2.1.6 Drugs that affect the cardiovascular system

2.1.6.1 Antidysrhythmics
  2.1.6.1.1 Calcium channel blockers
  2.1.6.1.2 Cardiac glycosides
  2.1.6.1.3 Sodium channel blockers

2.1.6.2 Antihypertensives
  2.1.6.2.1 Angiotensin system modulators
  2.1.6.2.2 Beta (and mixed alpha, beta) antagonists
  2.1.6.2.3 Centrally acting alpha receptor agonists
  2.1.6.2.4 Diuretics
  2.1.6.2.5 Vasodilators

2.1.6.3 Inotropes
Cardiac Action Potential

- Phase 0: depolarization
- Phase 1: overshoot
- Phase 2: plateau
- Phase 3: repolarization
- Phase 4: resting

- Phase 0
  - Begins with excitation from a stimulus
  - Fast sodium channels open
  - Rapid depolarization

- Phase 1
  - Sodium channels close
  - Partial outward potassium current occurs
  - Partial repolarization of the membrane
Cardiac Action Potential

- Phase 2
  - Inward calcium current
  - Outward potassium current

Cardiac Action Potential

- Phase 3
  - Calcium channels close
  - Continuation of potassium influx

Cardiac Action Potential

- Phase 4
  - Resting state for much of the myocardium
Antidysrhythmics

- Vaughn-Williams classification
- Based on electrophysiologic properties
- The Sicilian Gambit
  - Developed by European cardiologists
  - Based on mechanisms by which antidysrhythmics modify dysrhythmogenic mechanism
Cardiovascular Toxins

Classes

- Class I: sodium channel blockers
- Subclasses IA, IB, IC
- Class II: beta-adrenergic antagonists
- Class III: potassium channel blockers
- Class IV: calcium channel blockers

Class I

- IA: block Na channels in the resting state
- IB: block Na channels in the inactivate state
- IC: block Na channels in the activated state
Cardiovascular Toxins

Class I

• Examples of class IA
  • Disopyramide
  • Procainamide
  • Quinidine

• Examples of class IB
  • Lidocaine
  • Mexiletine
  • Moricizine
  • Phenytoin
  • Tocainide

• Examples of class IC
  • Flecainide
  • Propafenone
Cardiovascular Toxins

Class III

- Prevent and terminate reentrant dysrhythmias by prolonging the action potential duration and effective refractory period without slowing conduction velocity during phase 0 or 1 of the action potential.
- Amiodarone, dofetilide, ibutilide

Calcium Channel blockers

2.1.6.1.1

Classification

- Phenylalkylamines
- Benzothiazepines
- Dihydropyridines
- Diaryaminopropylamine ethers
- T-channel blockers
Cardiovascular Toxins

Classification

• Phenylalkylamines
  • Verapamil
  • Benzoazepines
  • Diltiazem

• Dihydropyridines
  • Nifedipine, isradipine
  • Amlodipine, felodipine
  • Nimodipine, nisoldipine, nicardipine

• Diarylaminopropylamine ether
  • Bepridil
  • T-channel blocker
  • None (mibefradil withdrawn)
Uses

• Hypertension, angina, dysrhythmias
• Migraine headaches, Raynaud’s phenomenon
• Subarachnoid hemorrhage

Pharmaco/Toxicokinetics

• All well absorbed orally
• Metabolized via CYP3A4
• Saturated in overdose, reducing effect of 1st pass, increasing bioavailability in OD
• All CCBs are highly protein bound

Verapamin & Diltiazem

• In contrast to other, much potential for drug interactions
• CYP3A4 substrate and inhibitors
• Decreases clearance of many drugs
• Also inhibit P-glycoprotein mediated drug transport
Drugs with decreased clearance with verapamil and diltiazem

- Carbamazepine
- Cisapride
- Quinidine
- Many HMG-CoA reductase inhibitors
- Cyclosporine
- Tacrolimus
- Most HIV-protease inhibitors

Pathophysiology

- Ca\(^{2+}\) is integral to excitation-contraction coupling
- L-type (voltage-dependent) Ca\(^{2+}\) channels are located in the plasma membrane of all types of muscle cells

Pathophysiology

- L-type Ca\(^{2+}\) channels
- Composed of homologous protein subunits
- The \(\alpha_1\) subunit is the pore-forming portion of the channel
- Where all CCBs bind to prevent Ca\(^{2+}\) influx
Pathophysiology

- Other Ca\(^{++}\) channels
- N, P, T, Q, R
- Found on sarcoplasmic reticulum (SR) or cell membranes (mainly neuronal and secretory tissue)
- Can be stretch-operated, receptor-operated, or voltage sensitive

Pathophysiology

- Skeletal muscle depends exclusively on intracellular Ca\(^{++}\) stores for E-C coupling
- Intracellular influx is inconsequential
- Cardiac and smooth muscle
- Intracellular influx is critical

Pathophysiology

- Smooth muscle cells
- Ca\(^{++}\) binds calmodulin, resulting complex stimulates myosin light-chain kinase (MLCK)
- MLCK phosphorylates/activates myosin
- Myosin binds actin, causing contraction
Pathophysiology

- Myocardial cells
  - Influx of Ca^{++} creates phase 2 of the AP
  - Ca^{++} binds to and opens Ca^{++} channels on the SR
  - Releases Ca^{++} from the vast store within the SR (Ca^{++} mediated Ca^{++} release)

Pathophysiology

- Myocardial cells
  - Ca^{++} then binds troponin C, causes conformational change
  - Displaces troponin & tropomyosin from actin
  - Allows actin and myosin to bind causing contraction

Pathophysiology

- Ca^{++} influx also important in myocardial conduction
- Ca^{++} influx plays a role in phase 4 spontaneous depolarization in the SA node
Pathophysiology

- All commercially available CCBs antagonize L-type Ca\(^{++}\) channels
- Differences in pharmacologic effect result of receptor affinity and type of antagonism

Pathophysiology

- Vascular smooth muscle
- Cytosolic [Ca\(^{++}\)] maintains basal tone
- Decrease in Ca\(^{++}\) influx = arterial vasodilation
Cardiovascular Toxins

Pathophysiology

• Myocardium
  • Decrease in Ca++ influx
    • Reduced contractility
    • Reduced heart rate
    • Reduced conduction velocity

Pathophysiology

• Each group of CCBs bind slightly different regions of the \( \alpha_1 \) subunit
  • Hence the different clinical effects
  • See Goldfranks 8th Ed, page 915 for discussion of therapeutic effects of different classes of CCBs

Clinical Manifestations

• In overdose, receptor selectivity is lost
  • Hypotension, bradycardia, (death)
  • There are subtle variations in presentations among the classes
Clinical Manifestations

• Hyperglycemia
• Numerous reports of hyperglycemia in severe poisoning
• B islet cell insulin release is dependent on Ca$^{++}$ influx from L-type Ca$^{++}$ channel
• This channel is blocked in severe CCB overdose

Management

• Usual measures typically ineffective in severe poisoning
• Atropine, calcium salts, inotropes, vasopressors
• No role for glucagon
• Insulin

Management

• Insulin
• Under stress, myocardium changes from free fatty acid energy substrate to carbohydrate (CHO)
• Cannot use CHOs because of insulin resistance
• High dose insulin seems to be effective
Cardiac Glycosides

Chemistry

- All cardioactive steroids (CAS) contain
  - Aglycone or “genin” nucleus
  - Steroid core
  - Unsaturated lactone ring at C-17
  - Additional sugar groups at C-3
Oleandrin

Oleandrin lactone ring

steroid core

sugar groups

Aglycone ("genin") nucleus

Image courtesy of Jeff Dahl via Wikimedia Commons

Uses

• Congestive heart failure
• Atrial tachydysrhythmias

Uses

• Most commonly prescribed CAS in US is digoxin
• Internationally available but less commonly used
• Digitoxin, ouabain, lanatoside C, deslanoside, gitalin
Other Sources

- Oleander
- *Nerium oleander, Thevetia peruviana*
- Foxglove (*Digitalis spp.*)
- Lily of the Valley (*Convallaria majalis*)
- Dogbane (*Apocynum cannabinum*)
- *Bufo marinus* toad (bufadionolide cardioactive steroid)

Pharmaco/Toxicokinetics

- Intravascular distribution & elimination of digoxin from plasma are described using the 2-compartment model
- Further discussion on page 973 of GF's

Pharmaco/Toxicokinetics

- Many drug-drug interactions
- These increase digoxin concentration
- Quinidine, verapamil, diltiazem, carvedilol, amiodarone, spironolactone, macrolide antibiotics
Mechanism of Action/Pathophysiology

- CAS increase the force of cardiac contraction (inotropy) by increasing cytosolic Ca\(^{++}\) during systole.

- Inhibit active transport of Na\(^{+}\)/K\(^{-}\) across cell membranes during repolarization
- Binds and inhibits the Na\(^{+}\)-K\(^{-}\)-ATPase
- The Na\(^{+}\)-Ca\(^{++}\) antiporter doesn’t use ATP, relies on Na gradient from the Na\(^{+}\)-K\(^{-}\)-ATPase
- Ca\(^{++}\) extrusion is reduced

Goldfrank's Toxicologic Emergencies, 8th ed
Mechanism of Action/Pathophysiology

- Electrophysiologic effects
- Increase excitability
- Increase automaticity
- Decrease conduction velocity
- Decrease refractoriness
Clinical Manifestations

- Noncardiac
  - Acute
    - Nausea, vomiting, lethargy, confusion, weakness
    - Hyperkalemia
      - Marker of lethality

Clinical Manifestations

- Chronic
  - Insidious and protean

Chronic effects

- Anorexia, nausea, vomiting, abdominal pain, weight loss
- Delirium, headache, hallucinations
- Amblyopia, photophobia, blurry vision
- Scotomata
- Photopsia, reduced visual acuity
- Chromatopsia, xanthopsia
Clinical Manifestations

• Cardiac
  • Every known type of dysrhythmia
    • Except rapidly conducted SVT
  • Bidirectional ventricular tachycardia is nearly diagnostic

Diagnostic Testing

• Serum concentration >2ng/mL 6 hours post ingestion
  • >40ng/mL for digitoxin
  • Assay may cross react with other CAS

Management

• Aggressive supportive care
• If life-threatening toxicity, treat with digoxin-specific antibody fragments (Fab)
Potassium Channel Blockers

2.1.6.1.2

Amiodarone

- Iodinated benzofuran derivative
- Structurally similar to both thyroxine and procainamide
- 40% of molecular weight is iodine
- Weak alpha- and beta-adrenergic antagonism
- Some blockade of Na and L-type Ca channels
Amiodarone

- Metabolized by CYP3A4 to desethylamiodarone (active metabolite)
- Competes for P-glycoprotein
- Increases serum concentrations of digoxin, cyclosporin, warfarin

Amiodarone

- Therapeutic use
  - Various dysrhythmias, particularly atrial fibrillation
  - EKG manifestations
  - Prolong PR and QTC intervals (not QRS)

Amiodarone

- Few reported cases of overdose
- Complications associated with long term use, dose related
  - Pulmonary, thyroid, corneal, hepatic, cutaneous toxicity
  - (all organs where amiodarone bioaccumulates)
Cardiovascular Toxins

Amiodarone

- Pulmonary
  - Pneumonitis, up to 5% of patients
  - Typically occurs after years of therapy
  - May be hastened by supplemental O2
  - CT most useful to make diagnosis

Amiodarone

- Thyroid
  - Approximately 4% of patients
  - Amiodarone-induced thyrotoxicosis (AIT)
  - Amiodarone-induced hypothyroidism (AIH)
  - AIH more common

Amiodarone

- Corneal microdeposits extremely common
- May lead to vision loss
- Abnormal hepatic enzymes occur in >30% of patients
- Slate gray or bluish discoloration of the skin is common
Sodium Channel Blockers

2.1.6.1.3

Class I

- IA: block Na channels in the resting state
- IB: block Na channels in the inactivate state
- IC: block Na channels in the activated state

Class I

- Examples of class IA
  - Disopyramide
  - Procainamide
  - Quinidine
Cardiovascular Toxins

Class I

• Examples of class IB
  • Lidocaine
  • Mexiletine
  • Moricizine
  • Phenytoin
  • Tocainide

Class I

• Examples of class IC
  • Flecainide
  • Propafenone

Management

• Aggressive supportive care with attention to dysrhythmias
• Sodium bicarbonate for widened QRS
Antihypertensives

2.1.6.2.1

Angiotensin System Modulators

Classes

- Angiotensin-converting enzyme inhibitors (ACE-I)
- Antiotensin II receptor blockers
Angiotensin Converting Enzyme Inhibitors

Uses

• Most widely prescribed antihypertensives

Pharmaco/Toxikokinetics

• Well absorbed by GI tract
• Peak plasma concentration in 1-4 hours
• Enalapril & ramipril are prodrugs
• Require hepatic metabolism
• Elimination via kidneys
Pathophysiology

- Core 2-methyl-propranolol-L-proline moiety
- Binds to active site of angiotensin converting enzyme (ACE)
- In lungs and vascular endothelium
- Prevents conversion of angiotensin I to angiotensin II

Captopril

[Chemical structure image]

2-methyl-propranolol-L-proline moiety

Pathophysiology

- Antiogensin II is a potent vasoconstrictor and activator of aldosterone secretion
- ACE inhibition results in
  - Vasodilation, reduced peripheral vascular resistance, reduced blood pressure, increased cardiac output

Image courtesy of Yikrazuul via Wikimedia Commons
Pathophysiology

- Side effects
  - Rash, dysgeusia, neutropenia, hyperkalemia, chronic cough, angioedema
- Teratogen
  - Should not be prescribed in the pregnant or those wanting to be pregnant

Angioedema

- ACE inactivates bradykinin and substance P
- ACE inhibition results in increased bradykinin concentration
- Primary cause of angioedema (and cough)

Angioedema

- Incidence is 0.1%
- 1/3 within hours of 1st dose
- 1/3 within 1st week
- No dose-response relationship
## Clinical Effects

- Overdose
- May present with hypotension
- Rare deaths in isolated overdose

## Management

- Intravenous crystalloid
- Naloxone?
- ACE-Is may inhibit metabolism of enkephalins and potentiate their opioid effects, including BP reduction

## Angiotensin II Receptor Blockers

...
Cardiovascular Toxins

Uses

- Antihypertensive
- Introduced in 1995
- Six member of the class

Pharmacokinetics

- Rapidly absorbed via GI tract
- Peak concentration in 1-4 hours
- Eliminated
  - unchanged in feces or
  - hepatic metabolism (CYP), bile excretion

Pathophysiology

- Antagonize angiotensin II at the type I angiotensin receptor (AT-1 receptor)
- Allows inhibition of angiotensin II without bradykinin effect
- Reduced incidence of cough
- Rare cases of angioedema reported
- Teratogen
Management

• Crystalloid

Beta (and mixed alpha) Antagonists

2.1.6.2.2

Uses

• 18 FDA approved beta blockers
• Used in the treatment of
  • Hypertension, coronary artery disease, tachy dysrhythmias, congestive heart failure, benign essential tremor
  • Panic attacks, stage fright, hyperthyroidism, glaucoma
Pharmaco/Toxicokinetics

- Wide range of
- Bioavailability, volume of distribution, elimination half-life, duration of effect
- Depends on which agent

Pathophysiology

- Already discussed myocyte pathophysiology as it relates to the Ca++ channel
- 3 types of beta receptors
  - beta-1, beta-2, beta-3
  - Focus on beta-1 (main type in heart)

Pathophysiology

- Beta receptors are coupled to Gs proteins
- When triggered, activate adenylate cyclase (AC), which converts ATP to cAMP
- cAMP activated protein kinase A (PKA)
Pathophysiology

- PKA then phosphorylates important myocyte proteins
- Voltage dependent calcium channel
- Enhancing Ca**+** influx
- Sarcoplasmic reticulum Ca**+** channels
- Enhancing Ca**+** release

Pathophysiology

- Beta blockade responsible for
- Reduced chronotropy, dromotropy, ionotropy, blood pressure
Pathophysiology

- Membrane stabilizing effects
  - Beta-antagonists that inhibit fast Na+ channels
  - Type I antidysrhythmic effects
  - Only occurs in overdose
  - Clinical effect is QRS widening

Pathophysiology

- Membrane stabilizing effects (MSE)
  - Agents:
    - Propranolol, oxprenolol, betaxolol, acebutolol

Pathophysiology

- Intrinsic sympathomimetic activity (ISA)
  - Agents that have partial agonism at beta receptors
  - No clinical benefit demonstrated
  - Agents
    - Acebutolol, oxprenolol, penbutolol, pindolol
Cardiovascular Toxins

Pathophysiology

- Potassium channel blockade
- Sotalol
  - Non-selective beta antagonist
  - No ISA, MSE, low lipophilicity
  - Blocks the delayed rectifier K channel

Pathophysiology

- Sotalol
  - Prolongs action potential
  - Increases QTc
  - Predisposes to torsades de pointes and ventricular dysrhythmias

Pathophysiology

- Vasodilation
  - Agents that are also vasodilators
  - Labetalol/carvedilol
  - Nonselective beta blockers that are also alpha-adrenergic antagonists
Cardiovascular Toxins

Pathophysiology

- Vasodilation
- Nebivolol
  - Selective beta-1 activity
  - Causes NO release to produce vasodilation

Pathophysiology

- Vasodilation
- Bucindolol/carteolol
  - Beta-1 blockers
  - Beta-2 agonists
  - Carteolol also has NO effects (but only available as ocular preparation)

Pathophysiology

- Betaxolol
  - Has Ca^{++} blocking effects
Clinical Manifestations

- Hypotension, bradycardia
- Refractory in severe cases
- Propranolol
  - Disproportionate number of deaths
  - Related to prevalence of use and lipophilicity and MSE

Management

- Aggressive supportive care
- Usual measures may be ineffective in severe cases
  - Atropine, inotropes, pressors
  - Glucagon
  - High-dose insulin

Management

- Glucagon
  - Humans have cardiac glucagon receptors
  - Coupled to Gs proteins
  - Trigger the same cascade of events at the beta receptor
Centrally Acting Alpha Receptor Agonists

2.1.6.2.3

Classification

• Imidazolines
  • Clonidine, oxymetazoline, tetrahydrozoline
• Others
  • Methyldopa, guanfacine, granabenz
  • Structurally different but work similarly

Uses

• Antihypertensives
• Clonidine
  • Most commonly used in this category
• Hypertension, ADHD, peripheral nerve & spinal anesthesia, adjunct in withdrawal (opioids, nicotine, ethanol)
Uses

- Other imidazolines
- Oxymetazoline, tetrahydrozoline
  - Ocular topical vasoconstrictors and nasal decongestants
- Similar effects as clonidine when ingested

Pathophysiology

- Clonidine
  - Well absorbed in the GI tract
  - Onset of action is 30-60 minutes
  - Peak plasma concentration in 2-3 hours
  - Lasts up to 8 hours
  - Eliminated unchanged in the kidneys

Pathophysiology

- Guanabenz & guanfacine
  - Structurally and pharmacologically similar
  - Well absorbed orally
  - Peak plasma concentration in 3-5 hours
  - No significant active metabolite
Pathophysiology

- Methyldopa
- Is a prodrug
- 3 active metabolites
  - alpha-methylnorepinephrine
  - alpha-methyldopamine
  - alpha-methylepinephrine

Pathophysiology

- All drugs in this category exert hypotensive activity via stimulation of presynaptic alpha-2-adrenergic receptors in the brain
- Enhances activity of inhibitory neurons in the nucleus tractus solitarius in the medulla

Pathophysiology

- Results in reduced norepinephrine release
- Reduction in heart rate, peripheral vascular tone and blood pressure
Clinical Manifestations

- Exaggeration of clinical effects
- CNS depression, bradycardia, hypotension

Clinical Manifestations

- Abrupt cessation can lead to excess sympathetic activity
- Agitation, insomnia, palpitations, hypertension
- Typically 16-48 hours after cessation

Management

- Supportive care
- Naloxone
- Data are mixed
Diruretics
2.1.6.2.4

Uses

• Antihypertensives

Classification

• 3 classes: thiazides, loops, potassium-sparing
• Thiazides
  • hydrochlorothiazide, chlorthalidone
• Loops
  • Furosemide, bumetanide, ethacrynic acid
Cardiovascular Toxins

Classification

- Potassium sparing
  - Amiloride, triamterene, spironolactone

Pathophysiology

- Thiazides
  - Inhibit Na/Cl reabsorption in the distal convoluted tubule
- Loops
  - Inhibit coupled transport of Na/K/Cl in the ascending loop of Henle

Pathophysiology

- Potassium-sparing
  - Act as aldosterone antagonists (spironolactone) or epithelial Na channel antagonists (triamterene) in the last distal tubule and collecting duct
Clinical Manifestations

• Hyponatremia predominately
• May have hyperkalemia with potassium-sparing diuretics
• Thiazides may increase hyperglycemia in diabetics (secondary to hypokalemia)
• Thiazides increase hyperuricemia, renal calculi, gout

Management

• Supportive care

Vasodilators

2.1.6.2.5
Vasodilators

- Hydralazine, minoxidil, diazoxide, nitroprusside
- All stimulate the release of NO from vascular endothelium resulting in vasodilation

Clinical Manifestations

- Reduction in blood pressure
- Hydralazine adverse effects
  - Hemolytic anemia, vasculitis, glomerulonephritis, lupus-like syndrome
- Nitroprusside adverse effects
  - Cyanide, thiocyanate toxicity

Inotropes

2.1.6.3