

Cardiovascular Pharmacotherapeutics

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Cardiovascular Pharmacotherapeutics

Third Edition

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Basic Principles of Clinical Pharmacology Relevant to Cardiology

William H. Frishman, MD

This chapter focuses on some of the basic pharmacologic principles that influence the manner by which cardiovascular drugs manifest their pharmacodynamic and pharmacokinetic actions. A discussion of drug receptor pharmacology is followed by a review of drug disposition, drug metabolism, excretion, and effects of disease states on pharmacokinetics.

Receptors

For over 100 years, it has been recognized that, in order to elicit a response, a drug must interact with a receptor, which is the interface between drug and body and the principal determinant of drug selectivity. The receptor, (1) recognizes and binds the drug, (2) undergoes changes in conformation and charge distribution, and (3) transduces information inherent in the drug structure (extracellular signal) into intracellular messages, resulting in a change in cellular function. A receptor may be any functional macromolecule and is often a receptor for endogenous regulatory substances, such as hormones or neurotransmitters.

Nature of Receptors

Receptors typically are proteins, lipoproteins, or glycoproteins including (1) regulatory proteins that mediate the action of endogenous substances such as neurotransmitters, hormones, etc.; (2) enzymes, which typically are inhibited by drugs; (3) transport proteins such as Na(+)/K(+) ATPase; and (4) structural proteins such as tubulin.

1. Gated channels involve synaptic transmitters (eg, acetylcholine, norepinephrine) and drugs mimicking their action. These receptors regulate ion flow through

membranes, altering transmembrane potentials. The well-characterized nicotinic acetylcholine receptor is a protein consisting of five subunits, two of which selectively bind acetylcholine, opening the Na⁺ channel through conformational alterations. In the absence of an agonist, the channel remains closed. Other drugs—eg, certain anxiolytics—act similarly at gamma amino butyric acid (GABA)-regulated Cl⁻ channels. The time sequence is extremely fast (milliseconds).

2. G proteins (which interact with guanine nucleotides) diffuse within the cell membrane, interacting with more than one receptor. They regulate enzymes, such as adenylyl cyclase, or ion channels. Their large number and great diversity may account for drug selectivity in some cases. A prominent example is the role of a specific G protein in the regulation of muscarinic receptors in cardiac muscle. Activation enhances potassium permeability, causing hyperpolarization and depressed electrical activity. Similarly, the α- and β-adrenergic receptors and the angiotensin II receptors are part of a major class of G protein-coupled receptors.
3. Transmembrane enzymes—eg, protein tyrosine kinases—recognize ligands such as insulin and several growth factors. These bind to an extracellular domain of the receptor and allosterically activate the enzyme site at the cytoplasmic domain, enabling phosphorylation of receptor tyrosines. The signaling process proceeds to phosphorylation of other intracellular proteins, involving serine and threonine as well. Downregulation of these receptors is frequently seen, limiting the intensity and duration of action of the ligand (drug).
4. Intracellular receptors: Here the lipophilic drug (agonist) penetrates the plasma membrane and binds selectively to an intracellular macromolecule. The drug-receptor complex subsequently binds to DNA-

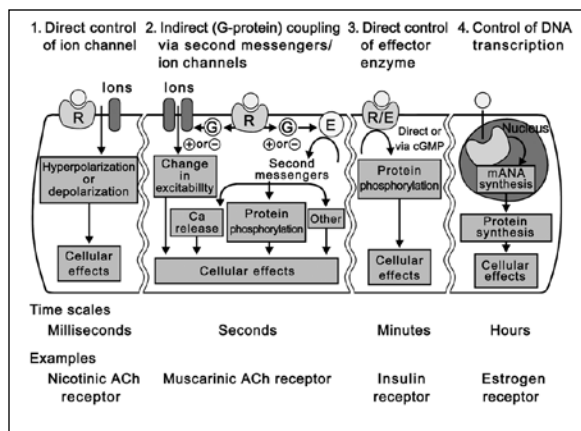


Figure 1-1. This shows the scheme for the four major types of drug receptors and linkage to their cellular effects. Included here are direct control of ion channel, indirect G protein coupling via messenger ion channels, direct control of effector-enzyme, and control of DNA transcription, as well as the various models that are looking at this. Essentially, one gated channel involves synaptic transmitters; an example of this could be acetylcholine and norepinephrine (and drugs mimicking their action). These receptors regulate ion flow through membranes, alternating transmembrane potentials. The well-characterized nicotinic-acetylcholine receptor is a protein consisting of five subunits, two of which selectively bind acetylcholine, opening the sodium channel through conformational alterations. In the absence of an agonist, the channel remains closed. Other drugs, for example, certain anxiolytics, act similarly at GABA-regulated chloride channels. The time sequence is extremely fast, measured in milliseconds.

The indirect G protein interacts with guanine nucleotides, which diffuse within the cell membrane, interacting with more than one receptor. They regulate enzymes such as adenylyl cyclase or ion channels. Their large number and great diversity may account for drug selectivity in some cases. A prominent example is the role of specific G protein in the regulation of muscarinic receptors in cardiac muscle. Activation enhances potassium permeability, causing hyperpolarization and depressed electrical activity.

Transmembrane enzymes such as protein tyrosine kinases recognize ligands such as insulin and several growth factors. These bind to an extracellular domain of the receptor and allosterically activate the enzyme site at the cytoplasmic domain, enabling phosphorylation of receptor tyrosines. The signaling process proceeds to phosphorylation of other intracellular proteins involving serine and threonine as well.

With the intracellular receptors, lipophilic drugs permeate the plasma membrane and bind selectively to an intracellular macromolecule. The drug-receptor complex subsequently binds to DNA, modifying gene expression.

The response time is slow (up to several hours) and duration of hours or days after disappearance of the drug, due to turnover time of the proteins expressed by the affected gene. These four major classes are depicted in Figure 1.

R = receptor molecule; G = G-protein; E = enzyme

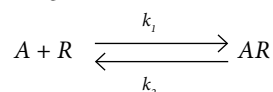
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modifying gene expression. Response time is slow (up to several hours) and duration of hours or days after disappearance of the drug due to turnover time of the proteins expressed by the affected gene.

The four major classes of receptors are depicted in Figure 1-1. Transmembrane signal transduction also involves a number of second messenger systems that respond to receptor activation. These systems include (1) cyclic AMP, which is formed by the action of ligand-activated adenylyl cyclase on ATP and, through activation of selective protein kinases, mediates numerous hormonal and drug responses; and (2) phosphatidylinositol, which, through hydrolysis by phospholipase C within the cell membrane, yields water-soluble inositol triphosphate, which enters the cell and releases bound Ca^{2+} and lipid-soluble diacylglycerol, which remains in the membrane, where it activates protein kinase C.

Kinetics of Drug-Receptor Interactions

Drug or agonist interacts with its receptor as follows:



where R = unoccupied receptor; AR = drug-receptor complex.

According to the law of mass action, the forward reaction rate is given by $k_1[A][R]$ and the reverse reaction rate by $k_2[AR]$.

$$\text{The dissociation constant (Kd)} = \frac{[A][R]}{[AR]}$$

$$\text{relates to } \frac{k_2}{k_1}$$

$$\text{The binding (affinity) constant (Ka)} = \frac{1}{Kd}$$

$$\text{relates to } \frac{k_1}{k_2}$$

Each constant is characteristic of a drug and its receptor.

Drug-receptor interaction may involve any type of bond: van der Waals, ionic, hydrogen, covalent. The in-

Cholinergic and Anticholinergic Drugs

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The term *parasympathetic nervous system* refers to those portions of the peripheral autonomic nervous system that begin as preganglionic fibers in 1 of 3 distinct regions of the central nervous system (CNS), exit the CNS in either the cranial or the sacral regions, and have their postganglionic fibers distributed in a variety of organs throughout the body. One of the 3 sites of origin for parasympathetic fibers is the midbrain. Fibers originating here join the third cranial nerve and course to the ciliary ganglion. At this ganglion they synapse, and postganglionic fibers innervate the iris and ciliary body.

The second site of origin for the parasympathetic system is in the medulla. Fibers originating here join the seventh, ninth, and tenth cranial nerves to exit the CNS. These preganglionic fibers distribute in the pattern of each of these nerves. Fibers in the tenth nerve (the vagus) are distributed to ganglia associated with various visceral organs, including the heart and gastrointestinal tract.

The third and final source of parasympathetic outflow is in the sacral portion of the spinal cord. Preganglionic fibers from this site lead to connections with the bladder, bowel, and pelvic organs.¹

The anatomic organization of the parasympathetic system differs from that of the sympathetic system. The preganglionic fibers of the parasympathetic system extend from their sites of origin in the CNS to the end organ they are innervating. Ganglia of the parasympathetic system are relatively smaller than those of the sympathetic system, and the ganglionic fibers that emerge from these ganglia are short and localized to a specific organ. The sympathetic system has preganglionic fibers that synapse in large paravertebral ganglia and has an extensive and diffuse postganglionic network that distributes to multiple organs of the body.¹

Inherent in the structural organization of the parasympathetic system is the ability to act on specific organs to

cause very specific responses via localized discharges. In general, where the sympathetic system tends to diffusely stimulate activity through its widespread postganglionic network, the effects of the parasympathetic system are to act on specific organs to accommodate periods of rest and recovery. The system lowers heart rate, increases gastrointestinal motility, stimulates bladder emptying, increases biliary contraction, and lowers blood pressure. The parasympathetic nervous system is exclusively cholinergic in character (using acetylcholine as a transmitter), whereas in the sympathetic system the postganglionic fibers are almost exclusively adrenergic.

Acetylcholine receptors were first recognized as being of two basic types in 1914, when Dale² noted that while acetylcholine could stimulate all types of cholinergic receptors, certain effects could be blocked by the administration of atropine. Effects that are blocked by atropine are termed *muscarinic effects*, named after a substance isolated from the poisonous mushroom *Amanita muscaria*, which produces these pharmacologic properties. These effects correspond almost directly to the actions of the parasympathetic system. After atropine blockade, higher doses of acetylcholine can elicit another constellation of effects that appear to be very similar to the properties of nicotine. Dale called these *nicotinic effects*.^{1,2}

Modern investigation into the muscarinic receptors that constitute the parasympathetic system has demonstrated that there are at least 5 major subtypes of muscarinic receptors (Table 7-1).³⁻⁷ All muscarinic receptors act via G proteins. Types 1, 3, and 5 activate a G protein that in turn stimulates phospholipase C, which then hydrolyzes phosphatidyl inositol. Ultimately activation of these receptors leads to increased intracellular calcium concentration. Type 2 and 4 receptors activate a different G protein that inhibits adenylate cyclase, activates K⁺ channels, and may also suppress voltage controlled Ca²⁺ channels.

Table 7-1. Types of Muscarinic Receptors

Receptor	Location	Effect	Mechanism	Agonists	Antagonists
M1 (neural)	Cortex, hippocampus Gastric parietal cells Enteric ganglia	Memory? Gastric acid secretion GI motility	Stimulates phospholipase C Increased intracellular Ca ²⁺	Acetylcholine, Oxotremorine	Atropine, Pirenzepine
M2 (cardiac)	SA node Atrium AV node Ventricle	Slowed spontaneous depolarization Shortened action potential duration, decreased contractile force Decreased speed of conduction Decreased contractile force	Inhibition of adenylate cyclase Activation of K ⁺ channels	Acetylcholine	Atropine, Gallamine, AF-DX116
M3	Smooth muscle Vascular endothelium Secretory glands	Contraction Vasodilation Increased secretions	Increased phospholipase C Vasodilation via nitric oxide	Acetylcholine Hexahydrosiladifenidol	Atropine
M4	CNS	?	Like M2 via adenylate cyclase	Acetylcholine	?Himbacine
M5	CNS	?	?Increased phos-pholipase C	Acetylcholine	?

AV, atrioventricular; CNS, central nervous system; GI, gastrointestinal; SA, sinoatrial; ?, unknown

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The most important subgroup of muscarinic receptors for the cardiovascular system are the M2 or cardiac receptors.⁸ Activation of these receptors and alteration of potassium transport produces the negative chronotropic and inotropic effects noted in Table 7-1. Most muscarinic receptors are located in the specialized conduction tissue of the heart, and direct innervation of the myocardium itself is sparse. Effects of muscarinic stimulation lead to a decreased rate of spontaneous depolarization of the sinoatrial (SA) node, a consequent delay in the achievement of threshold potential, and a slowing of spontaneous firing. The rate of conduction in the atrioventricular (AV) node is also decreased, and the refractory period to repetitive stimulation is prolonged. The effects of mus-

carinic receptors on the contractility of the ventricle are substantially less intense than on the conduction system.⁹ Blockade of cholinergic receptors produces positive inotropic effects; negative inotropic effects with cholinergic stimulation can be demonstrated in experimental situations. The clinical relevance of the aforementioned effects remains unknown.^{1,9,10} All effects of muscarinic stimulation are enhanced in the context of activation of the sympathetic nervous system. M3 receptors have vasodilatory properties. Since direct muscarinic innervation of the vasculature has not been demonstrated and acetylcholine is a local neurotransmitter, the exact role of these receptors as part of the parasympathetic nervous system is debatable. It appears that the pharmacologic effect of M3

Selective and Nonselective Dopamine-Receptor Agonists

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Dopamine, the endogenous precursor of both norepinephrine and epinephrine, is used predominantly in intensive care unit settings as an intravenous pharmacotherapy for patients with ventricular dysfunction and various forms of shock. Dopamine acts at low doses by stimulating specific peripheral dopaminergic receptors, which are classified into 2 major subtypes (Figure 26-1): (1) D_{A1} receptors, which, when stimulated, mediate arterial vasodilation in the coronary, renal, cerebral, and mes-

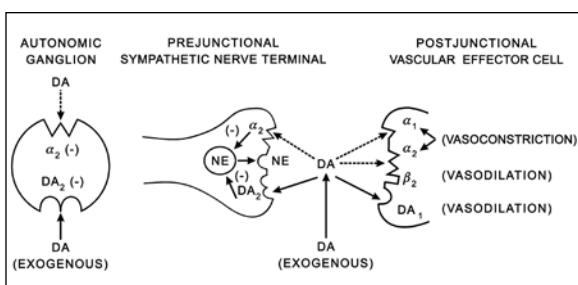


Figure 26-1. Receptors α_2 and D_2 are located on the autonomic ganglion and prejunctional sympathetic nerve terminal to inhibit release of norepinephrine. Receptors α_1 and α_2 are located on the postjunctional vascular effector cell to cause vasoconstriction. D_1 receptors and β_2 adrenoceptors are also located on the postjunctional vascular effector cell and induce vasodilation. When dopamine is injected exogenously, it acts on D_1 and D_2 receptors at lower doses and on α_1 and α_2 adrenoceptors at higher doses. Dopamine has little or no effect on β_2 adrenoceptors. Dopamine also acts on β_1 adrenoceptors on myocardial cells to increase cardiac contractility.

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enteric arteries as well as natriuresis and diuresis; and (2) D_{A2} receptors, which are located in presynaptic areas and, when stimulated, mediate the inhibition of norepinephrine release.¹⁻³ At increasingly higher doses, dopamine, in addition, selectively activates the β_1 -adrenergic receptors, leading to both a positive inotropic and a chronotropic effect on the heart (see Chapter 13, Inotropic Agents). Next, the α_1 - and α_2 -adrenergic receptors are activated, leading to an increase in systemic vascular resistance and blood pressure due to vasoconstriction (Table 26-1).

For a number of years, there has been interest in developing new pharmacologic agents that share some of the qualities of dopamine but have their own unique advantages. Each is an agonist at one or both of the peripheral dopaminergic receptors (Table 26-2).

Fenoldopam is an intravenous dopamine agonist that has specificity for the D_1 receptor and had been used in the treatment of congestive heart failure (CHF); it is approved for use in hypertensive emergencies. The pharmacologic action of fenoldopam is to dilate selected arteries, and it has the advantage of maintaining renal perfusion, despite reducing blood pressure. Problems with the drug's oral bioavailability have limited its use to parenteral treatment of severe hypertension.

In this chapter, the clinical pharmacology of the dopaminergic agonists are reviewed, and the peripheral dopaminergic receptors are discussed.

Dopaminergic Receptors

Molecular pharmacologists have divided the dopaminergic receptors into various subtypes. The peripheral dopaminergic receptors, D_{A1} and D_{A2} , have been the target

Table 26-1. Adrenergic and Dopaminergic Receptors: Locations, Roles, and Agonists

Receptors	Location	Roles	Agonists
α_1	Postsynaptic	↑ Vascular contraction and cardiac inotropism	PE, NE, E, EP, DA
α_2	Presynaptic	↑ Vascular (vein) contraction	E, NE, EP, DA
	Postsynaptic	↓ NE & renin release, ↓ H ₂ O, Na ⁺ reabsorption	
β_1	Postsynaptic	↑ Cardiac inotropism and chronotropism, ↑ Lipolysis	I, NE, EP, DA
β_2	Presynaptic	↑ Vasodilation (artery)	I, EP
	Postsynaptic	↑ NE and renin release, ↑ Cardiac chronotropism and inotropism	
D _{A1}	Postsynaptic	↑ Vasodilation, ↓ H ₂ O, Na ⁺ reabsorption	Fenoldopam, EP, DA
D _{A2}	Presynaptic	↓ Ganglionic transmission, ↓ NE and aldosterone release	Bromocriptine, EP, DA

PE = phenylephrine; NE = norepinephrine; E = epinephrine; EP = epinine; DA = dopamine; I = isoproterenol; ↑ = increase; ↓ = decrease.

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Table 26-2. Actions of Dopaminergic Agonists and Their Oral Availability

	Dopamine	Fenoldopam	Bromocriptine
D _{A1} (vasodilation)	+++	+++	–
D _{A2} (vasodilation, Emisis inhibits prolactin)	+++	–	+++
a (vasoconstriction)	++	–	–
b ₁ (inotropic, chronotropic)	–	++	–
b ₂ (vasodilation)	+	–	–
Oral availability	–	minimal	yes

+++ , major action; ++ , moderate action; + , minimal action; – , no action.

Adapted with permission from Frishman WH, Hotchkiss H. Selective and nonselective dopamine-receptor agonists. In: Frishman WH, Sonnenblick EH, Sica DA, eds. *Cardiovascular Pharmacotherapeutics*. 2nd ed. New York: McGraw-Hill; 2003:445.

of various cardiovascular pharmacotherapies that do not cross the blood–brain barrier and therefore do not affect the central nervous system's dopaminergic receptors. A number of distinct dopamine receptors in the central nervous system have been found.⁴ They have been broken down into 2 groups: D₁-like and D₂-like. The D₁-like group includes the specific receptors D_{1A}, D_{1B}, and D₅. These are G protein–linked receptors that stimulate adenylate cyclase, causing an increase in intracellular cAMP. The D₂-like group includes D₂, D₃, and D₄. These are also G protein–linked receptors, but they inhibit adenylate cyclase and thus also the formation of cAMP.

The D₁- and D₂-like receptors are all distinct; however, they are currently grouped on the basis of their similarities. The peripheral dopamine receptors have a different nomenclature and are classified into 2 distinct families—D_{A1} and D_{A2} receptors.^{5,6} Studies have found the D_{A1} receptors to be similar to the D₁-like central receptors and the D_{A2} receptors to be similar to the D₂-like central receptors. However, additional study is required before a firm conclusion can be made regarding the significance of these similarities. The remainder of this chapter concentrates solely on the peripheral dopamine receptors and their activation.

Pediatric Cardiovascular Pharmacology

32

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Paul Woolf, MD

William H. Frishman

Infants and children with cardiovascular disorders, even those with complex problems, are living through childhood into their adult years. The quality of life, with growth, development, and successful psychologic maturation as markers, continues to steadily improve as well for these patients. Much of this success is related to better refinement of pharmacologic supports, which has developed through increased understanding of the interplay of developing biologic systems and pharmacotherapeutics.

This chapter reviews several important issues relating to the treatment of cardiovascular problems in infants and children with the broadening spectrum of agents available to the clinician. In many instances, pharmacologic treatments reflect modification of approaches learned from practice in the adult population. In others, novel approaches have been developed specifically for the unique problems encountered in children, either as a result of their primary disorder or as a result of its palliation. In all circumstances, however, documented differences in gastrointestinal physiology, in volumes of distribution, in receptor physiology, and in other key elements of metabolic and circulatory dynamics exist that impact on cardiovascular pharmacotherapeutics. Many of these important differences are reviewed in this chapter as well.

Recognition of the fact that important differences exist between infants and children as compared to adults with regard to pharmacotherapeutics has led to continuing actions on the part of the US Food and Drug Administration (FDA) and the pharmaceutical industry to understand how these differences impact on the use of specific pharmaceuticals.^{1,2} However, given the large amount of information still to be developed, the overall view should be one of a work in progress, as each day more and more agents become officially approved for use in children with attendant modification and alteration.

Finally, this chapter builds upon the information de-

veloped in the pediatric chapter in previous editions of this text, reiterating important points made in those efforts, amplifying them where appropriate, and updating them as new information has developed.

There are important conditions that do have overlap between the adult and pediatric populations, and we will start with a review of the pharmacotherapeutics of these problems.

Congestive Heart Failure

Table 32-1 reviews the causes of congestive heart failure (CHF) in childhood. Most of these problems are amenable to surgical correction or to substantial palliation of the underlying anatomic disorder. An important proportion, however, are related to either inherited or acquired problems of cardiac muscle mechanics.³ Survival in this population is generally increasing, although recovery can require an extended period, even as long as several years.^{4,5} Thus, medical therapy has become increasingly important in the childhood management of CHF for a variety of reasons: (1) to allow underlying reparative mechanisms to develop after acquired or iatrogenic acute insults to cardiac muscle; (2) to enable chronic survival while awaiting extreme interventions, such as orthotopic transplantation or longer-term mechanical supports; (3) to improve lifestyle quality after surgical intervention for complete repair or for palliation.

Inotropes and Vasopressors

Digoxin

In the pediatric population, digoxin remains the most extensively used digitalis glycoside and, essentially, the only inotropic agent available for oral administration. The

Table 32-1. Etiologic Considerations for Congestive Heart Failure

Congenital Heart Disease	Acquired Heart Disease	Endocrine-Metabolic	Other
Pressure Overload <ul style="list-style-type: none"> • LV outflow obstruction (eg, aortic stenosis, severe coarctation) • LV inflow obstruction (eg, cor triatriatum) Hypoglycemia Volume Overload <ul style="list-style-type: none"> • L→R shunts (eg, ventricular septal defect) • Anomalous pulmonary venous return • Valvular regurgitation (eg, aortic insufficiency) • Arteriovenous fistulae Other Structural Disease <ul style="list-style-type: none"> • Anomalous coronary artery • Traumatic injury Rhythm Disturbance <ul style="list-style-type: none"> • SVT • Complete heart block Postoperative Heart Disease <ul style="list-style-type: none"> • Malfunctioning prosthetic valve 	Myocarditis <ul style="list-style-type: none"> • Viral infections • Kawasaki disease • Collagen-vascular disease Cardiomyopathy <ul style="list-style-type: none"> • Chronic anemia (eg, thalassemia major) • Nutritional disorders • AIDS Pericardial Disease Rheumatic Heart Disease Cor Pulmonale <ul style="list-style-type: none"> • Acute (eg, upper airway obstructions) • Cystic fibrosis • Neuropathies • Endocarditis 	Electrolyte Disturbance Hypothyroidism Calcium/Magnesium Disorders Lipid Disorders <ul style="list-style-type: none"> • Carnitine deficiency • Carbolic acid disorders • Fatty acid disorders Storage disease	Ingestions/Toxins <ul style="list-style-type: none"> • Cardiac toxins (eg, digitalis) Arrhythmogenics (eg, tricyclic antidepressants) Chemotherapy Agents (eg, adriamycin)

LV = left ventricular; L→R = left to right; AIDS = acquired immunodeficiency syndrome; SVT = supraventricular tachycardi

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desired effects of digoxin are mechanical and electrical; that is, to improve contractility of the failing heart and prolong the refractory period of the atrioventricular (AV) node, respectively (see Chapter 13, Inotropic Agents). Inhibition of the sarcolemmal Na^+/K^+ -ATPase pump with an associated increase in available intracellular calcium results in digoxin's positive inotropic effect. It slows conduction velocity and increases refractoriness at the AV node, mediated mostly through its vagal effect. In canine studies, the electrophysiologic effects of digoxin are less pronounced in neonatal Purkinje fibers than they are in human adult myocardium.⁶ This difference may be related, in part, to the increased concentrations of Na^+/K^+ -ATPase (the enzyme inhibited by digoxin) in the neonatal myocardium.

Digoxin is used in a variety of circumstances causing CHF. In infants with large left-to-right shunts or with severe valvular regurgitation, surgical correction is pre-

ferred, but when not feasible, digoxin may help with the accommodation to large-volume loads. This has been a controversial indication because in many of these situations, normal or even increased myocardial contractility is present. In this circumstance, if useful at all, the effect of digoxin on sympathetic tone is probably key as it helps to counter the catabolic effects of increased catecholamine output in these infants. The classic indication for digoxin involves diminished myocardial performance, when it is used in conjunction with diuretics and afterload reduction agents.

Digoxin toxicity is relatively common because of the drug's narrow therapeutic window. As in adults, digoxin toxicity in children includes sinus bradycardia, sinus arrest, complete AV block, and ventricular arrhythmias.⁷ Other effects include anorexia in older children and vomiting in infants, as well as central nervous system (CNS) disturbances. A variety of drugs may predispose to di-

Appendix 2

Therapeutic Use of Available Cardiovascular Drugs

Alpha-Adrenergic Blockers

1. Doxazosin (doxazosin, Cardura)

Indications

Hypertension
Benign prostatic hyperplasia (BPH)

Dosage

Adults

As an antihypertensive, initiate at 1 mg/d. Dosage may be increased gradually according to blood pressure response. May increase every 1-2 weeks to 2, 4, 8, and 16 mg/d as needed.

Elderly

Initiate at lowest dose and titrate to response.

Children

Safety and efficacy have not been established.

Preparations

Doxazosin (generic); Cardura (Pfizer): 1, 2, 4, and 8 mg tablets

2. Prazosin (Prazosin, Minipress)

Indication

Hypertension

Dosage

Adults

As an antihypertensive, initiate therapy at 1 mg two to three times daily and slowly increase to the usual maintenance dose of 6-15 mg/d in divided doses. Most patients can be maintained on a twice-daily regimen after

initial titration. Doses above 20 mg usually do not have increased effect. Some patients may respond to up to 40 mg/d.

Elderly

Initiate at lowest dose and titrate to response.

Children

Safety and efficacy have not been established. However, there has been some experience with the use of this drug in children and the following dosage regimen has been suggested: for children younger than 7 years: Initiate at 250 μ g (0.25 mg) two to three times daily and adjust to response. For children 7-12 years, initiate at 500 μ g (0.5 mg) two to three times daily and adjust to response.

Preparations

Prazosin (generic); Minipress (Pfizer): 1, 2, 5 mg capsules.

Fixed-Dose Combinations for Treatment of Hypertension:

Minizide-prazosin/polythiazide combination tablet: 1 mg/0.5 mg, 2 mg/0.5 mg, 5 mg/0.5 mg

3. Terazosin (Terazosin, Hytrin)

Indications

Hypertension
Benign prostatic hyperplasia (BPH)

Dosage

Adults

As an antihypertensive, initiate therapy with 1 mg at bedtime. Dosage may be increased slowly to achieve desired response. There seems to be little benefit in exceeding a dose of 20 mg/d. Usual maintenance dose is 1-5 mg/d.

Elderly

Initiate at lowest dose and titrate to response.

Children

Safety and efficacy have not been established.

Preparations

Terazosin (generic); Hytrin (Abbott Laboratories): 1, 2, 5, 10 mg capsules

4. Phenoxybenzamine (Dibenzylamine)

Indication

Symptomatic management of pheochromocytoma

Dosage

Adults

Initiate with 10 mg twice daily. Dose may be increased every other day by 10 mg until the desired response is obtained. Usual dose range is 20-40 mg two to three times per day. Phenoxybenzamine may be used concurrently with a beta-blocker if troublesome tachycardia coexists.

Elderly

Initiate at lowest dose and titrate to response.

Children

Safety and efficacy have not been established. However, there has been some experience with the use of this drug in children, and the following dosage regimen has been suggested: initiate at 0.2 mg/kg once daily (maximum dose of 10 mg/d). Dosage may be increased gradually by 0.2 mg/kg increments until an adequate response is achieved. The usual pediatric maintenance dosage is 0.4-1.2 mg/kg/d given every 6-8 h; higher doses may be needed in some cases.

Preparation

Dibenzylamine (Wellspring): 10 mg capsules

5. Phentolamine (Regitine)

Indications

Diagnosis of pheochromocytoma

Prevention/control of hypertensive episodes that may occur in a patient with pheochromocytoma as a result of stress or manipulation during preoperative preparation and surgical excision

Prevention/treatment of dermal necrosis and sloughing following intravenous administration or extravasation of norepinephrine

Dosage

Prevention/control of hypertensive episodes associated with pheochromocytoma

Adults

Preoperative—5 mg (1 mg for children) administered intravenously (IV) or intramuscularly (IM) 1-2 h before surgery and repeat if indicated.

Intraoperative—5 mg IV (1 mg for children) and repeat as indicated to prevent or control paroxysms of hypertension, tachycardia, respiratory depression, convulsions, or other effects related to epinephrine intoxication.

Elderly

No dosage adjustment is required.

Children

Use lower dose in children as described above.

Prevention/treatment of dermal necrosis and sloughing associated with IV norepinephrine:

Adults

Prevention—10 mg of phentolamine is added to each liter of norepinephrine solution.

Treatment—Initiate within 12 h (as soon as possible) of extravasation; 5-10 mg of phentolamine in 10 mL of 0.9% sodium chloride is infiltrated into the area using a small needle syringe.

Diagnosis of pheochromocytoma (not the first test of choice; all nonessential medications should be withheld for at least 24 h prior to the test):

Adults

5 mg IV or IM (1 mg IV or 3 mg IM for children) is administered. Five milligrams of phentolamine should be dissolved in 1 mL of sterile water for injection before administration. Following the IV dose, blood pressure should be monitored immediately, every 30 s for the first 3 min, and every minute for the next 7 min. Following IM dose, blood pressure should be monitored every 5 min for 30-45 min. A blood pressure decrease of at least 35 mmHg systolic and 25 mmHg diastolic within 2 min after IV or 20 min after IM administration of phentolamine is considered a positive test for pheochromocytoma.

Elderly

No dosage adjustment is required.

Children

Use lower dose in children as described above.

Preparation

Phentolamine mesylate for injection (Bedford); Regitine (Ciba): 5 mg vials

Appendix 6

Selected Cardiovascular Medications and Gender Issues

Drug	Evidence for Efficacy in Women	Considerations When Treating Women
<i>Antiplatelet Drugs</i>		
Aspirin	Primary Prevention: US Nurses' Cohort shows decreased MI [†] . Secondary CAD Prevention: Decreases reinfarction [†]	Women have higher rate of hemorrhagic stroke than men; Physician's Health Study showed an increased risk of bleeding when on aspirin; increased risk of bleeding at term in pregnancy; present in breast milk.
Glycoprotein IIb/IIIa antagonists	Effective in women undergoing PTCA	Women have higher risk than men with PTCA but benefit as much from treatment.
<i>Agents that Affect Blood Pressure</i>		
ACE Inhibitors	Post-MI: decreased mortality [†] CHF: decreased mortality [†]	Cough is two to three times greater in women; increased fetal abnormalities possible; present in breast milk.
Angiotensin-II-Receptor Blockers		Increased fetal abnormalities possible
Beta-Blockers	Antihypertension: effective in preventing MI, CVA, and death in women [†] Post-MI: decreases mortality [†]	Present in breast milk; blood levels of propranolol may be higher in men.
Calcium Blockers	Increased risk of MI in women [†] Increased effect of amlodipine in women in reducing blood pressure [†]	Edema may be more common in women; verapamil clearance may be greater in women than in men; present in breast milk.
Clonidine	No data about efficacy in women	Inability to achieve orgasm; possible decreased craving for tobacco more common in women [†]
Thiazide Diuretics	Decreased CVA, MI, death [†]	Decreased urinary calcium excretion; women have greater increase in risk of gout; acute pulmonary edema and allergic interstitial pneumonitis is more common in women; excreted in breast milk.
Guanethidine		Orthostatic hypotension more common in women.
Hydralazine	Effective in hypertension in pregnancy and peripartum	SLE more common in women than men; present in breast milk

(Table continued on p. 744.)

Appendix 8

Selected Cardiovascular Medications and Ethnic Issues

Drug or Drug Class	Evidence of Efficacy in Various Ethnic Groups	Consideration in Treatment
<i>α-Adrenergic Antagonists</i>	Prazosin is less effective in blacks.	Blacks may need higher doses, generally a second-line agent.
<i>Beta-Blockers</i>		
Propranolol	No difference in plasma concentrations of propranolol between Malays, Indians, and Chinese. Compared to white patients, black patients have lower plasma concentration of propranolol when this drug is taken orally. S-isomer clears more slowly than R-isomer. All metabolic pathways have higher metabolic rates in blacks as compared to whites. Chinese have lower plasma concentrations and higher clearance of propranolol, mainly secondary to increased ring oxidation and conjugation.	Blacks may need higher doses of propranolol to achieve same effects as whites.
Metoprolol	No differences in metabolism of metoprolol between whites and blacks in the United States; Chinese have a higher incidence of slow metabolizers (with one or two copies of CYP2D6*10) and have significantly higher plasma concentrations of R- and S-metoprolol. The S-isomer (which confers beta-blocking activity) reaches higher concentrations than the R-isomer. In poor metabolizers, there is a lasting effect after 24 hours, which correlates with reduced clearance of the S-isomer.	Lower doses of metoprolol are required in Chinese.
Others	Response of blacks to other beta-blockers is similar to the response of whites. Labetalol and nebivolol seem to be effective in blacks. Carvedilol was effective in CHF treatment in all subgroups. In blacks, bucindolol was worse than placebo in advanced heart failure. Unusually high plasma concentrations of alprenolol and timolol have been found in subjects with CYP2D6-poor metabolizer phenotype. The plasma concentrations and the degree of beta-blockade were greater in subjects with the CYP2D6-PM-phenotype taking timolol.	Carvedilol can be used in blacks for heart failure. Bucindolol should be avoided in blacks with advanced heart failure.

(Table continued on p. 752.)