2 receptors in the lung, isoproterenol can cause bronchodilation, thereby decreasing airway resistance. Following its introduction, isoproterenol became a mainstay of asthma therapy. However, because we now have even more selective beta-adrenergic agonists (ie, drugs that activate beta receptors only), use of isoproterenol for asthma has been abandoned.

Adverse Effects
Because isoproterenol does not activate alpha-adrenergic receptors, it produces fewer adverse effects than NE or epinephrine. The major undesired responses, caused by activating beta_1 receptors in the heart, are tachydysrhythmias and angina pectoris. In diabetic patients, isoproterenol can cause hyperglycemia (by promoting beta_2-mediated glycogenolysis).

Drug Interactions
The major drug interactions of isoproterenol are nearly identical to those of epinephrine. Effects are enhanced by MAO inhibitors and tricyclic antidepressants and reduced by beta-adrenergic blocking agents. Like epinephrine, isoproterenol can cause dysrhythmias in patients receiving certain inhalation anesthetics.

Preparations and Administration
Isoproterenol hydrochloride is available in solution (0.2 and 0.02 mg/mL) for parenteral administration.

When used to stimulate the heart, isoproterenol can be administered IV and IM and by intracardiac injection. The dosage for IM administration is about 10 times greater than the dosage employed for the other two routes.

When used to relieve bronchospasm, isoproterenol is administered IV.

**Dopamine**
- **Receptor specificity:** dopamine, beta_1, and, at high doses, alpha_1
- **Chemical classification:** catecholamine

**Receptor Specificity**
Dopamine has dose-dependent receptor specificity. When administered in low therapeutic doses, dopamine acts on dopamine receptors only. At moderate therapeutic doses, dopamine activates beta_1 receptors in addition to dopamine receptors. And at very high doses, dopamine activates alpha receptors along with beta_1 and dopamine receptors.

**Therapeutic Uses**
- **Shock.** The major indication for dopamine is shock. Benefits derive from effects on the heart and renal blood vessels. By activating beta_1 receptors in the heart, dopamine can increase cardiac output, thereby improving tissue perfusion. By activating dopamine receptors in the kidney, dopamine can dilate renal blood vessels, thereby improving renal perfusion. Success can be evaluated by monitoring output of urine.
- **Heart Failure.** Heart failure is characterized by reduced tissue perfusion secondary to reduced cardiac output. Dopamine can help alleviate symptoms by activating beta_1 receptors on the heart, which increases myocardial contractility, and thereby increases cardiac output.
- **Acute Renal Failure.** Because of its ability to increase renal blood flow and urine output, low-dose dopamine has long been used in efforts to preserve renal function in patients with evolving acute renal failure (ARF). However, we now have evidence that the drug is not effective: In patients with early ARF, dopamine failed to protect renal function, shorten hospital stays, or reduce the number of patients needing a kidney transplant. Accordingly, it would appear that it is time to abandon low-dose dopamine as a treatment for ARF.

**Adverse Effects**
The most common adverse effects of dopamine—tachycardia, dysrhythmias, and anginal pain—result from activation of beta_1 receptors in the heart. Because of its cardiac actions, dopamine is contraindicated for patients with tachydysrhythmias or ventricular fibrillation. Since high concentrations of dopamine cause alpha_1 activation, extravasation may result in necrosis from localized vasoconstriction. Tissue injury can be minimized by local infiltration of phentolamine, an alpha-adrenergic antagonist.

**Drug Interactions**
MAO inhibitors can intensify the effects of dopamine on the heart and blood vessels. If a patient is receiving an MAO inhibitor, the dosage of dopamine must be reduced by at least 90%. Tricyclic antidepressants can also intensify dopamine’s actions, but not to the extent seen with MAO inhibitors. Certain general anesthetics can sensitize the myocardium to stimulation by dopamine and other catecholamines, thereby increasing the risk of dysrhythmias. Diuretics can complement the beneficial effects of dopamine on the kidney.

Preparations, Dosage, and Administration
- **Preparations.** Dopamine hydrochloride is supplied in aqueous solutions that range in concentration from 0.8 to 160 mcg/mL.
- **Dosage.** Concentrated solutions must be diluted prior to infusion. For treatment of shock, a concentration of 400 mcg/mL can be used. The recommended initial rate of infusion is 2 to 5 mcg/kg/min. If needed, the infusion rate can be gradually increased to a maximum of 20 to 50 mcg/kg/min.
- **Administration.** Dopamine is administered IV. Because of extremely rapid inactivation by MAO and COMT, the drug must be given by continuous infusion. A metering device is needed to control flow rate. Cardiovascular...
status must be closely monitored. If extravasation occurs, the infusion should be stopped and the affected area infiltrated with an alpha-adrenergic antagonist (eg, phentolamine).

**Dobutamine**

- **Receptor specificity:** beta1
- **Chemical classification:** catecholamine

**Actions and Uses.** At therapeutic doses, dobutamine causes selective activation of beta1-adrenergic receptors. The only indication for the drug is heart failure.

**Adverse Effects.** The major adverse effect is tachycardia. Blood pressure and the electrocardiogram (ECG) should be monitored closely.

**Drug Interactions.** Effects of dobutamine on the heart and blood vessels are intensified greatly by MAO inhibitors. Accordingly, in patients receiving an MAO inhibitor, dobutamine dosage must be reduced at least 90%. Concurrent use of tricyclic antidepressants may cause a moderate increase in the cardiovascular effects. Certain general anesthetics can sensitize the myocardium to stimulation by dobutamine, thereby increasing the risk of dysrhythmias.

**Preparations, Dosage, and Administration.** Dobutamine hydrochloride is supplied in concentrated and dilute solutions. The concentrated solution (12.5 mg/mL in 20- and 40-mL vials) must be diluted prior to use. The dilute solutions (1, 2, and 4 mg/mL in 250-mL single-use containers) can be used as is. Because of rapid inactivation by MAO and COMT, dobutamine is administered by continuous IV infusion. The usual rate is 2.5 to 10 mcg/kg/min.

**Phenylephrine**

- **Receptor specificity:** alpha1
- **Chemical classification:** noncatecholamine

Phenylephrine [Neo-Synephrine, others] is a selective alpha1 agonist. The drug can be administered locally to reduce nasal congestion and parenterally to elevate blood pressure. In addition, phenylephrine eye drops can be used to dilate the pupil. Also, phenylephrine can be coadministered with local anesthetics to retard anesthetic absorption.

**Albuterol**

- **Receptor specificity:** beta2
- **Chemical classification:** noncatecholamine

**Therapeutic Uses**

**Asthma.** Albuterol [Ventolin, VoSpire, others] can reduce airway resistance in asthma by causing beta2-mediated bronchodilation. Because albuterol is “selective” for beta2 receptors, it produces much less activation of cardiac beta1 receptors than does isoproterenol. As a result, albuterol and other beta2-selective agents have replaced isoproterenol for therapy of asthma. Remember, however, that receptor selectivity is only relative: If administered in large doses, albuterol will lose selectivity and activate beta1 receptors as well as beta2 receptors. Accordingly, patients should be warned not to exceed recommended doses, since doing so may cause undesired cardiac stimulation. Preparations and dosages for asthma are presented in Chapter 76.

**Adverse Effects**

Adverse effects are minimal at therapeutic doses. Tremor is most common. If dosage is excessive, albuterol can cause tachycardia by activating beta1 receptors in the heart.

### DISCUSSION OF ADRENERGIC AGONISTS IN OTHER CHAPTERS

All of the drugs presented in this chapter are discussed again in chapters that address specific applications. For example, the use of alpha1 agonists to relieve nasal congestion is discussed in Chapter 77. Table 17–4 summarizes the chapters in which adrenergic agonists are discussed again.

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**TABLE 17–4** Discussion of Adrenergic Agonists in Other Chapters

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Discussion Topic</th>
<th>Chapter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha1 Agonists</td>
<td>Nasal congestion</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>Ophthalmology</td>
<td>104</td>
</tr>
<tr>
<td>Alpha2 Agonists</td>
<td>Cardiovascular effects</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Pain relief</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Ophthalmology</td>
<td>104</td>
</tr>
<tr>
<td>Beta1 Agonists</td>
<td>Heart failure</td>
<td>48</td>
</tr>
<tr>
<td>Beta2 Agonists</td>
<td>Asthma</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>Preterm labor</td>
<td>64</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>Basic pharmacology</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Attention-deficit/hyperactivity disorder</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Drug abuse</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Appetite suppression</td>
<td>82</td>
</tr>
</tbody>
</table>

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161
Adrenergic agonists are also known as sympathomimetics. Why? Because their effects mimic those caused by the sympathetic nervous system.

Most adrenergic agonists act by direct activation of adrenergic receptors. A few act by indirect mechanisms: promotion of norepinephrine release, blockade of norepinephrine uptake, and inhibition of norepinephrine breakdown.

Adrenergic agonists fall into two chemical classes: catecholamines and noncatecholamines.

Agents in the catecholamine family cannot be taken orally (because of destruction by MAO and COMT), have a brief duration of action (because of destruction by MAO and COMT), and cannot cross the blood-brain barrier (because they are polar molecules).

Adrenergic agonists that are noncatecholamines can be taken orally, have a longer duration than the catecholamines, and can cross the blood-brain barrier.

Activation of alpha_1 receptors causes vasoconstriction and mydriasis.

Alpha_1 agonists are used for hemostasis, nasal deconges- tion, and elevation of blood pressure, and as adjuncts to local anesthetics.

Major adverse effects that can result from alpha_1 activation are hypertension and local necrosis (if extravasation occurs).

Activation of alpha_2 receptors in the periphery is of minimal clinical significance. In contrast, drugs that activate alpha_2 receptors in the CNS produce useful effects (see Chapters 19 and 28).

All of the clinically relevant responses to activation of beta_1 receptors result from activating beta_1 receptors in the heart.

Activation of cardiac beta_1 receptors increases heart rate, force of contraction, and conduction through the AV node.

Drugs that activate beta_1 receptors can be used to treat heart failure, AV block, and cardiac arrest caused by asystole.

Potential adverse effects from beta_1 activation are tachycardia, dysrhythmias, and angina.

Drugs that activate beta_2 receptors are used primarily for asthma.

Principal adverse effects from beta_2 activation are hyperglycemia (mainly in diabetic patients) and tremor.

Activation of dopamine receptors dilates renal blood vessels, which helps maintain renal perfusion in shock.

Epinephrine is a catecholamine that activates alpha_1, alpha_2, beta_1, and beta_2 receptors.

Epinephrine is the drug of choice for treating anaphylactic shock: By activating alpha_1, beta_1, and beta_2 receptors, epinephrine can elevate blood pressure, suppress glottal edema, and counteract bronchoconstriction.

Epinephrine can also be used to control superficial bleeding, restart the heart after cardiac arrest, and delay absorption of local anesthetics.

Epinephrine should not be combined with MAO inhibitors, and should be used cautiously in patients taking tricyclic antidepressants.

Isoproterenol is a catecholamine that activates beta_1 and beta_2 receptors.

Isoproterenol can be used to enhance cardiac performance (by activating beta_1 receptors) and to treat bronchospasm (by activating beta_2 receptors).

Dopamine is a catecholamine whose receptor specificity is highly dose dependent: at low therapeutic doses, dopamine acts on dopamine receptors only; at moderate doses, dopamine activates beta_2 receptors in addition to dopamine receptors; and at high doses, dopamine activates alpha_1 receptors along with beta_1 receptors and dopamine receptors.

Albuterol is a noncatecholamine that produces selective activation of beta_2 receptors.

Albuterol is used to treat asthma.

Because albuterol is “selective” for beta_2 receptors, it produces much less stimulation of the heart than does isoproterenol. Accordingly, albuterol and related drugs have replaced isoproterenol for therapy of asthma.

**KEY POINTS**

**Summary of Major Nursing Implications**

**EPINEPHRINE**

**Preadministration Assessment**

**Therapeutic Goal**

Epinephrine has multiple indications. The major use is treatment of anaphylaxis. Other uses include control of superficial bleeding, delay of local anesthetic absorption, and management of cardiac arrest.

**Identifying High-Risk Patients**

Epinephrine must be used with great caution in patients with hyperthyroidism, cardiac dysrhythmias, organic heart disease, or hypertension. Caution is also needed in patients with angina pectoris or diabetes and in those receiving MAO inhibitors, tricyclic antidepressants, or general anesthetics.

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Implementation: Administration

Routes
Topical, inhalation, and parenteral (IV, IM, subQ, intracardiac, intraspinal). Rapid inactivation by MAO and COMT prohibits oral use.

Administration
The concentration of epinephrine solutions varies according to the route of administration (see Table 17–3). To avoid serious injury, check solution strength to ensure that the concentration is appropriate for the intended route. Aspirate prior to IM and subQ administration to avoid inadvertent injection into a vein.

Epinephrine solutions oxidize over time, causing them to turn pink or brown. Discard discolored solutions.

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects
In patients receiving IV epinephrine, monitor cardiovascular status continuously.

Minimizing Adverse Effects

Cardiovascular Effects. By stimulating the heart, epinephrine can cause anginal pain, tachycardia, and dysrhythmias. These responses can be reduced with a beta-adrenergic blocking agent (eg, propranolol).

By activating alpha₁ receptors on blood vessels, epinephrine can cause intense vasoconstriction, which can result in severe hypertension. Blood pressure can be lowered with an alpha-adrenergic blocking agent (eg, phentolamine).

Necrosis. If an IV line delivering epinephrine becomes extravasated, necrosis may result. Exercise care to avoid extravasation. If extravasation occurs, infiltrate the region with phentolamine.

Hyperglycemia. Epinephrine may cause hyperglycemia in diabetic patients. If hyperglycemia develops, insulin dosage should be increased.

Minimizing Adverse Interactions

MAO Inhibitors and Tricyclic Antidepressants. These drugs prolong and intensify the actions of epinephrine. Patients taking these antidepressants require a reduction in epinephrine dosage.

General Anesthetics. When combined with certain general anesthetics, epinephrine can induce cardiac dysrhythmias. Dysrhythmias may respond to a beta₁-adrenergic blocker.

DOPAMINE

Preadministration Assessment
Therapeutic Goal
Dopamine is used to improve hemodynamic status in patients with shock or heart failure. Benefits derive from enhanced cardiac performance and increased renal perfusion.

Baseline Data
Full assessment of cardiac, hemodynamic, and renal status is needed.

Identifying High-Risk Patients
Dopamine is contraindicated for patients with tachydysrhythmias or ventricular fibrillation. Use with extreme caution in patients with organic heart disease, hyperthyroidism, or hypertension, and in patients receiving MAO inhibitors. Caution is also needed in patients with angina pectoris and in those receiving tricyclic antidepressants or general anesthetics.

Implementation: Administration
Route
Intravenous.

Administration
Administer by continuous infusion, employing a metering device to control flow rate.

If extravasation occurs, stop the infusion immediately and infiltrate the region with an alpha-adrenergic antagonist (eg, phentolamine).

Ongoing Evaluation and Interventions

Evaluating Therapeutic Effects
Monitor cardiovascular status continuously. Increased urine output is one index of success. Diuretics may complement the beneficial effects of dopamine on the kidney.

Minimizing Adverse Effects

Cardiovascular Effects. By stimulating the heart, dopamine may cause anginal pain, tachycardia, or dysrhythmias. These reactions can be decreased with a beta-adrenergic blocking agent (eg, propranolol).

Necrosis. If the IV line delivering dopamine becomes extravasated, necrosis may result. Exercise care to avoid extravasation. If extravasation occurs, infiltrate the region with phentolamine.

Minimizing Adverse Interactions

MAO Inhibitors. Concurrent use of MAO inhibitors and dopamine can result in severe cardiovascular toxicity. If a patient is taking an MAO inhibitor, dopamine dosage must be reduced by at least 90%.

Tricyclic Antidepressants. These drugs prolong and intensify the actions of dopamine. Patients receiving them may require a reduction in dopamine dosage.

General Anesthetics. When combined with certain general anesthetics, dopamine can induce dysrhythmias. These may respond to a beta₁-adrenergic blocker.
## Summary of Major Nursing Implications—cont’d

<table>
<thead>
<tr>
<th>DOBUTAMINE</th>
<th>Ongoing Evaluation and Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preadmission Assessment</strong></td>
<td><strong>Evaluating Therapeutic Effects</strong></td>
</tr>
<tr>
<td><strong>Therapeutic Goal</strong></td>
<td>Monitor cardiac function (heart rate, ECG), blood pressure, and urine output. When possible, monitor central venous pressure and pulmonary wedge pressure.</td>
</tr>
<tr>
<td>Improvement of hemodynamic status in patients with heart failure.</td>
<td><strong>Minimizing Adverse Effects</strong></td>
</tr>
<tr>
<td><strong>Baseline Data</strong></td>
<td>Major adverse effects are <em>tachycardia</em> and <em>dysrhythmias</em>. Monitor the ECG and blood pressure closely. Adverse cardiac effects can be reduced with a beta-adrenergic antagonist.</td>
</tr>
<tr>
<td>Full assessment of cardiac, renal, and hemodynamic status is needed.</td>
<td><strong>Minimizing Adverse Interactions</strong></td>
</tr>
<tr>
<td><strong>Identifying High-Risk Patients</strong></td>
<td><em>MAO Inhibitors.</em> Concurrent use of an MAO inhibitor with dobutamine can cause severe cardiovascular toxicity. If a patient is taking an MAO inhibitor, dobutamine dosage must be reduced by at least 90%.</td>
</tr>
<tr>
<td>Use with <em>great caution</em> in patients with organic heart disease, hyperthyroidism, tachydysrhythmias, or hypertension and in those taking an MAO inhibitor. <em>Caution</em> is also needed in patients with angina pectoris and in those receiving tricyclic antidepressants or general anesthetics.</td>
<td><em>Tricyclic Antidepressants.</em> These drugs can prolong and intensify the actions of dobutamine. Patients receiving them may require a reduction in dobutamine dosage.</td>
</tr>
<tr>
<td><strong>Implementation: Administration</strong></td>
<td><em>General Anesthetics.</em> When combined with certain general anesthetics, dobutamine can cause cardiac dysrhythmias. These may respond to a beta-1-adrenergic antagonist.</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td></td>
</tr>
<tr>
<td>Intravenous.</td>
<td></td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td></td>
</tr>
<tr>
<td>Administer by continuous IV infusion. Dilute concentrated solutions prior to use. Infusion rates usually range from 2.5 to 10 mcg/kg/min. Adjust the infusion rate on the basis of the cardiovascular response.</td>
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</tbody>
</table>