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.

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.

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

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.