Pharmacology
of
Anti-arrhythmic drugs

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Cardiac Function

- Dependent upon
  - Adequate amounts of ATP
  - Adequate amounts of Ca$^{++}$
  - Coordinated electrical stimulus
Adequate Amounts of ATP

- Needed to:
  - Maintain electrochemical gradients
  - Propagate action potentials
  - Power muscle contraction
Adequate Amounts of Calcium

- Calcium is ‘glue’ that links electrical and mechanical events.
Coordinated Electrical Stimulation

- Heart capable of automaticity
- Two types of myocardial tissue
  - Contractile
  - Conductive
- Impulses travel through ‘action potential superhighway’.
A.P. SuperHighway

- Sinoatrial node
- Atrioventricular node (Bundle of His)
- Bundle Branches
  - Fascicles
- Purkinje Network
Electrophysiology

- Two types of action potentials
  - Fast potentials
    - Found in contractile tissue
  - Slow potentials
    - Found in SA, AV node tissues
Fast potential

- K⁺, Cl⁻ (out)
- I_{to_{1,2}} (transient outward)
- Ca^{2+} (in), K⁺ (out)
- I_{Ca-L} (Ca long)
- I_{KS} (K slow delayed rect.)
- Na⁺ (in)
- I_{Na} (rapid)
- K⁺ (out)
- I_{KS} (K slow delayed rect.)
- I_{KR} (K rapid delayed rect.)
- I_{K1} (inward rect.)

+52 mV
-96 mV
200 ms
Slow Potential

dependent upon **Ca**^{++} **channels** = “slow channels”

ANS receptors play a role in pacemaker activity
Slow Potential

- Self-depolarizing
  - Responsible for automaticity
- Phase 4 depolarization
  - ‘slow sodium-calcium channels’
  - ‘leaky’ to sodium
- Phase 3 repolarization
  - $K^+$ efflux
Cardiac Pacemaker Dominance

- Intrinsic firing rates:
  - SA = 60 – 100
  - AV = 45 – 60
  - Purkinje = 15 - 45
Cardiac Pacemakers

- SA is primary
  - *Faster depolarization rate*
    - Faster Ca\(^{++}\) ‘leak’
- Others are ‘backups’
  - *Graduated depolarization rate*
    - Graduated Ca\(^{++}\) leak rate
Electrical conduction

- P-SA
- AV=PRI
- QRS=Vent
- T= repolarisation
Cardiac Conduction Cycle

mV

Seconds
0 0.04 0.08 0.12 0.16 0.20 0.40 0.60 0.80

TP = Threshold Membrane Potential
RP = Resting Membrane Potential
Dysrhythmia Generation

- Abnormal genesis
  - Imbalance of ANS stimuli
  - Pathologic phase 4 depolarization
    - Ectopic foci
Causes of dysrhythmia

- **Cardiac tissue injury** - inflammatory, post-cardiac surgery
- **Electrolyte disturbances** - Na+, K+, Mg++
- **Drugs** - antidysrhythmic drugs, stimulants
- **Sympathetic stimulation** - hyperthyroidism, CHF
- **Bradycardia** - escape rhythms
- **Ischaemia** - angina, Coronary artery dss
- **Stretching of myocardium** - CHF, hypertrophy, valve disease
- **General hypoxia** - lung dss, shock
Warning!

- All antidysrhythmics have arrhythmogenic properties
- In other words, they all **CAN CAUSE** dysrhythmias too!
AHA Recommendation
Classifications

- Describes weight of supporting evidence NOT mechanism

- Class I
- Class IIa
- Class IIb
- Indeterminant
- Class III
Singh-Vaughan Williams Classification

- Class 1
  - **Ia**
  - **Ib**
  - **Ic**
- Class II
- Class III
- Class IV
- Miscellaneous

- Description of mechanism NOT evidence

*Sičilian gambit classification*
Class I: Fast Sodium Channel Blockers

- Decrease Na\(^+\) movement in phases 0 and 4
- Decreases rate of propagation (conduction) via tissue with fast potential (Purkinje)
  - Ignores those with slow potential (SA/AV)
- Indications: ventricular dysrhythmias
Class Ia Agents

- Slow conduction through ventricles
- Decrease repolarization rate
  - *Widen QRS and QT intervals*
  - *May promote Torsades des Pointes!*

procainamide (Pronestyl®),
disopyramide (Norpace®),
quinidine (Quinidex®)
Quinidine
✓ Muscarinic receptor blockade (pro-arythmic effect)
✓ Alpha block possible (reverse tachycardia)
✓ Used clinically in A-fib

- Side effects
  ✓ Cinchonism, hypotension, prolonged QRS and QT interval (torsades)

- Interaction
  ✓ Digoxin (displaces from binding site)
  ✓ Hyperkalaemia

Procainamide
✓ Less anti-muscarinic
✓ Metabolised by acetylation

- Adverse effect
  ✓ Systemic lupus erythematosus-like syndrome
  ✓ Torsades
  ✓ Haematotoxicity
Class Ib Agents

- Blocks *inactivated* Na channel to prevent cells from going to resting state to start new AP
- Slow conduction through ventricles
- Increase rate of repolarization
- Reduce automaticity
  - *Effective for ectopic foci*
- May have other uses

*lidocaine (Xylocaine®), tocainide (Tonocard®), mexiletine (Mexitil®), phenytoin (Dilantin®)*
<table>
<thead>
<tr>
<th><strong>Lidocaine</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Given post-MI</td>
</tr>
<tr>
<td>✓ Digoxin toxicity</td>
</tr>
<tr>
<td>✓ Open-heart surgery</td>
</tr>
<tr>
<td>■ Side effects</td>
</tr>
<tr>
<td>✓ Seizures</td>
</tr>
<tr>
<td>■ Given IV (first pass metabolism)</td>
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</tbody>
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<table>
<thead>
<tr>
<th><strong>Mexiletine &amp; Tocainide</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Same as Lidocaine</td>
</tr>
<tr>
<td>■ Orally administered</td>
</tr>
</tbody>
</table>
Class Ic Agents

- Slow conduction through ventricles, atria & conduction system
- Decrease repolarization rate
- Decrease contractility
- Rare last chance drug

flecainide (Tambocor®)
Encaïnide (Enkaid®)
propafenone (Rythmol®)
Flecainide

✓ No AP and ANS effect
✓ Limited in use due to its pro-arrhythmogenic effect
✓ Cases of sudden death after administration

■ Why is it still in used??
Class II: Beta Blockers

- Decrease SA and VA nodal activity
- Beta\textsubscript{1} receptors in heart attached to Ca\textsuperscript{++} channels
  - Gradual Ca\textsuperscript{++} influx responsible for automaticity
- Beta\textsubscript{1} (G\textsubscript{s}) blockade decreases Ca\textsuperscript{++} influx
  - Effects similar to Class IV (Ca\textsuperscript{++} channel blockers)
- Used mainly post-MI
- Limited number approved for tachycardias
  - Supraventricular tachycardia
Class II: Beta Blockers

- propranolol (Inderal®)
- acebutolol (Sectral®)
- esmolol (Brevibloc®)
- Metoprolol
Class III: Potassium Channel Blockers

- Decreases $K^+$ efflux during repolarization (Prolongs repolarization)
- Extends effective refractory period
- Prototype: bretyllium tosylate (Bretylol®). Others, amiodarone, ibutilide, dronedarone, sotalol.
  - *Initial NE discharge may cause temporary hypertension/tachycardia*
  - *Subsequent NE depletion may cause hypotension*
Amiodarone

✓ Prolongs AP duration
✓ Used in any arrhythmias
✓ Half-life of >80 days

■ Side effect

✓ Pulmonary fibrosis
✓ Blue skin pigmentation
✓ Corneal deposition
✓ Hepatic necrosis
✓ Thyroid dysfunction
✓ Photosensitivity
Class IV: Calcium Channel Blockers

- Similar effect as β blockers
- Decrease SA/AV automaticity
- Decrease AV conductivity
- Useful in breaking reentrant circuit
- Prime side effect: hypotension & bradycardia
- verapamil (Calan®)
- diltiazem (Cardizem®)
- Note: nifedipine doesn’t work on heart
Verapamil and Diltiazem

- Employed in supraventricular tachycardia

- Side effects
  - Constipation (verapamil)
  - Dizziness
  - Hypotension
  - Flushing
  - AV block

- Interaction
  - Beta-blocker
  - Digitoxin
Misc. Agents

- **adenosine (Adenocard®)**
  - *Decreases Ca\(^{++}\) influx & increases K\(^+\) efflux via 2\(^{nd}\) messenger pathway*
    - Causes Gi-coupled decrease in cAMP
    - Hyperpolarization of membrane
    - Decreased conduction velocity via slow potentials
    - No effect on fast potentials

- Drug of choice for paroxysmal SVT and AV nodal arrhythmia

- Profound side effects possible (but short-lived)
  - *Flushing, sedation, profound dyspnea*
Misc. Agents

- **Magnesium Sulfate**
  - Used specifically for Torsade de pointes
  - Slows SA node impulse formation in myocardium and prolongs conduction time; stabilizes excitability of muscle cells
Cardiac glycosides

- Drugs originally obtained from plant source, *Digitalis purpurea* and *Digitalis lanata*
- Digoxin and digitoxin are the only cardiac glycosides currently available
- Main pharmacologic effect of cardiac glycosides is to increase the contractile force of myocardial contraction
- Cardiac glycosides also decrease heart rate and atrioventricular conduction
Mechanism of Action

- Cardiac glycosides inhibit Na+/K+ ATPase, the “sodium pump” which causes more Na to remain inside myocardial cells

- Increased intracellular Na stimulates Na/Ca exchange that brings more Ca inside heart cells to increase the force of contraction

- Cardiac glycosides also stimulate the vagus nerve which decreases heart rate, hence...
  1. Slow HR
  2. Slows atrioventricular conductance.
  3. Prolongs the refractory period of the atrioventricular node.
Positive Inotropic Mechanism of Digoxin

1. ↓Na⁺ extrusion
2. ↓Ca²⁺ extrusion
3. ↑Ca²⁺ stores
4. ↑Myofibril contraction

Na⁺/Ca²⁺ exchanger and Na⁺/K⁺-ATPase are involved in this mechanism.
- Digoxin is water soluble and eliminated mostly unmetabolized by the urinary tract
- Digitoxin is more lipid soluble, requires metabolism, and has a longer half-life
- In acute CHF, initial “digitalization” doses are administered to rapidly attain effective therapeutic concentration
- Lower daily maintenance doses are then given to maintain desired therapeutic concentrations

- High serum potassium levels “hyperkalemia” decrease the actions of the cardiac glycosides
- Increased serum calcium levels “hypercalcemia” can increase the actions and toxicity of the cardiac glycosides
Adverse Effects

- Common complaints include headache, anorexia, dizziness, nausea, and vomiting
- Visual disturbances “halo effect” around lights often signals overdosage
- Bradycardia, ectopic beats, and a variety of other cardiac arrhythmias can occur and can be life-threatening
Antiarrhythmic Drugs

Sinus bradycardia
- atropine i.v.

Ventricular and supraventricular

CLASS III
- amiodarone
- sotalol

CLASS I A
- quinidine
- disopyramide

CLASS I C
- flecaïnide

Ventricular

CLASS I B
- lidocaine i.v.

Pacemaker potential
- gK decreasing; gNa increasing

Cardiac action potential (AP)
- (Composite diagram pacemaker potentials occur only in the SAN and AVN)

Decrease fast Na⁺ current

Supraventricular

- adenosine i.v.
- digoxin
- verapamil

Stress induced

CLASS II
- β-blockers
- propranolol
- atenolol
- sotalol

Stress
- norepinephrine
- epinephrine release
- β-receptors gNa↑

Most drugs
- Increase refractory period VS AP duration

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Case presentation

- Sinus bradycardia
- Sinus tachycardia
- Sinus arrest (sick sinus syndrome)
- V-Tach, V-fib
- A-Fib, Atrial flutter
- Heart block

- Assessment, causes, intervention