Cardiovascular Drugs (cont.)

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β-ADRENERGIC RECEPTOR ANTAGONISTS

β-adrenergic receptors are **members** of the superfamily of **G protein–coupled receptors**.

There are at least **three** β-adrenergic receptor subtypes:

1. **β1**, found in **heart** and **coronary blood vessels** predominantly but **also** present in **liver**, **kidneys** and **adipose tissue**.

2. **β2**, found in **lungs**, **muscle** tissue and **most** other **sympathetic** target **organs**.

3. **β3**, located primarily in **adipose tissue**.

Classification of β-Adrenergic Receptor Antagonists (β-Blockers or Class II Antiarrhythmics)

Pharmacological classification	Compound	MOA
Nonselective β-blockers	Propranolol, nadolol, timolol, pindolol, labetalol	Inhibit β1-receptor activation Net effect: decreased cardiac chronotropy and inotropy Inhibit β2 receptor activation Net effect: blocked bronchial relaxation resulting in bronchoconstriction
Selective β1-blockers	Metoprolol, atenolol, esmolol, acebutolol, bisoprolol	Predominantly inhibit β1-receptor activation Net effect: decreased cardiac chronotropy and inotropy
β-Blockers with vasodilation activity	Carvedilol, bucindolol, nebivolol	In addition to β-receptor antagonism, significant vasodilation with decrease in blood pressure

Upon β-receptor occupation, **G proteins** undergo a **conformational change** that **activates adenylyl cyclase**.

The enhanced enzyme activity **results** in **increased** levels of **intracellular cAMP**, which stimulates protein kinase A, **phosphorylates Ca^{2+} channels** and **allows Ca^{2+}** to **enter** into the **cell**.

The influx of Ca^{2+} **triggers additional Ca^{2+}** to **release** from the **SR**.

β1-receptors stimulation results in **increased chronotropy and inotropy** in the **heart**, as well as **increased renin secretion** by the kidneys, **both** of which **result** in **increase blood pressure**.

β2-receptors stimulation activates **relaxation** of **smooth muscle** cells in **blood vessels** and the **bronchial tree**.

The β3-receptor stimulation appears to be involved in the **increased metabolism** of **lipid**.

Pharmacology and Clinical Use

β-adrenergic receptor **antagonists** (β-blockers) **inhibit sympathetic stimulation**.

As a result, **heart rate** and **blood pressure decrease** in response to the adrenergic receptor inhibition.

Consequently, the drugs are among the primary pharmacological modality **used** in the **treatment** of **hypertension, ischemic heart disease, congestive heart failure** and certain **arrhythmias**.

Non-CV and off-label uses include the **treatment** of essential tremor, pheochromocytoma, glaucoma, anxiety and migraine headaches.

Due to their **broad clinical applications** and availability, β-blocker **overdoses** and **intoxications** are **commonly** encountered.

Clinical Manifestations of Toxicity

The **toxicology** of **β-blocker** overdose is an **extension** of the **pharmacology** that is, the drugs **cause** deleterious **effects** on the **CV** system**, CNS** and **pulmonary system** through **excessive inhibition** of β-adrenergic receptors.

Cardiac toxicity presents as **bradycardia**, **conduction delay**, and **decreased cardiac contractibility** with systemic **hypotension**.

Cardiotoxicity of β-blockers, however, may also be mediated through disruption of ion transport and homeostasis in cardiac muscle cells.

Manifestations of **CNS toxicity** in severe intoxication include **psychosis, loss of consciousness** and **seizures**.

The **mechanism** underlying **CNS toxicity** is **unclear** but **may** be associated with **cellular hypoxia** resulting from **suppressed cardiac output** or direct neuronal toxicity.

Blocking β2-receptors in bronchial smooth muscle **may** also precipitate **life-threatening bronchoconstriction** in patients with predisposition to pulmonary disease.

Clinical Management of Intoxication

The **goal** of clinical **management** of β-blocker intoxication is to **restore perfusion** to **critical organs** by **improving myocardial contractility** or **increasing heart rate** or **both**.

General measures include **supportive care** and **GI decontamination**.

Pharmacotherapy includes the **use** of **glucagon, β-adrenergic receptor agonists, phosphodiesterase inhibitors and atropine**.

Glucagon enhances cardiac performance by **increasing intracellular cAMP** through action on distinct **glucagon receptors** on **cardiac muscle cells**, thus **restoring** suppressed **cardiac function**.

CALCIUM CHANNEL ANTAGONISTS

Pharmacology and Clinical Use

Ca^{2+} channel antagonists **affect** the **contractility** of **both smooth** and **cardiac muscle cells**.

Physiologically, **three** distinct **mechanisms** have been suggested to **lead** to **increased levels** of **cytosolic Ca^{2+}** and the subsequent **contraction** of **smooth muscle**:

1. **Extracellular Ca^{2+} enters** the **muscle cell through voltage-sensitive Ca^{2+} channels** in **response** to the **depolarization of** the **membrane**.
2. **Inositol triphosphate** (a second messenger) mediates **release** of **Ca^{2+} from** the **SR**.
3. There is **influx of extracellular Ca^{2+} via receptor-operated Ca^{2+} channels** in **response** to **receptor occupancy**.

Classification of Ca^{2+} Channel Antagonists (Class IV Antiarrhythmics)

Chemical classification	Compound	MOA
Phenylalkylamines	Verapamil	Diminished inward movement of Ca^{2+} through the L-type voltage-dependent Ca^{2+} channels located in sarcolemma
Benzothiazepines	Diltiazem	Similar mechanism as with the phenylalkylamines
Dihydropyridines	Amlodipine Felodipine Isradipine Nicardipine Nifedipine Nimodipine Nisoldipine	In addition to the above, a greater degree of peripheral vasodilation
Diarylaminopropylamine esters	Bepridil	Similar mechanism as with the phenylalkylamines

All of the **Ca^{2+} channel antagonists** are capable of inducing **relaxation** of **vascular smooth muscle**, resulting in **vasodilation**.

By **blocking** the L-type **voltage-dependent Ca^{2+} channels**, Ca^{2+} channel antagonists exert a **negative inotropic effect** on the **myocardium**.

Depolarization of **SA** and **AV nodes** is also largely **dependent** on the **influx** of **extracellular Ca^{2+}** through the L-type channels.

Therefore, **Ca^{2+} channel antagonists** have the potential to **depress** the **rate** of the **sinus node pacemaker** and to **slow AV conduction**.

In addition, **Ca^{2+} channel antagonists** are able to **decrease coronary vascular resistance** and thereby **increase coronary blood flow**.

In view of the above pharmacological effects, **the drugs** are efficacious in the **treatment** of **various types of CV disorders, including hypertension, angina pectoris, myocardial infarction, and cardiac arrhythmias**.

Clinical Manifestations of Toxicity

The **most common toxic effects** caused by the Ca^{2+} channel antagonists, particularly the dihydropyridines, are **due to excessive vasodilation**.

These effects may be manifest as **dizziness, hypotension, headache, flushing, and nausea**.

Patients **may also** experience **constipation, peripheral edema, coughing, wheezing, and pulmonary edema**.

At **moderate toxic doses**, **dihydropyridines** are well recognized to produce **reflex increases** in **heart rate** with an **increase** in **left ventricular stroke volume**, **leading** to an **increase** in **cardiac output**.

With **severe overdoses** that result in dramatic Ca^{2+} channel blockage, **all Ca^{2+} channel antagonists exert a negative inotropic effect with depressed cardiac contraction, conduction blockage, hypotension,** and **shock**.

Other overdose **effects** may present as **metabolic acidosis with hyperglycemia**.

The **mechanism of hyperglycemia** is likely related to the **suppressive effect** of the drugs **on pancreatic β-cell insulin release**.

Clinical Management of Intoxication

Patients with **unexplained hypotension and conduction abnormalities**, followed by careful history, may suggest **overdose** with **Ca^{2+} channel blockers**.

As the toxicity produces significant morbidity and mortality, general **management** revolves around providing **supportive care, decreasing drug absorption,** and **augmenting myocardial function with cardiotonic agents**.

Cardiotonic drugs may include **glucagon, atropine,** and **catecholamines**.

IV calcium salts is the **first-line treatment** of Ca^{2+} channel **antagonist overdoses**.

OTHER CV DRUGS

Pharmacological classification	Compound	MOA
ACE inhibitors	Benazepril, captopril, enalapril, enalaprilat, fosinopril sodium, lisinopril, moexipril, perinopril, quinapril, ramipril, trandolapril	Block ACE, thereby decreasing the formation of angiotensin II—net effect: vasodilation
Direct vasodilators	Hydralazine	Activates guanylate cyclase, resulting in vascular smooth muscle relaxation and vasodilation
	Minoxidil	Metabolite activates ATP-sensitive K^+ channels and hyperpolarizes arterial smooth muscle cells, resulting in vasodilation
	Diazoxide	Similar to minoxidil
	Nitroprusside	Metabolized to nitric oxide, which produces vasodilation as per hydralazine
Antiarrhythmic agents	*Class IA*: disopyramide, procainamide, quinidine	Block Na^+ and K^+ channels Depress rapid action potential upstroke Decrease conduction velocity Prolong repolarization
	Class IB: lidocaine, mexiletine, moricizine, tocainide	Weakly block Na^+ channels Depress rapid action potential upstroke Decrease conduction velocity Prolong repolarization
	Class IC: flecainide, propafenone	Strongly block Na^+ channels Depress rapid action potential upstroke No effect on conduction velocity, repolarization, or K^+ channels
	Class III: amiodarone, bretylium, sotalol[a]	Block K^+ channels Depress repolarization No effect on Na^+ channels

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors **block ACE**, thereby **decreasing** the **formation** of **angiotensin II**, a **potent vasopressor**, which is critically involved in **raising** systemic **blood pressure**.

As such, **ACE inhibitors** are commonly **used** in the **treatment** of **hypertension**.

These drugs are **also** effective in the **treatment** of **congestive heart failure, left ventricular systolic dysfunction**, acute **myocardial infarction,** and **chronic renal disease**.

Hypotension is the **most common** manifestation in patients with **ACE inhibitor overdoses**.

Adverse effects reported at **therapeutic doses** include first dose **hypotension, headache, cough, hyperkalemia, dermatitis, renal dysfunction,** and **angioedema**.

The drugs may also cause **adverse fetal effects**; thus, this class of drugs is **contraindicated** in **pregnancy**.

Direct Vasodilators

The direct vasodilators represent another **class of antihypertensive drugs** also used in the **management** of **angina pectoris, congestive heart failure,** and peripheral vascular disease, which relax vascular smooth muscle independent of innervation or known pharmacological receptors.

Among these, the **most** potentially **toxic** agent capable of inducing **both arterial** and **venous vasodilation** is **nitroprusside**.

Hydralazine activates guanylate cyclase, which precipitates an **increased** cyclic guanosine monophosphate (**cGMP**) in arterial vascular smooth muscle, **resulting** in vascular **smooth muscle relaxation** and **vasodilation**.

Formation of **cGMP** results in **decreased** levels of **cytosolic Ca^{2+}** in **smooth muscle**.

Minoxidil undergoes **hepatic biotransformation**, producing the active N-O **sulfate metabolite**.

Minoxidil sulfate is able to **activate** the adenosine triphosphate **(ATP)- sensitive K^+ channels**, which causes **vasodilation by hyperpolarizing arterial smooth muscle cells**.

The drug has **proven** to be **effective** in patients with the most **severe** and **drug-resistant forms** of **hypertension**.

Diazoxide also produces **vasodilation** via **activation** of **ATP-sensitive K^+ channels**.

This drug is clinically used in the **treatment** of **hypertensive emergencies**.

Nitroprusside is **metabolized** by the vessel wall to form **nitric oxide,** which **activates guanylyl cyclase, increases** levels of **cGMP**, and produces subsequent **vasodilation**.

Nitroprusside is **used** mainly in the **treatment** of **hypertensive emergencies**.

Two types of adverse effects have been observed with **hydralazine intoxication**:

1. Toxicity due to **extensions** of the **pharmacological effects** of the drug, including **hypotension, headache, nausea, flushing, palpitation, dizziness, tachycardia,** and **angina pectoris**.

2. **Hydralazine-induced autoimmune reactions**, including **lupus syndrome, vasolitis, serum sickness, hemolytic anemia,** and **rapidly progressive glomerulonephritis**. The **reactions** probably **result** from **T-cell autoreactivity**.

The clinical manifestations of **minoxidil intoxication** may include **edema, CV compromise, hypertrichosis, hypotension, tachycardia,** and **lethargy**.

Hypertrichosis occurs in all patients who receive **minoxidil** for an **extended period of time** and is probably a consequence of K^+ channel activation.

The most common manifestations of **diazoxide intoxication** are **myocardial ischemia, peripheral and systemic edema,** and **hyperglycemia**.

Myocardial ischemia may be precipitated or aggravated by diazoxide, and it **results from** the reflex **adrenergic stimulation of the heart** and **from increased blood flow to nonischemic regions**.

Hyperglycemia appears to **result** from its **inhibition** of the **secretion** of **insulin** from **pancreatic β-cells**.

The short-term **toxic effects** of **nitroprusside** are caused by **excessive vasodilation** and ensuing **hypotension**.

Toxicity may **also** result from the **conversion** of **nitroprusside** to **cyanide** and **thiocyanate**.

Nitroprusside-induced cyanide poisoning is a result of development of an anion gap **metabolic acidosis**.

Cardiac failure, asystole, and **ventricular dysrhythmias** are serious CV terminal events, initially **presenting as restlessness** and **agitation**, and may progress to **convulsion**.

Encephalopathy, coma, and **cerebral death** often occur **simultaneously with** the terminal **CV event**.

The **management** of vasodilator intoxication includes **general supportive measures** and **correction** of **hypotension** and **cardiac arrhythmias**.

Ca^{2+} channel antagonists and **β-adrenergic receptor antagonists** may be **useful** in the **treatment** of **myocardial ischemia caused by** the **vasodilators**.

Discontinuation of **nitroprusside** administration, followed by **oxygen supplementation**, is essential for **nitroprusside-suspected cyanide toxicity**.

As with cyanide toxicity, **sodium nitrite** and **sodium thiosulfate** should be **given immediately** to enhance transsulfuration of **cyanide to thiocyanate**.

Antiarrhythmic Drugs

Antiarrhythmic drugs are used in the **treatment** of **cardiac arrhythmias** and have selective **classification** based on the **mechanisms of action**.

The drugs, classification, and MOA are briefly stated:

1. Class I depress myocardial **Na^+ channels**.
2. Class II possess **sympatholytic** activities, such as the **β-adrenergic receptor antagonists**.
3. Class III depress **K^+ channels** and prolong action potential duration and refractoriness.
4. Class IV are **Ca^{2+} channel antagonists**.

The most severe manifestation of **class IA intoxication** is CV compromise, including **sinus tachycardia, cardiac arrhythmia** with **ventricular tachycardia**, and **fatal ventricular fibrillation**.

Depressed myocardial contractility frequently **manifests** as **vasodilation and hypotension**.

CNS toxicity presents as lethargy, confusion, coma, respiratory depression, and seizure.

Quinidine intoxication causes cinchonism, a symptom complex that includes headache, tinnitus, vertigo, and blurred vision.

Diarrhea is the most **common adverse effect** during **quinidine therapy**.

Disopyramide also has **strong anticholinergic** activity, which can be manifest as precipitation of **glaucoma, constipation, dry mouth,** and **urinary retention**.

Class IB and **IC drug toxicity** is marked by similar **cardiac effects as** with **class IA drugs**.

CNS toxicity is **more common** and may be manifest as **confusion, coma, seizure, nystagmus** (an early sign of lidocaine toxicity), **tremors,** and **nausea**.

Toxicity with **class III** drugs is **not** explained by **blocking of K^+ channels only**.

For example, **sotalol also** has a marked **β-adenergic receptor antagonist** activity, which **explains** most of the **CV compromise** in **overdosage**.

Sotalol intoxication may cause **QT prolongation, bradycardia,** and **hypotension**.

Coma, respiratory depression, seizure, and **ventricular dysrhythmia** occur in **severe sotalol overdoses**.

Acute amiodarone toxicity following overdose is **rare** but may include **hypotension**.

Although the mechanism is not understood, **pulmonary fibrosis** is a known complication of **chronic amiodarone therapy,** there is currently **no** effective **treatment** for the **condition**, and it carries a **poor prognosis**.

Clinical **management** of **intoxication** with **class I and III** antiarrhythmic drugs follows **general supportive measures** and **institution** of the **ABCs** of emergency care.

The **slow absorption of amiodarone** allows for **late GI decontamination** in cases of significant ingestion, while **sodium bicarbonate** is **effective** in the **treatment** of the **cardiotoxic effects** of **class IA** and **IC** drugs.