Cardiovascular Drugs - 2

Angina, Heart Failure, Arrhythmias

PHRM 203
Allison Beale
Overview

- Angina
  - Typical
  - Variant
  - Unstable
- Heart Failure
- Antiarrhythmics
Ischemic Heart Disease: *Angina*

- The heart doesn’t receive enough $O_2$ to function properly
- **Two forms of ischemic HD**
  - **Acute**
    - Myocardial infarction (MI)
      - Usually due to thrombosis (clot inside a blood vessel)
  - **Chronic**
    - Angina pectoris (typical or stable, unstable and variant)
      - ↓ blood supply due to coronary atherosclerosis (plaques in coronary arteries)
      - MI is in the future
Typical Angina

- AKA: “Classic,” “stable,” or “effort”
  - Pain follows effort or stress
  - No pain at rest
  - Coronary atherosclerosis present

Treat with Nitroglycerin, β blocker or pFOX Θ’r

Resting Exercise Resting Exercise

Coronary artery

Arteriole

O₂ demand Blood flow

+ + ++ +
++ +
++ +
++ +
++ +
Variant angina

- AKA: Prinzmetal’s angina
  - Pain at rest due to *coronary vasospasm*
    - Large coronary arteries spasm for unknown reason
      - May be a problem with the endothelium not releasing Nitric oxide (NO) in response to Vagal stimulation
    - Circulating vasoactive substances?
      - Autocoids?
      - Hormones?

*Treat with CCB or Amyl nitrate*
Unstable angina

- Pain at **rest and with exertion**
- **MI eminent**
  - Thrombus forming at atheroma
    - Atheroma = build up of fat, Ca$^{++}$, and cells in the intima, start of atherosclerosis.
    - Occlusion of artery is complete and causes pain at rest
    - As thrombus is broken down, pain subsides
    - Pain on exertion for same reason as stable a.
    - If the thrombus lingers, MI due to ischemia

Treat with CCB
Typical angina therapy

• Goal = ↓ myocardial O$_2$ demand

1. ↓ Preload (factors stressing - stretching - myocardium at end of diastole)
   – Nitrovasodilators

2. ↓ Myocardial contractility
   – β-blockers (- ionotrope)

3. ↓ Afterload (factors stressing myocardium at the end of systole)
   – Ca$^{++}$ channel blockers (- ionotrope)

4. ↓ Fatty acids as energy source (it takes less O$_2$ to metabolize glucose)
   – pFOX inhibitors
Antianginal Drugs: Vasodilators

♥ Nitrites and nitrates
  • Amyl nitrite
    • Acute Angina and Prinzmetal’s
    • Cyanide poisoning
  Nitroglycerin (Nitro-Bid) & Isosorbide dinitrate
  • Typical Angina or MI
  • Prodrugs that release nitric oxide (NO)
    • Mostly venous vasodilation
  • Pharmacodynamic tolerance to vasodilation effects
  • ADRs: SEVERE headache & hypotension, tachycardia, flushing

⚠ Warning ⚠ don’t take with PDE-5 θ’s like sildenafil!

Light sensitive

Nitro-Bid t ½ ~3 min.
ISDN t ½ ~5 hrs.
Nitroglycerin notes

- Tolerance controlled by keeping 10-12 hour gap between doses
- Lots of formulations
  - Transdermal patch and topical ointment must be applied to non-hairy skin (NOT hands or feet)
    - May still be toxic when “spent”
  - Transdermal patch has aluminum backing
    - Remove patch before defibrillation to avoid damage and burns from arcing

Nitroglycerin is absorbed into the PVC of IV sets, this ↓s dose up to 80%!

Paste may be mistaken for hand cream!

Capsules may be broken and waved under the nose
Antianginal Drugs: 
Ca\(^{++}\) channel blockers

❤ Several unrelated classes

- **Dihydropyridines - smooth muscle selective**
  - Amlodipine (Norvasc)
  - Felodipine (Plendil\(^\circledR\)), Isradipine, Nicardipine, Nifedipine and Nimodipine

- **Benzothiazepine - mixed smooth and cardiac**
  - Diltiazem (Cardizem, Tiazac)

- **Myocardium specific L-type channel blockers**
  - Verapamil (Covera)

Verelan \(\&\) Vivarin (caffeine), Voltaren (diclofenac), Virilon (methyltestosterone)

CCBs must be individually titrated to correct dose

Amiloride (\(K^+\) sparing diuretic)
Cardene (a different CCB)
P450↓
Antianginal Drugs: Calcium Channel Blockers (CCB)

ADRs include:

- Amlodipine PO – HT, angina
  - Edema, palpitations, fatigue, dizziness, flushing, headache
- Diltiazem PO/IV – angina, HT
  - Headaches, edema, dizziness, bradycardia, dyspnea
- Verapamil PO/IV – HT, angina, arrhythmias
  - Arrhythmias, dizziness, headache, exfoliative rash, edema, dyspnea, dark urine, clay-colored stools, jaundice, constipation

*Note: Diltiazem & verapamil are substrates of P-GP & P450’s*
Amlodipine
• Angina or MI may worsen at start of therapy
  – Use nitrate to control

Verapamil
• Lots of drug interactions
  – ↑β-blocker effects
  – IV slowly

CCB Notes

Diltiazem
• Often 2 weeks before effects are seen
• Incompatible with furosemide (ppt)
• Lots of drug interactions
  – ↑CNS depression of sedative hypnotics and anesthetics
**Antianginal Drugs:**

**β-adrenergic blockers**

- Prophylactic for Typical angina & acute MI

- Atenolol (Tenormin)
- Metoprolol (Lopressor, Toprol)
- Nadolol
- Propranolol (Inderal) c

Drugs that ↓ myocardial contractility (& thus, workload) are called **inotropes**

Examples of **inotropes** include: β-blockers, CCBs and certain anti-arrhythmics (e.g., quinidine, procainamide, disopyramide, flecainide)

β blockers must be individually titrated to correct dose NEVER suddenly discontinue!
Antianginal Drugs:  
*pFOX inhibitors, etc.*

❤ pFOX inhibitors

- Partial fatty acid oxidation inhibitors
  - Used to treat *Chronic stable angina*
  - Heart gets bulk of energy from fatty acid oxidation
  - Blocks FAO, improving glucose use which decreases O₂ demand

- **Trimetazidine (Vastarel)**  ☺ NOT FDA APPROVED YET (☺ Vistaril = hydroxyzine)
  - No reported drug interactions

- **Ranolazine (Ranexa)**  ☭
  - Affects Na⁺- dependent Ca²⁺ channels which may cause “Long QT syndrome”
  - Indirectly prevents XS Ca²⁺ that causes cardiac ischemia
  - Metabolized by CYP3A
  - Lots of drug interactions
Heart Failure

• Acute versus Chronic

• Congestive heart failure
  – Edema
    • Ankles/feet
    • Legs
    • Lungs (if recumbent)
    • Eventually, the abdomen (ascites)

Ambulance Meds
• Adenosine
• Atropine
• Aspirin
• Albuterol
• Diphenhydramine
• Dopamine
• Epinephrine
• Furosemide
• Glucagon
• Lidocaine
• Midazolam
• Morphine
• Naloxone
• Nitroglycerine
• Sodium bicarbonate
Heart Failure Risk Factors

- Pre-existing heart disease
  - CAD, HT, valve disease, cardiomyopathy
- Family history of HD
- Diabetes
- Obesity
- Alcoholism or drug abuse
- Excessive sodium intake
- Sustained rapid heart rate (tachycardia)
- Lung disease such as COPD
- Anemia
- Kidney disease
Heart Failure

• Multiple CV disorders → HF
  – CHF = #1 dischg Dx (ER) for >60yr olds
    • LV failure presents with shortness of breath
    • RV failure presents with fluid accumulation
  – Outpatient meds
    – www.heartfailure.org/eng_site/treatinghf_med_op.asp
  – Inpatient meds
    – www.heartfailure.org/eng_site/treatinghf_med_ip.asp
Treatment of Heart Failure

• Acute (acute decompensated HF, ADHF)
  – IV

  ▶ Diuretics
    - Furosemide (Lasix) ▶ C

  ▶ Vasodilators
    - Nitroglycerin (Nitrostat, Nitro-Bid) ▶ C, nitroprusside

  + Inotropic agents
    - β agonists
      - Dobutamine (Dobutrex) ▶ B, dopamine
    - Phosphodiesterase-3 inhibitor
      - Milrinone (Primacor) ▶ C

  ▶ Natriuretic peptide
    - Nesiritide (Natrecor) ▶ C

*Lasix can’t be given in same IV as Primacor as combo will form a PPT*

*Atrial Natriuric Peptide* is a potent *vasodilator* secreted by myocardium, triggered by AngII, HT, Endothelin, ↑ Na+ and β-receptor stimulation
Treatment of Acute HF

• **Diuretic resistance**
  – Neurohormonal activation
  – Rebound Na+ uptake following water loss
  – Hypertrophy of distal nephron
  – ↓ tubular secretion
  – ↓ renal perfusion
  – Altered absorption of diuretic
  – Patient noncompliance

• **Managing resistance**
  – Combo: furosemide + thiazide/sprinolactone,….
  – Add dopamine to increase cardiac output
  – ↓ ACE-I

1/3 of patients experience resistance: diuretic effects cease before edema resolved

More common in moderate to severe HF, especially in those taking NSAIDs or with diet high in Na+
Treatment of Chronic Heart Failure

- Diuretics
- Digitalis
- Anticoagulants
- Cholesterol lowering medications
- Vasodilators
  - Direct acting vasodilators
  - α or β blockers (cardio⊕)
  - Nitrodilators
  - Aldosterone blockers

- Vasodilators, continued
  - ACEI
  - ARBs
  - Ca^{++} channel blockers
  - α or β agonists (cardio⊕)
  - CNS α agonists (cardio⊖)
  - Ganglion blockers
  - Endothelin receptor ⊗
  - Renin ⊗’s
  - Phosphodiesterase⊖’s
  - Potassium channel openers

Avoid NSAIDS which can worsen CHF
Arrhythmias

• Normal heart rhythm
  – Sinoatrial (SA) node
    • Pacemaker
    • Modified myocardial cells that self-depolarize at 60-100/min
      – Innervated by PSNS and SNS
    • Initiates electrical signal and pace of heart
  – Atrioventricular (AV) node
    • At base of right atrium, receives signal from SA
    • Acts as a “Gatekeeper,” limiting signal frequency
      – Also innervated by PSNS and SNS
  – Bundle of HIS
    • Carries signal to ventricles and left atrium

PSNS - Direct HR control only (SA & AV nodes)
SNS - HR & contractility control (SA & AV nodes + myocardium)
Arrhythmias

• An abnormal rate or rhythm of HR
• Classified by speed (fast/slow) & location (atria/ventricles)
• Symptoms include:
  – Syncope or lightheadedness
  – Palpitations
  – Angina or chest pain
• Causes
  – Coronary ischemia or other injury (e.g., surgery)
  – Electrolyte balance problems
  – Over activity of the sympathetic nervous system
  – Drugs, including general anesthetics, that alter transmembrane potentials/characteristics → abnormal formation or conductance of action potentials
Risk factors for arrhythmias

- Age
- Genetics
- CAD, previous heart surgery and other heart disease
- Thyroid problems
- Drugs
  - OTC sympathomimetics like pseudoephedrine
- HT
- Obesity
- Diabetes
- Obstructive sleep apnea
- Electrolyte imbalance
- Alcohol
  - “Holiday Heart” AF
- Stimulants
  - Caffeine & nicotine

Also digoxin & TCAs for PVCs
Types of arrhythmias
Tachycardia

- Atrial
  - Fibrillation
  - Flutter
  - Supraventricular tachycardia
  - Wolff-Parkinson-White syndrome

- Ventricular
  - Tachycardia
  - Fibrillation
  - Long QT syndrome

Affects 1-2% of adults, ↓ cardiac output by 20-50%

By far, the most important cause of sudden cardiac death

Drugs that ↑ HR are called ☀ chronotropic agents

Electrical remodeling: repeated AF ↑ likelihood of another AF lasting longer
Types of arrhythmias
Bradycardia and Premature beats

• Bradycardia
  – Sick Sinus syndrome
  – Conduction block

• Premature heartbeat
  – Ventricular
  – Atrial

Drugs that ↓HR are called Θ chronotropic agents

Premature ventricular contractions (PVC) – the ventricles are initiating HR – are common. They are perceived as a “missed beat.”
Treatment for arrhythmias

• Bradycardia
  – Treat primary cause e.g., hypothyroidism
  – Pacemaker implant

Note: Anti-arrhythmic drugs treat tachyarrhythmias

Two mandates of AF treatment:
1. Control ventricle rate
2. Adequate anticoagulants

• Tachycardias
  – Vagal maneuvers
    • Valsalva
    • Carotid sinus massage
  – Medications (atrial)
    • Anti-arrhythmics
    • Anticoagulants
  – Cardioversion
    • DC Electroshock
  – Cardiac ablation
    • Kill tissue to cause electrical block
Antiarrhythmics

- Vaughan Williams classification

- Classified by mechanism of action

- Flaws (things not taken into account)
  - Multiple mechanisms of action of drugs
  - Active metabolites
  - Some drugs don’t fit anywhere

*All antiarrhythmics may cause arrhythmias!*
Antiarrhythmics

Vaughan Williams classification

- **Class Ia-c**
  - Na+ channel blockade *act to slow electrical conduction in heart*

- **Class II**
  - Adrenergic antagonists - mostly β blockers *act to block impulses*

- **Class III**
  - Ω K+ influx *act to slow electrical conduction*

- **Class IV**
  - Ca++ channel blockade and AV node effects *act to block impulses*

- **Class V**
  - Other or unknown mechanism
Antiarrhythmic therapy
Class I Na+ Channel Blockers

– **Ia** - *Atrial fib/flutter, supravent. & ventricular tachyarrhythmias*
  
  • Quinidine, *Procainamide (Pronestyl, Procanbid)* *, disopyramide*

– **Ib** - *Ventricular tachyarrhythmias*
  
  • Lidocaine (*Xylocaine*) *, Phenytoin (*Dilantin*) *, D, mexiletine*

– **Ic** - *Life threatening supra- & ventricular tachyarrhythmias*
  
  • Flecainide (*Tambocor*) * and propafenone*

**Procinamide: Procanbid ☝️ probenecid** Do Not Crush ER tablets. May contain Tartrazine (lemon yellow food color, allergen)
ER tablet may leave a wax “ghost” that may pass in stools.

**Verapamil may cause HF in combo with flecainide or disopyramide**
Antiarrhythmic therapy
Na+ Channel Blockers

- ↓ Transmission of AV electrical impulses → ↑ contractility
- General ADRs
  - Constipation, nausea
  - Flushing, swelling
  - Dizziness, head ache
  - Fatigue
  - Low BP
  - P - +ANA test
  - F - Arrhythmias
  - Procainamide ADRs
    - Fever, seizures, bradycardia, ventricular fibrillation, rash, flushing, lupus-like syndrome
  - Flecainide ADRs
    - HF, cardiac arrest, blurred vision, dyspnea, syncope, depression
Phenytoin ADRs
Class 1b Na\(^{+}\) channel blocker

Phenytoin must be administered slowly

- It can’t be used in:
  - Sinus bradycardia
  - Sino-atrial block
  - AV block

\textit{Dilantin} \& \textit{Dilaudid} (hydromorphone)

\textit{May turn urine pink or reddish}

- CV collapse!
  - Hypotension
  - Bradycardia (pro-arrhythmic)
- CNS
  - Drowsiness/confusion
  - In some patients, EPS
- Bleeding gums/petechia/rashes
  - Blood dyscrasias
  - Purple Glove Syndrome
- Stevens-Johnson Syndrome
- Drug-induced Lupus
- GI
  - Upset/constipation/vomiting
- Hirsutism
- Nastigmus (blurred vision)
- Muscle twitches; seizures w/TCA
- Known human teratogen
- Osteomalacia (\(\otimes\)VitD metab.)
- Connective tissue \(\Delta\)’s
  - Gingival hyperplasia
  - Coarsening of face

\(\text{P}450\uparrow\)
Antiarrhythmic therapy

Class II - $\beta$-blockers

- $\otimes$ Catacholamines $\rightarrow$ ↓ HR by ↓ AV node conduction

- General ADRs
  - Depression
  - Dizziness or lightheadedness
  - Weakness and fatigue
  - Sexual dysfunction (impotence)
  - Sleep disruptions

- Examples
  - Propranolol $\to$ C
  - Esmolol
  - Timolol
  - Metoprolol
  - Sotalol
  - Atenolol

- Uses
  - ↓ MI mortality
  - ↓ Tachycardia return
Antiarrhythmic therapy

Class III - K⁺ channel blockers

- \( \otimes \) \( K^+ \) influx \( \rightarrow \) \( \uparrow \) repolarization (takes longer before the next action potential)

Amiodarone ADRs
- Interstitial lung disease
- Thyroid function issues
- Corneal microdeposits
- Blue-grey skin, UV-A sensitivity
- \( \beta \)-blocker effects
- Headache
- Torsade de pointes (form of tachycardia, may be fatal)
- Liver failure, ARDS

Amiodarone (Pacerone)
- Acts as III, Ia, II & IV
- Blocks multiple sites
  - Multiple \( K^+ \) channels
  - \( \alpha \) & \( \beta \) & muscarinic receptors
  - \( Na^+ \) and \( Ca^{++} \) channels
  - Thyroid hormone receptors
- Still the most effective antiarrhythmic for rhythm control

Leaches plasticizers like DEHP from IVs

Inamirone & Amiloride

Requires individualization and monitoring

P450 ↓
Antiarrhythmic therapy

Class IV: Ca\textsuperscript{++} Channel Blockers

- $\otimes$ Ca\textsuperscript{++} from entering heart muscle
  - $\rightarrow$ ↓ contractility, dilates blood vessels, ↓BP
  - Uses
    - Paroxysmal supraventricular tachycardia
    - Slow ventricular rate in atrial fibrillation
- General ADRs
  - Constipation, nausea, heart burn
  - Flushing
  - Dizziness, head ache
  - Fatigue
  - Low BP, edema
  - Changes in Heart Rate

$\text{CCBs are pro-arrhythmic and can cause significant edema}$
Antiarrhythmic therapy Class V: Others

Digoxin (Lanoxin) 🧐 🌵 C PO/IV
- cardiac glycoside from foxglove 1st described in 1785!
- Indications: atrial fibrillation & HF
- ADRs
  - Nausea, heart burn
  - Flushing, edema
  - Dizziness, head ache
  - Fatigue
  - Low BP
  - Palpitations
  - Halo vision

Amiodarone may ↑↑ digoxin levels by 70-100%!!
Cholestyramine & metoclopramide ↓ absorption

Digoxin ⚠️
- Doxepram (CNS stim.)
- Doxepin (antidepressant)
- Deptran (doxepin HCl)
- Doxazosin (α1 blocker)
- Doxidan (laxative)

Contraindicated in ventricular arrhythmias

Digoxin toxicity:
1. Low potassium or magnesium
2. 10% of population has GIT bacteria that eat digoxin - if they take tetracycline
3. Abnormal pGP allows digoxin to accum.

Furosemide & thiazides ↓ K+ which ↑↑ digoxin toxicity

A Beale
PHRM 203 - Cardio 2
Antiarrhythmic therapy Class V: Others

- **Adenosine (Adenocard)**
  - IV for arrhythmias, very short \( t_{\frac{1}{2}} \)
  - Indicated for acute supraventricular tachycardia
    - Other formulations used to decrease wrinkles!
    - Antagonized by methyl xanthines (caffeine)