Antiarrhythmic Agents

Objectives

• Describe indications of, and mechanism of action for, the various classes of antiarrhythmic drugs

• Describe adverse reactions, precautions, and contraindications of antiarrhythmic agents

• Discuss considerations when choosing an antiarrhythmic to treat supraventricular and ventricular tachyarrhythmias
Electrical conduction

Pacemaker cells
- Possess automaticity
- SA node, AV node, and ventricular conduction system (bundle of His, bundle branches, and Purkinje fibers)

Non-pacemaker cells
- Do not possess automaticity (normally)
- Atrial and ventricular myocytes

Action Potentials

Phase 0=rapid depolarization
Phase 1= early repolarization
Phase 2= plateau phase
Phase 3= rapid repolarization
Phase 4= resting phase
Electrical dysfunction

1) Abnormal impulse formation
   • Impaired or enhanced automaticity of the SA node
   • Ectopic beats
2) Impulse conduction defects
   • Conduction Blocks
   • Re-entry
   • Accessory Tract Pathways
3) Triggered activity
   • A normal action potential “triggers” abnormal depolarizations
Electrical dysfunction

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Re-entry

Mechanism responsible for the majority of arrhythmias
   • Atrial fibrillation
   • Atrial flutter
   • Atrioventricular nodal reentrant tachycardia (AVNRT)
   • AV re-entrant tachycardia (AVRT)
   • Ventricular tachycardia (after MI, with presence of scar)
   • Ventricular fibrillation
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Triggered Activity

• Sustained (early) afterdepolarizations can lead to Torsade de Pointe
Vaughn-Williams Classification

Class I (1A, 1B and 1C): Na+ Channel Blockers

Class II: Beta Blockers

**Class III: K+ Channel Blockers**

Class IV: Ca+ Channel Blockers

{And (Class V): Others}
Beta Blockers (Class II)

- Decrease automaticity by decreasing slope of phase 4 depolarization and by inhibiting sympathetic stimulation of receptors in the SA and AV node
- Prolong repolarization which decreases incidence of re-entry

<table>
<thead>
<tr>
<th>Selectivity</th>
<th>Drugs</th>
<th>Lipophilicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Generation</td>
<td>Non-selective (beta-1 and beta-2)</td>
<td>Propranolol Nadolol</td>
</tr>
<tr>
<td>Second Generation</td>
<td>Relatively beta-1 selective</td>
<td>Atenolol Metoprolol Bisoprolol</td>
</tr>
<tr>
<td>Third Generation</td>
<td>Beta-1 selective</td>
<td>Labetolol Carvedilol</td>
</tr>
</tbody>
</table>
Calcium channel blockers (Class IV)

- Effect pacemaker cells at the SA and AV node
- Slow the rise of Phase 0
- Prolong the repolarization of AV nodal cells
- Overall effect is prolonged AV nodal conduction
- Especially useful for arrhythmias that involve re-entry through the AV node
Calcium Channel Blockers (Class IV)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Action</th>
<th>Side effects / precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydropyridines</td>
<td>Nefedipine Amlodipine</td>
<td>Pedal edema</td>
</tr>
<tr>
<td></td>
<td>Greater effect on calcium channels in smooth muscle, cause vasodilation</td>
<td></td>
</tr>
<tr>
<td>Non-dihydropyridines</td>
<td>Verapamil Diltiazem</td>
<td>Avoid in CHF patients</td>
</tr>
<tr>
<td></td>
<td>Greater effect on cardiac tissues</td>
<td>Constipation</td>
</tr>
</tbody>
</table>

Digoxin (Other, Class V)

Cardiac glycoside
- Selective inhibitor of the plasma membrane sodium pump
- Has effects on cardiac myocytes
  - Overall rise in intracellular calcium concentration increases myocardial contractility
- Has direct effects on conduction system in the heart
  - Decreases automaticity at the AV node
  - Decreases conduction velocity through the AV node
- Also inhibits sympathetic output and increases vagal tone by binding to neurons in the central and peripheral nervous systems

Keep in mind:
- Narrow therapeutic window
- Digoxin toxicity
- Drug interactions
The “Real” Antiarrhythmic Agents

<table>
<thead>
<tr>
<th>Class IA</th>
<th>Class IB</th>
<th>Class IC</th>
<th>Class III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>Lidocaine</td>
<td>Flecainide</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Mexiletine</td>
<td>Propafenone</td>
<td>Dronedarone</td>
</tr>
<tr>
<td>Disopyramide</td>
<td></td>
<td></td>
<td>Dofetilide</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Sotalol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ibutilide</td>
</tr>
<tr>
<td>AF, AFL, AT, SVT, VT</td>
<td>VT</td>
<td>AF, AFL, AT, SVT, WPW, PVC’s</td>
<td>AF, AFL, AT, SVT, VT</td>
</tr>
</tbody>
</table>

Class I agents

- All Class 1 (A, B, and C) agents have similar effects on the SA node action potential resulting in decreased automaticity.
- The difference between classes is effect on the ventricular action potential.

Image: cvpharmacology.com
Moderate Na+ channel blockers

- Decrease conduction velocity through the myocardium
- Also block K+ channels resulting in prolonged repolarization

**Quinidined (Class IA)**

- Also has vagolytic effects which cause increased conduction velocity through the AV node
- Can be dangerous in patient’s with aflutter
  - Atrial firing rate decreases due to class I decreased conduction velocity through the myocardium BUT increases AV nodal conduction can encourage 1:1 A:V ratio
  - Should be used with an AV nodal blocker
- *Used infrequently, Class III agents have replaced it for treatment of Afib/Flutter*

- Side effects difficult to tolerate
  - Diarrhea, nausea, headache, dizziness, rash
  - Cinchonism=decreased hearing, tinnitus, blurred vision, delirium
- Contraindicated in patients with prolonged QT
- Increases digoxin levels
- Careful monitoring of K+ levels
  - Hypokalemia decreases efficacy, exacerbates QT prolongation and contributes to development of Torsades

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**Procainamide (Class IA)**

- Used for supraventricular and rarely ventricular tachyarrhythmias
- Can be used safely in setting of acute MI to decrease likelihood of re-entrant rhythms
- Unlike Quinidine, has few anticholinergic effects and does not alter digoxin levels
- Hepatic metabolism results in an active metabolite (NAPA)
- Class III antiarrhythmic effects prolongs refractory period and causes QT prolongation
- Limiting side effects: (reversible) lupus-like syndrome and gi side effects
- "Procainamide Challenge"—used to unmask Brugada pattern

**Disopyramide (Class IA)**

- Similar to quinidine in action
- Side effects:
  - Less gi side effects that quinidine but more profound anticholinergic effects
- Contraindications:
  - Sinus node dysfunction, heart blocks
  - CHF
- Strong negative inotropic effects
  - Role in HOCM
- *Trend is toward Class III agents (and ICDs)*
• Little effect on normal cardiac tissue
• Exhibit use dependent block in diseased myocardium
• Do not prolong QT

Lidocaine (Class IB)

• Used for freq PVCs or VT/VF that causes hemodynamic compromise (IV)
• Can be used in combination with amiodarone
• Short half-life (20 min)
• CNS effects:
  • Block Na+ channels in the CNS too
  • Confusion, dizziness, seizures
Mexiletine (Class IB)

- Developed originally as anticonvulsant
- Used for VT
  - May be given with amiodarone
- Little effect on HR, BP, CO, or intracardiac pressures
- 90% metabolized in the liver
- Can be difficult to obtain

- Strongest Na+ channel blockers
- Decrease rate of phase 0 upstroke in atrial and ventricular cells
- Can cause widening of QRS (esp. with exercise)
- Use for atrial arrhythmias and frequent PVCs
- CAST (Cardiac Arrhythmia Suppression Trial)
  - Proarrhythmic effects in patients with pre-existing tachyarrhythmias or MI
  - “Pill-in-the-pocket” or daily
- Use with an AV nodal blocker to prevent organization into 1:1 flutter (especially flecainide)
Class 1C antiarrhythmics

Flecainide
- Use with beta blocker
- 40% excreted in urine, rest metabolized by the liver
- Can have CNS effects: blurred vision, headache, ataxia

Propafenone
- Has some beta blocking properties
- Metabolized by the liver
- Side effects: nausea, dizziness, metallic taste (especially with dairy products), blurred vision, paresthesia, constipation, increased LFTs

Class III antiarrhythmics

- Potassium channel blockers
  - Dofetilide (Class III)
  - Sotalol (mixed Class II and Class III)
  - Amiodarone (mainly Class III, has properties of Class I, II, and IV antiarrhythmics too)
  - Dronedarone (mainly Class III, has properties of Class I, II, and IV antiarrhythmics too)
- Prolonged repolarization decreases the incidence of re-entry
- QT prolongation, risk of torsades de pointes
Dofetilide (Class III)

- 3 day hospitalization
- Dose adjusted
  - Kidney function
  - QTc
- Must be a registered provider

Measuring the corrected QT (QTc)

QT intervals vary with heart rate

**Normal QTc:**
- adult men \(<\= 440\) msec
- adult women \(<\= 460\) msec

**QTc >500 msec highly abnormal for men and women**

QT = 0.32 sec (320 msec)
RR = 0.8 sec (800 msec, 75 bpm)
QTc = 0.358 (358 msec)
Dofetilide (Class III)

- Ongoing surveillance monitoring as an outpatient for QTc and kidney function/electrolytes
- Risk of Torsade due to QT prolongation
- Multiple drug interactions

Drug Contraindications:
- HCTZ (alone or in combination drugs)
- Verapamil
- Cimetidine
- Ketoconazole
- Trimethoprim
- Prochlorperazine
- Megestrol
- Dolutegravir
- Macrolide and fluoroquinolone antibiotics
- Anti-depressants

Sotalol (Mixed Class II and Class III)

- Non-selectively antagonizes Beta-adrenergic receptors (Class II action)
  - can cause significant bradycardia and hypotension
- K+ channel blocker (Class III action)
- Used to treat atrial and ventricular arrhythmias
- Started either in hospital setting or with close EKG monitoring as an outpatient (for QTc monitoring)
- Renally excreted, may require dose adjustment based on kidney function
Amiodarone

- Mainly a Class III agent but also acts as a class I, II, and IV agent
- K⁺ channel blocker (Class III): lengthens refractory period in all cardiac tissues (which decreases re-entry)
- Na⁺ channel blocker (Class I): decreases rate of firing in pacemaker cells
- Alpha and beta blocker (Class II): inhibits sympathetic stimulation
- Ca++ channel blocker (Class IV): AV node blockade/bradycardia

- Diverse effects attributed to ability to alter the lipid membrane where ion channels and receptors are located
- Onset of action with oral amiodarone takes 2-3 days
- Elimination half-life 25 to 100 days

### Type and Incidence of Major Side Effects Associated with Amiodarone Therapy

| Type of Side Effect | Incidence
<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>3% to 20%</td>
</tr>
<tr>
<td>Heart</td>
<td>2% to 12%</td>
</tr>
<tr>
<td>Liver</td>
<td>3% to 5%</td>
</tr>
<tr>
<td>Skin</td>
<td>25% to 75%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>3% to 10%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>5% to 10%</td>
</tr>
<tr>
<td>Ocular</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

### Diverse Side Effects
- Ongoing monitoring:
  - LFTs
  - TFTs
  - Annual eye exam
  - PFTs
- Little correlation between plasma concentration and drug efficacy or toxicity
- Can be used safely in patients with CHF and post MI
- Warfarin dose will likely need to be reduced
Amiodarone QT prolongation

Dronederone

• Derivative of amiodarone
• Class III agent, also has Class I, II and IV actions
• Less lipophilic, less associated toxicities
• Half-life about 24 hours (amiodarone=up to 50 days)
• Hepatic metabolism
Dronedarone

- ANDROMEDA Trial, 2012 meta-analysis
- Contraindicated in patients with CHF
- Associated liver injury
- Should not be used as a rate controlling agent
- Only rarely effective for the chemical cardioversion of AF or atrial flutter to sinus rhythm

Monitoring:
- Baseline LFTs and then within 6 months, then yearly
- Yearly ECG

Drug interactions:
- Avoid CYP3A4 inhibitors (ketoconazole, macrolide antibiotics, also grapefruit juice)
- Diltiazem, Digoxin, statins require dose adjustment
- Warfarin may require dose adjustment, not as significant as with amiodarone

Common side effects:
- Crampy abdominal pain, diarrhea, nausea, and rash.
Summary

• **Goal of antiarrhythmic agents:**
  - To restore and maintain sinus rhythm without development of worse conduction or rhythm disturbances

• **Achieved by:**
  - Suppressing enhanced automaticity
  - Decreasing conduction velocity
  - Changing the effective refractory period to suppress re-entry
### Remember....”Some Block Potassium Channels”

<table>
<thead>
<tr>
<th>Class</th>
<th>Word</th>
<th>Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Some</td>
<td>Sodium Channel Blockers</td>
</tr>
<tr>
<td>Class II</td>
<td>Block</td>
<td>Beta-Blockers</td>
</tr>
<tr>
<td>Class III</td>
<td>Potassium</td>
<td>Potassium Channel Blockers</td>
</tr>
<tr>
<td>Class IV</td>
<td>Channels</td>
<td>Calcium Channel Blockers</td>
</tr>
</tbody>
</table>

### Questions?

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References


Up to Date