Agents used in HT, CHF, Arrhythmia and Angina

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Hypertension</th>
<th>HF</th>
<th>Arrhythmia</th>
<th>Angina</th>
<th>Contraindications/Cautions/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HF (CI: unstable HF, broncho-rcode: significant bradycardia, depression): Caution in diabetes, asthma (see Q1)</td>
</tr>
<tr>
<td>Ca++-Channel blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HF, constipation, gingival hyperplasia, edema, reflex tachycardia</td>
</tr>
<tr>
<td>ACEI / ARBs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Angioedema, hyperkalemia, cough (acei), tetragenic, glossitis, taste (acei, CCB)</td>
</tr>
<tr>
<td>Diuretics (Thiazides)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GFR &gt;30, hyperkalemia (CI), TCa++, diabetes, glucose tolerance</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Many Rx interactions, [K+], Loxe HF, important, low K+, Toxicity</td>
</tr>
<tr>
<td>Vasodilators</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Flushing, dizziness, headache, nausea, reflex tachycardia</td>
</tr>
<tr>
<td>Na+-Channel blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Effects enhanced in depolarized, damaged tissue, Phase 3, CI CV</td>
</tr>
<tr>
<td>Nitrates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NO/NOS, tolerance (off period), flushing, dizziness, headache, reflex tachycardia, many forms</td>
</tr>
</tbody>
</table>

Heart Physiology

 unfolds system
Pressure driven
Supply nutrients/O₂
Remove metabolites

P - atria depolarization
QRS - ventricle depolarization
PR - conduction A-V
T - ventricle repolarization
QT - duration ventricle of repolarization

P - atria depolarization
QRS - ventricle depolarization
PR - conduction A-V
T - ventricle repolarization
QT - duration ventricle repolarization

Can’t see the forest for the trees

Hung up on the detail, you can not see the big picture
Review of Physiology

- The response of excitable cells to electrical stimulation is a function of # of available Na channels (an index is dV/dt or Phase 0)
- Steady membrane depolarization decreases Na current, dV/dt and conduction velocity
- Abnormal heart tissue is usually depolarized
- Na channel availability results from Na channels being in different states

Effect of drugs on # channels available and recovery time constant... depends on the resting membrane potential

What this means:
1. Conduction in damaged/abnormal heart tissue is decreased
2. Antidysrhythmics will work better on Na channels in depolarized cells, and slow their recovery from excitation

Na Channel States

Classification of dysrhythmias

1. Characteristics:
   a. flutter – very rapid but regular depolarization
   b. tachycardia – increased rate
   c. bradycardia – decreased rate
   d. fibrillation – disorganized depolarization activity

2. Sites involved:
   a. ventricular
   b. atrial
   c. sinus
   d. AV node
   e. supraventricular (SVT, atrial myocardium or AV node)

Characteristics of Dysrhythmias

Definitions:
- normal sinus rhythm (60-100bpm), SA node pacemaker
- arrhythmia: any abnormality of firing rate, regularity or site of origin of cardiac impulse or disturbance of conduction that alters the normal sequence of activity of atria and ventricles.

Occurrence:
- 80% of patients with acute myocardial infarctions
- 50% of anaesthetized patients
- about 25% of patients on digitalis

Examples of Arrhythmias

The ECG reveals the heart's activity through changes in electrical activity. The P wave, the QRS complex, and the T wave are associated with the heart's contractions. The P wave reflects atrial depolarization, the QRS complex and T wave reflect activity in the lower chambers.
Mechanisms of dysrhythmias

1. Abnormal impulse generation (abnormal automaticity)
   a. automaticity of normally automatic cells (SA, AV, His)
   b. generation of impulses in normally non-automatic cells
      - development of phase 4 depolarization in normally non-automatic cells
      - 'triggered activity' due to afterdepolarizations
        - early afterdepolarization
        - delayed afterdepolarization

2. Abnormal impulse conduction (more common mechanism)
   a. AV block – ventricle free to start own pacemaker rhythm
   b. Re-entry: re-excitation around a conducting loop, which produces tachycardia
      - unidirectional conduction block
      - establishment of new loop of excitation
      - conduction time that outlasts refractory period

Unidirectional Block

Damaged tissue is usually depolarized → ↓ conduction velocity

Abnormal impulse generation: ‘triggered activity’:
EADs and DADs

Early Afterdepolarizations

Delayed Afterdepolarizations

Strategies of Antidysrhythmic Agents

Suppression of dysrhythmias

A. Alter automaticity
   i. decrease slope of Phase 4 depolarization
   ii. increase the threshold potential
   iii. decrease resting (maximum diastolic) potential

B. Alter conduction velocity
   i. mainly via decrease rate of rise of Phase 0 upstroke
   ii. decrease Phase 4 slope
   iii. decrease membrane resting potential and responsiveness

C. Alter the refractory period
   i. increase Phase 2 plateau
   ii. increase Phase 3 repolarization
   iii. increase action potential duration

Ion Permeability

<table>
<thead>
<tr>
<th>mM</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Ca²⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Out</td>
<td>140</td>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td>In</td>
<td>10</td>
<td>150</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Cardiac Action Potentials

Ion Flow

<table>
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<tr>
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</table>
Classification of Antidysrhythmic Drugs

Vaughan-Williams classification (1970), subsequently modified by Harrison.

Helpful, But?
1. based on electrophysiological actions in normal tissue
2. presumes a mechanism of action of antidysrhythmic drugs
3. consists of four main classes and three subclasses
4. does not include actions of other agents (i.e. adenosine)

Shortcomings: Vaughan-Williams system (V-W)
1. Based on response in normal tissue, not damaged.
   Hybrid: Class I, III & IV agents block ion channels, Class II block receptors.
2. Incomplete: eg. adenosine, digitalis, cholinergic agonists, alpha adrenergic blockers or agents that modulate gap junctions, ion pumps or exchangers. Also ignores drug metabolites.
4. Describes drugs that block ion channels/receptors and does not consider drugs that activate channels or receptors.
5. Does not incorporate variable mode of action: slowing tachycardias, terminating dysrhythmias, or preventing them.

Drugs work better on depolarized tissue…..

Amiodarone: Only Antiarrhythmic with All Four Vaughan-Williams’ Class Effects

Class I effect
Sodium channel blockade

Class II effect
Noncompetitive alpha- and beta-adrenergic inhibition

Class III effect
Prolongation of repolarization and refractoriness by increased action potential duration

Class IV effect
Calcium channel blockade

Prototype Mechanism Subclass

Amiodarone

Class I effect
Sodium channel blockade

Class II effect
Noncompetitive alpha- and beta-adrenergic inhibition

Class III effect
Prolongation of repolarization and refractoriness by increased action potential duration

Class IV effect
Calcium channel blockade

<table>
<thead>
<tr>
<th>Vaughan-Williams Classification</th>
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<tbody>
<tr>
<td>Subclass</td>
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<tr>
<td>IA.</td>
</tr>
<tr>
<td>IB.</td>
</tr>
<tr>
<td>IC.</td>
</tr>
<tr>
<td>Class II</td>
</tr>
<tr>
<td>Class III</td>
</tr>
<tr>
<td>Class IV</td>
</tr>
<tr>
<td>Others</td>
</tr>
</tbody>
</table>

VAUUGHAN- WILLIAMS CLASSIFICATION
Key Aspects of Drug Action and Therapy...

a. Drug action is state-dependent: channel open, closed, or inactivated). Two current models:
   i. modulated receptor hypothesis: different states have different affinities
   ii. guarded receptor hypothesis: channel gate limits drug access to site

b. Drugs selectively affect firing and conduction in abnormal/depolarized cells.

c. Transitions between states dependent on membrane voltage and cell firing frequency, membrane voltage and spike frequency. Binding to inactivated states and slowing recovery from inactivation, some drugs can increase the time needed for recovery from inactivation.

Key Aspects of Drug Action and Therapy...

D. Drugs affect different parts of the heart: Beta-blockers and CCBs used for SVT

1. Ca channel blockers (Class IV) are selective for A-V and S-A nodes, where Ca action potentials predominate.

2. Lidocaine (Class IB) has been useful for treating PVCs in Purkinje fibers, since longer APDs in Purkinje yield more inactivated Na channels. Lidocaine selectively blocks inactivated state and some open Na channels. Lidocaine has little effect, in contrast, on atrial tissue.

3. Quinidine affects both atrial and ventricular dysrhythmias (but has been mostly used to treat atrial fibrillation).

Actions of Quinidine

Cardiac effects

a. ↓ automaticity, conduction velocity and excitability of cardiac cells.

b. Preferentially blocks open Na channels

c. Recovery from block slow in depolarized tissue; lengthens refractory period (RP)

d. All effects are potentiated in depolarized tissues

e. Increases action potential duration (APD) and prolongs AP repolarization via block of K channels; decreases reentry

f. Indirect action: anticholinergic effect (accelerates heart), which can speed A-V conduction.

Actions & Toxicity of Quinidine

Extracardiac

a. Blocks alpha-adrenoreceptors to yield vasodilatation.

b. Other strong antimuscarinic actions

Toxicity

- "Quinidine syncope" (fainting) due to disorganized ventricular tachycardia
- associated with greatly lengthened Q-T interval; can lead to Torsades de Pointes (VT, precursor to ventricular fibrillation)
- negative inotropic action (decreases contractility)
- GI - diarrhea, nausea, vomiting
- CNS effects - headaches, dizziness, tinnitus (quinidine "Cinchonism")

Prolonged QT interval

Torsades de pointes "twisting of the points"
Quinidine: Pharmacokinetics/therapeutics

- Oral, rapidly absorbed, 80% bound to membrane proteins
- Hydroxylated in liver; $T_{1/2} = 6-8$ h
- Drug interaction: displaces digoxin from plasma binding sites; so avoid giving drugs together or reduce dose
- Effective in treatment of nearly all dysrhythmias, including:
  1) Premature atrial contractions
  2) Paroxysmal atrial fibrillation and flutter
  3) Intra-atrial and A-V nodal reentrant dysrhythmias
  4) Wolff-Parkinson-White tachycardias (SVT, A-V bypass)
  5) Premature ventricular contractions (PVCs)
- Useful in treating chronic dysrhythmias requiring outpatient treatment

Procainamide (Class 1A) also Disopyrimide

Cardiac effects
- Similar to quinidine, less muscarinic & alpha-adrenergic blockade
- Has negative inotropic action also

Extracardiac effects
- Ganglionic blocking reduces peripheral vascular resistance

Toxicity
- Cardiac: Similar to quinidine; cardiac depression
- Noncardiac: Syndrome resembling lupus erythematosus

Pharmacokinetics/therapeutics
- Administered orally, i-v
- Major metabolite in liver is N-acetylprocainamide (NAPA), a weak Na channel blocker with class III activity. Bimodal distribution in population of rapid acetylators, who can accumulate high levels of NAPA.
- $T_{1/2} = 3-4$ hours; necessitates frequent dosing; kidney chief elimination path. NAPA has longer $T_{1/2}$ and can accumulate
- Usually used short-term. Commonly used in CCUs for ventricular dysrhythmias associated with acute myocardial infarctions (MI)

Lidocaine (Class IB prototype)

Other examples: Mexiletine, Phenytoin, Tocainide

General
- Commonly used antidysrhythmic agent in emergency care (decreasing use)
- Given i-v; widely used in ICU-critical care units (old DOC, prior 2001)
- Low toxicity (especially cardiac, good therapeutic index)
- A local anesthetic, works on nerve at higher doses

Lidocaine Actions

Cardiac effects
- Generally decreases APD, hastens AP repolarization, decreases automaticity and increases refractory period in depolarized cells.
- Exclusively acts on Na channels in depolarized tissue by blocking open and inactivated (mainly) Na channels
- Potent suppresser of abnormal activity
- Most Na channels of normal cells rapidly unblock from lidocaine during diastole; few electrophysiological effects in normal tissue

Toxicity:
- Least cardiotoxic, high dose can lead to hypotension - tremors, nausea, slurred speech, convulsions

Pharmacokinetics/therapy
- i-v, since extensive first pass hepatic metabolism
- $T_{1/2} = 0.5-4$ hours
- Effective in suppressing dysrhythmia associated with depol. tissue (ischemia; digitalis toxicity); ineffective against dysrhythmias in normal tissue (atrial flutter)
- Suppresses ventricular tachycardia; prevents fibrillation after acute MI; rarely used in supraventricular dysrhythmias

Phenytoin (Class IB)

1. Non-sedative anticonvulsant used in treating epilepsy ("Dilantin")
2. Limited efficacy as antidysrhythmic (second line antiarrythmic)
3. Suppresses ectopic activation by blocking Na and Ca channels
4. Especially effective against digitalis-induced dysrhythmias
5. $T_{1/2} = 24$ hr – metabolized in liver
6. Gingival hyperplasia (40%)

Gingival Hyperplasia

- Phenytoin (Dilantin) – anticonvulsant (40%)
- Calcium blockers – especially nifedipine (<10%)
- Cyclosporine – immunosuppressant (30%)
Flecainide (Class IC prototype)

Other examples: Lorcainide, Propafenone, Indecainide, Moricizine

Depress rate of rise of AP without change in refractoriness or APD
1. Decreases automaticity, conduction in depolarized cells.
2. Marked block of open Na channels (decreases Ph 0); no change repolarization.
3. Used primarily for ventricular dysrhythmias but effective for atrial too
4. No antimuscarinic action
5. Suppresses premature ventricular contractions (PVCs)
6. Associated with significant mortality, thus, use limited to last resort applications like treating ventricular tachycardiais
7. Significant negative inotropic effect

Propranolol (Class II, beta-adrenoreceptor blockers)

Other agents: Metoprolol, Esmolol (short acting), Sotalol (also Class III), Acebutolol

a. Slow A-V conduction
b. Prolong A-V refractory period
c. Suppress automatically

cardiac effects of (propranolol), a non-selective beta blocker
a. Main mechanism of action is block of beta receptors; ↓ Ph 4 slopes. which decreases automaticity under certain conditions
b. Some direct local anesthetic effect by block of Na channels (membrane stabilization) at higher doses
c. Increases refractory period in depolarized tissues
d. Increases A-V nodal refractory period

Non-cardiac: Hypotension

Therapeutics
a. Blocks abnormal pacemakers in cells receiving excess catecholamines (e.g. pheochromocytoma) or up-regulated beta-receptors (e.g. hyperthyroidism)
b. Blocks A-V nodal reentrant tachycardias, inhibits ectopic foci
c. Beta-blockers are used to treat supraventricular tachydysrhythmias
d. Propranolol contraindicated in ventricular failure; can lead to A-V block.

Beta-Adrenoceptor Antagonists

Properties of several beta-receptor blocking drugs

Clinical use – Beta-blockers

Clinical uses: Beta-Blockers

- Hypertension: frontline agents
- Angina (non-selective or β1-selective)
  - Cardiac: ↓O₂ demand more than O₂ supply
  - Exercise tolerance ↑ in angina patients
- Arrhythmia (β1-selective, LA-action)
  - ↓ SNS-induced increases in conductivity and automaticity
- Glaucoma (non-selective)
  - Lacraneous humor formation (Timolol)
- Congestive Heart Failure (non-selective or β1-selective)
  - CI: unstable CHF, bronchospasm, depression, bradycardia
- Other
  - block of tremor of peripheral origin (β2-AR in skeletal muscle)
  - migraine prophylaxis (mechanism unknown)
  - hyperthyroidism: cardiac manifestation (only propranolol)
  - panic attacks, stage fright

- Clinical use – Beta-blockers

<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>HT</th>
<th>Angina</th>
<th>MI</th>
<th>HF</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Non-selective β₁/β₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carteolol X</td>
<td>X</td>
<td>ISA; long acting; also for glaucoma</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Carvedilol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>α-blocking activity</td>
</tr>
<tr>
<td>Labetalol X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>ISA; α-blocking activity</td>
</tr>
<tr>
<td>Nadolol X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>long acting</td>
</tr>
<tr>
<td>Pindolol X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>ISA</td>
</tr>
<tr>
<td>Propranolol X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>MSA; prototypical beta-blocker</td>
</tr>
<tr>
<td>Sotalol X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>also K-channel blocker</td>
</tr>
<tr>
<td>Timolol X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>primarily used for glaucoma</td>
</tr>
<tr>
<td>β₁-selective Acbutolol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>ISA</td>
</tr>
<tr>
<td>Atenolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betaxolol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>MSA</td>
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<tr>
<td>Bisoprolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esmolol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>short acting; operative arrhythmia</td>
</tr>
<tr>
<td>Metoprolol X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>MSA</td>
</tr>
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</table>

Cardiac Action Potentials

Ion Flow

<table>
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<td>10</td>
<td>150</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Na⁺/Ca²⁺ - exchange (3:1)
Na⁺/K⁺ - ATPase (3:2)
### β-Blockers: Untoward Effects, Cautions

- **Supersensitivity**: Rebound effect with β-blockers, less with β-blockers with partial agonist activity (ie. pindolol). Gradual withdrawal
- **Asthma**: Blockade of pulmonary β2-receptors leads to increase in airway resistance. β1-selective agents preferred
- **Diabetes**: Compensatory hyperglycemic effect of EPI in insulin-induced hypoglycemia is removed by block of β2-ARs in liver. β1-selective agents preferred
- **Raynaud D**: Decreased peripheral circulation
- **Elderly**: Effectiveness is decreased, more CNS effects (ie. depression)

---

<table>
<thead>
<tr>
<th>AHA Guidelines for VT/VF 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Amiodarone</td>
</tr>
<tr>
<td>2. Procainamide, [Bretylium]</td>
</tr>
<tr>
<td>3. Sotalol</td>
</tr>
<tr>
<td>4. Lidocaine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AHA Guideline Prior to 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lidocaine</td>
</tr>
<tr>
<td>2. Procainamide</td>
</tr>
<tr>
<td>3. Bretylium</td>
</tr>
<tr>
<td>4. Electrical cardioversion</td>
</tr>
</tbody>
</table>

### Cardiac effects of Amiodarone

- **A. Cardiac**
  - i. Sinus bradycardia, **increase QT interval** risk TdP
  - ii. Negative inotropic action due to block of Ca channels and beta receptors, but can improve heart failure via vasodilation.
  - iii. A-V block, paradoxical VTs.

- **B. Non-cardiac**
  - i. Deposits into almost every organ
  - ii. Reduces clearance of drugs like procainamide, flecainide, digitalis, quinidine and diltiazem.
  - iii. **Thyroid dysfunction** (hypo or hyperthyroidism)
  - iv. **Pulmonary fibrosis** is most serious adverse effect
  - v. Parasthesias (tingling, pricking, or numbness)
  - vi. Photosensitivity
  - vii. **Corneal microdeposits** and blurred vision
  - viii. Ataxia, dizziness, tremor
  - ix. Anorexia, nausea

### Amiodarone (Class III)

<table>
<thead>
<tr>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. New DOC for ventricular dysrhythmias (Lidocaine, old DOC)</td>
</tr>
<tr>
<td>b. Prolongs refractory period by blocking potassium channels</td>
</tr>
<tr>
<td>c. Also member of Classes IA,II,III,IV since blocks Na, K, Ca channels and alpha and beta adrenergic receptors</td>
</tr>
<tr>
<td>d. Serious side effects (cardiac depression, pulmonary fibrosis, thyroid)</td>
</tr>
<tr>
<td>e. Effective against atrial, A-V and ventricular dysrhythmias</td>
</tr>
<tr>
<td>f. Widely used, very long acting (&gt;25 d)</td>
</tr>
</tbody>
</table>

### Adverse effects: Amiodarone

**A. Cardiac**
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- ix. Anorexia, nausea

---

**Pulmonary fibrosis**

- **Inflammatory Cells**
- **Pulmonary Fibrosis**
- **Gas Exchange**
- **Abnormal Alveoli**
- **Prolonged QT interval**
Amiodarone: Pharmacokinetics and therapeutics

Dronedarone ~ 24 hr

- $T_{1/2} = 13-103$ days (weeks) very long for one dose; very lipid soluble; metabolized in liver
- Effective against many arrhythmias: atrial, A-V and ventricular dysrhythmias; prevention of atrial fibrillation/flutter; PVCs, nonsustained & sustained VTs.
- Multiple interactions with other drugs such as:
  i. **Amiodarone is a CYP3A4 substrate and inhibitor** and thus may enhance the effect of other CYP3A4 substrates eg. Warfarin, Simvastatin, Verapamil
  ii. Amiodarone may increase the serum concentration of Cardiac Glycosides

Ibutilide (Class III).

1. Prolongs cardiac action potential without additional effects.
2. Administered I-V. Most effective current agent to convert atrial fibrillation and flutter of recent onset to normal rhythm. Low incidence of Torsades de Pointes (TdP, about 2%), compared to other drugs.
3. More effective for flutter than fibrillation
4. Generally well tolerated

Sotalol (Class III and Class II)
1. Non-selective beta blocker,
2. Increases AP duration, increase QT interval
3. Uses: dysrhythmias of supraventricular (very effective) & ventricular origin

Verapamil (Class IV, Ca++ channel blockers)

Other example: Diltiazem - CCBs increasing use and importance

- Blocks active and inactivated Ca channels, prevents Ca entry
- More effective on depolarized tissue, tissue firing frequently or areas where activity dependent on Ca channels (SA node; A-V node)
- Increases A-V conduction time and refractory period; directly slows SA node automaticity
- Suppresses oscillatory depolarizing after depolarizations due to digitalis
- Dihydropyridine CCBs are generally poor antiarrhythmics

Dysrhythmics - Others

A. Adenosine: i.v. (15 secs), activates P1 purinergic receptors (A1) coupled to K channels, \( J_{CV} \), refractory period. SVT. Flushing, hypotension, burning sensation
B. Potassium ions (K+): Depress ectopic pacemakers → can depress CV → reentrant dysrhythmia
C. Digoxin: used to treat atrial flutter and fibrillation
- AV node conduction (vagal stimulation)
- myocardium refractory period
- Purkinje fibers refractory period, ↓ conduction
D. Magnesium: used to treat Torsades de Pointes
E. Autonomic agents: used to treat A-V block
- \( \beta \)-agonists (ie.EPI), anticholinergics (ie. atropine)

Anticoagulant therapy:
- prevent formation of systemic emboli & stroke
Drug interactions involving antidysrhythmics

A. These drugs must be used very carefully
B. Sometimes interactions can be counter-intuitive

Problems with selecting drugs:

A. Do not always know the cause of the dysrhythmia, thus what to treat?
B. Multiple mechanisms of dysrhythmogenesis
C. Drugs are both anti- and pro-dysrhythmias
D. Drugs do not really fix the damage; usually they restore function by breaking something else

### Cardiac Effects of Antiarrhythmic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Auto.</th>
<th>CV</th>
<th>RP</th>
<th>AFD</th>
<th>ANS effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>IA</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>M-block, α-block</td>
</tr>
<tr>
<td>Propanidide</td>
<td>IA</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>M-block, α-block</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>IA</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>M-block, α-block</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>IB</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tocainide</td>
<td>IB</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mexiletine</td>
<td>IB</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Flecainide</td>
<td>IC</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td>IC</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td>II</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>β-block</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>II</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>β-block</td>
</tr>
<tr>
<td>Esmolol</td>
<td>II</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>β-block</td>
</tr>
<tr>
<td>Sotalol</td>
<td>III</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>β-block</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>III</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>α-β-block</td>
</tr>
<tr>
<td>Bretylium</td>
<td>III</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Sympatholytic.</td>
</tr>
<tr>
<td>Verapamil</td>
<td>IV</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Adenosine</td>
<td>Other</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>vagal stimulation</td>
</tr>
</tbody>
</table>

More important agents

### Pharmacokinetic Properties of Antiarrhythmic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Plasma Binding %</th>
<th>T_{1/2} (hrs)</th>
<th>Drug Excretion</th>
<th>Unchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>IA</td>
<td>90</td>
<td>6</td>
<td>50-60%</td>
<td></td>
</tr>
<tr>
<td>Propanidide</td>
<td>IA</td>
<td>15</td>
<td>4</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>Disopyramide</td>
<td>IA</td>
<td>39-55</td>
<td>5</td>
<td>50-70%</td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td>IB</td>
<td>40</td>
<td>2</td>
<td>&lt;10%</td>
<td></td>
</tr>
<tr>
<td>Tocainide</td>
<td>IB</td>
<td>10</td>
<td>14</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Mexiletine</td>
<td>IB</td>
<td>95</td>
<td>12</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Flecainide</td>
<td>IC</td>
<td>45</td>
<td>15</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>II</td>
<td>40</td>
<td>4</td>
<td>&lt;1%</td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>II</td>
<td>15</td>
<td>4</td>
<td>&lt;1%</td>
<td></td>
</tr>
<tr>
<td>Esmolol</td>
<td>II</td>
<td>Hydro. esterase</td>
<td>9 min</td>
<td>&lt;1%</td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td>III</td>
<td>9</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>III</td>
<td>9</td>
<td>&gt; 25 days</td>
<td>&lt;7%</td>
<td></td>
</tr>
<tr>
<td>Bretylium</td>
<td>III</td>
<td>5</td>
<td>9</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>IV</td>
<td>50</td>
<td>5</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Adenosine</td>
<td>Misc (other)</td>
<td>15 sec</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Considerations for treating Dysrrhythmias

1. Acute vs chronic treatment
2. Ventricular vs supraventricular

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Supraventricular</strong></td>
<td><strong>Ventricular</strong></td>
</tr>
<tr>
<td>Adenosine</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Procaainamide</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>Sotalol, Bretylium</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>Lidocaine</td>
</tr>
</tbody>
</table>

### Antiarrhythmics Question 1

When used as an antiarrhythmic agent, procainamide typically?

a. increases cardiac contractility
b. increases action potential duration
c. increases AV conduction
d. decreases QT interval
e. decreases Na-channel recovery time