Antiarrhythmias

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Agents used in HT, CHF, Arrhythmia and Angina

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Hyper-tension</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-spasm, significant bradycardia, depression); Raynaud D. Caution in diabetes, asthma (use β1-)</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), tensive, glossitis, taste</td>
</tr>
<tr>
<td>Diuretics (Thiazides)</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓</td>
<td>✓ ✓</td>
<td></td>
<td>GFR &gt;30, hypokalemia (CG); ↑Ca++, diabetes (; glucose tolerance)</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td>✓ ✓</td>
<td>✓ ✓</td>
<td></td>
<td></td>
<td>Many Rx interactions, [K+] ↓use 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 0, ↓CV</td>
</tr>
<tr>
<td>Nitrates</td>
<td>✓ ✓</td>
<td>✓ ✓</td>
<td>✓ ✓</td>
<td></td>
<td>NO/cGMP, tolerance (off periods), flushing, dizziness, headache, reflex tachycardia, many forms</td>
</tr>
</tbody>
</table>
Can't see the forest for the trees

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

Heart Physiology

Closed system
Supply nutrients/O₂

Pressure driven
Remove metabolites
Heart Physiology

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

Closed system
Pressure driven
Supply nutrients/O₂
Remove metabolites

P - atria depol.
QRS - ventricle depol.
PR - conduction A-V
T - ventricle repol.
QT - duration ventricle repolarization
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
Characteristics of Arrhythmias

Definitions:
- normal sinus rhythm (60-90bpm), 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
Classification of arrhythmia

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

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

Examples of Arrhythmias

The EKG breaks down each heartbeat into a series of electrical waves. Three of the waves, the P wave, the QRS complex and the T wave, are associated with the heart’s contractions. The P wave reflects activity in the heart’s upper chambers. The QRS complex and T wave reflect activity in the lower chambers.
Premature ventricular contraction (PVC)  
[Ventricular premature beat (VPB)]

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>
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- 0 Na⁺i - open
- 1 Na⁺ - close  
  K⁺o - open/close
- 2 Ca²⁺i - open  
  K⁺o - leak
- 3 Ca²⁺ - close  
  K⁺o - open
- 4 K⁺ - close

Na⁺/Ca²⁺ - exchange (3:1)  
Na⁺/K⁺ - ATPase (3:2)
Cardiac Action Potentials

Ion Flow

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Heart Physiology

Closed system
Pressure driven
Supply nutrients/O₂
Remove metabolites

P - atria depol.
QRS - ventricle depol.
PR - conduction A-V
T - ventricle repol.
QT - duration
ventricle repolarization
Mechanisms of arrhythmias

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

A. Normal

Nerve impulse

Ventricle wall

B. Unidirectional Block

Impulse blocked in one direction

Impulse travels in retrograde direction and reenters the conduction pathway causing an extra or irregular heart beat.

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
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 (ie. adenosine)

<table>
<thead>
<tr>
<th>Vaughan-Williams Classification</th>
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<tbody>
<tr>
<td><strong>Subclass</strong></td>
</tr>
<tr>
<td>IA.</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>IB.</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>IC.</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Class II</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Class III</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Class IV</td>
</tr>
<tr>
<td>Others</td>
</tr>
</tbody>
</table>
**Electrophysiological Properties Of Specialized Cardiac Fibers**

<table>
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<th>CLASS OF ANTIARRHYTHMIC DRUG</th>
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<tbody>
<tr>
<td>IA</td>
</tr>
<tr>
<td>Sinus node</td>
</tr>
<tr>
<td>Automaticity</td>
</tr>
<tr>
<td>AV node</td>
</tr>
<tr>
<td>Effective refractory period (ERP)</td>
</tr>
<tr>
<td>Purkinje fibers</td>
</tr>
<tr>
<td>Action potential amplitude</td>
</tr>
<tr>
<td>Phase-0 Vmax</td>
</tr>
<tr>
<td>Action potential duration (APD)</td>
</tr>
<tr>
<td>Effective refractory period (ERP)</td>
</tr>
<tr>
<td>ERP/APD</td>
</tr>
<tr>
<td>Membrane responsiveness</td>
</tr>
<tr>
<td>Automaticity</td>
</tr>
</tbody>
</table>
Shortcomings: Vaughan-Williams system (V-W)

1. Hybrid: Class I, III & IV agents block ion channels, Class II block receptors. Single class can effect multiple mechanisms. Amiodarone: properties of classes (I-IV).

2. Describes drugs that block ion channels/receptors and does not consider drugs that activate channels or receptors.

3. Incomplete: eg. adenosine, digitalis, cholinergic agonists, alpha adrenergic blockers or agents that modulate gap junctions, ion pumps or exchangers. Also ignores drug metabolites.

4. Based on response in normal tissue, not damaged

5. Does not incorporate variable mode of action: slowing tachycardias, terminating dysrhythmias, or preventing them.

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
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---

### Drugs work better on depolarized tissue.....

<table>
<thead>
<tr>
<th>Drug</th>
<th>Block of Sodium Channel</th>
<th>Refractory Period</th>
<th>Calcium Channel Blockade</th>
<th>Effect on Precorder Activity</th>
<th>Sympathetic Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine (adenosine)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Amiodarone (Cabergine)</td>
<td>-</td>
<td>***</td>
<td>??</td>
<td>???</td>
<td>*</td>
</tr>
<tr>
<td>Verapamil (Ervaloe)</td>
<td>0</td>
<td>0</td>
<td>??</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Digoxin (Novo)</td>
<td>-</td>
<td>***</td>
<td>??</td>
<td>*</td>
<td>0</td>
</tr>
<tr>
<td>Enalapril (Soluvel)</td>
<td>+</td>
<td>***</td>
<td>↑</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Flecainide (Tambon)</td>
<td>0</td>
<td>#</td>
<td>↑</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Imipramine (imipramine)</td>
<td>+</td>
<td>*</td>
<td>↑</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Lidocaine (Xylocaine)</td>
<td>0</td>
<td>***</td>
<td>↓</td>
<td>↑↑</td>
<td>0</td>
</tr>
<tr>
<td>Metoprolol (Metol)</td>
<td>0</td>
<td>***</td>
<td>0</td>
<td>??</td>
<td>0</td>
</tr>
<tr>
<td>Mexiletine (Tambon)</td>
<td>-</td>
<td>*</td>
<td>↑</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td>Flecainide (Ervaloe)</td>
<td>0</td>
<td>*</td>
<td>↓</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Flecainide (Ervaloe)</td>
<td>-</td>
<td>***</td>
<td>↑</td>
<td>↑↑</td>
<td>0</td>
</tr>
<tr>
<td>Propafenone (Ponstel, Lexem)</td>
<td>-</td>
<td>***</td>
<td>↑</td>
<td>↑</td>
<td>0</td>
</tr>
<tr>
<td>Propafenone (Kynestra)</td>
<td>-</td>
<td>*</td>
<td>↑</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Flecainide (Ervaloe)</td>
<td>0</td>
<td>*</td>
<td>↑</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mexiletine (Tambon)</td>
<td>0</td>
<td>***</td>
<td>0</td>
<td>⬇</td>
<td>0</td>
</tr>
<tr>
<td>Sotalol (investigational)</td>
<td>0</td>
<td>0</td>
<td>↑</td>
<td>??</td>
<td>0</td>
</tr>
<tr>
<td>Flecainide (Tambon)</td>
<td>0</td>
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<td>0</td>
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<td>↑</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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Key Aspects of Drug Action and Therapy...

A. **Drug action is state-dependent:** channel open, closed, or inactivated. Two current models:
   1. modulated receptor hypothesis: different states have different affinities
   2. 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.

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**Na Channel States**

Quinidine 1A: Open

Lidocaine 1B: Open & Inactive

In depolarized tissue
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).

Other Aspects of Drug Action and Therapy...

A. Multiple actions hinder understanding MOA

B. **Can be prodysrhythmic under certain circumstances**

C. Often affect ANS and cardiovascular system

D. May have significant cardiac and extracardiac toxicity; eg. Class 1A drugs can depress cardiac contractility

E. **Can interact with other drugs.** Useful interactions as well as deleterious interactions occur, with the former exploited in combination therapy (e.g. quinidine and digoxin to treat supraventricular tachycardias). Combinations of antidysrhythmics are used to increase the efficacy of therapy and to avoid the necessity of using higher doses of any particular drug alone.
Quinidine (Class IA prototype)

Other examples: Procainamide, Disopyrimide

1. General properties:
   a. D-isomer of quinine
   b. As with most of the Class I agents
      - moderate block of sodium channels
      - decreases automaticity of pacemaker cells
      - increases effective refractory period/AP duration

2. 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
- Blocks alpha-adrenoreceptors to yield vasodilatation.
- 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 "Cinchenism")

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 binding sites; so avoid giving drugs together or reduce dose
- Probably are active metabolites of quinidine
- 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**
- a. Similar to quinidine, less muscarinic & alpha-adrenergic blockade
- b. Has negative inotropic action also

**Extracardiac effects**
- a. Ganglionic blocking reduces peripheral vascular resistance

**Toxicity**
- a. Cardiac: Similar to quinidine; cardiac depression
- b. Noncardiac: Syndrome resembling lupus erythematosus

**Pharmacokinetics/therapeutics**
- a. Administered orally, i-v and intramuscularly
- b. 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.
- c. $T_{1/2} = 3-4$ hours; necessitates frequent dosing; kidney chief elimination path. NAPA has longer $T_{1/2}$ and can accumulate
- d. Usually used short-term. Commonly used in CCUs for ventricular dysrhythmias associated with acute myocardial infarctions (MI)

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**Lidocaine (Class IB prototype)**

**Other examples: Mexiletine, Phenytoin, Tocainide**

**General**
- a. Commonly used antidysrhythmic agent in emergency care (decreasing use)
- b. Given i-v and i-m; widely used in ICU-critical care units (old DOC, prior 2001)
- c. Low toxicity
- d. 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, i-m 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 arrythmias.
- Drug interaction: Propranolol, cimetidine, ↓ plasma clearance.

## 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 tachycardias
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 automaticity

Cardiac effects (of propranolol), a non-selective beta blocker
  a. Main mechanism of action is block of beta receptors; ↓ Ph 4 slope. 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 (i.e. hyperthyroidism)
  b. Blocks A-V nodal reentrant tachycardias; inhibits ectopic foci
  c. Propranolol used to treat supraventricular tachydyrsrhythmias
  d. Contraindicated in ventricular failure; also can lead to A-V block.

Oral (propranolol) or IV. Extensive metabolism in liver.

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Na⁺/K⁺ - ATPase (3:2)
Beta-Adrenoceptor Antagonists

Properties of several beta-receptor blocking drugs

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Selectivity</th>
<th>Partial Agonist Activity</th>
<th>Local Anesthetic Action</th>
<th>Lipid Solubility</th>
<th>Elimination Half-Life</th>
<th>Approximate Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>β1</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>3-4 hours</td>
<td>50</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>β1</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>6-9 hours</td>
<td>40</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>β1</td>
<td>No</td>
<td>Slight</td>
<td>Low</td>
<td>14-22 hours</td>
<td>50</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>β1</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>6-12 hours</td>
<td>80</td>
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<tr>
<td>Carvedilol</td>
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<td>Yes</td>
<td>No</td>
<td>Low</td>
<td>6 hours</td>
<td>85</td>
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<tr>
<td>Captopril</td>
<td>β1</td>
<td>Yes1</td>
<td>No</td>
<td>Low</td>
<td>4-5 hours</td>
<td>70</td>
</tr>
<tr>
<td>Fosmidol</td>
<td>β1</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>10 minutes</td>
<td>...</td>
</tr>
<tr>
<td>Labetalol</td>
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<td>Yes1</td>
<td>Yes</td>
<td>Moderate</td>
<td>5 hours</td>
<td>30</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>β1</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
<td>3-4 hours</td>
<td>50</td>
</tr>
<tr>
<td>Nadolol</td>
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<td>No</td>
<td>No</td>
<td>Low</td>
<td>14-24 hours</td>
<td>33</td>
</tr>
<tr>
<td>Nebutolol</td>
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<td>Yes</td>
<td>No</td>
<td>High</td>
<td>5 hours</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Pindolol</td>
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<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
<td>3-4 hours</td>
<td>60</td>
</tr>
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<td>Propranolol</td>
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<td>No</td>
<td>Yes</td>
<td>High</td>
<td>3-6 hours</td>
<td>50</td>
</tr>
<tr>
<td>Sotalol</td>
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<td>No</td>
<td>No</td>
<td>Low</td>
<td>12 hours</td>
<td>50</td>
</tr>
<tr>
<td>Timolol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Moderate</td>
<td>4-5 hours</td>
<td>50</td>
</tr>
</tbody>
</table>

*Partial agonists at β1 receptors. *Labetalol also causes α1-selective blockade. *Bioavailability is dose-dependent.

**Clinical uses: Beta-Blockers**

- **Hypertension**: frontline agents
- **Angina (non-selective or β1-selective)**
  - Cardiac: \( \downarrow \)O\(_2\) demand more than O\(_2\) supply
  - Exercise tolerance \( \uparrow \) in angina patients
- **Arrhythmia (β1-selective, LA-action)**
  - \( \downarrow \) SNS-induced increases in conductivity and automaticity
- **Glaucoma (non-selective)**
  - \( \downarrow \) aqueous 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: \( \downarrow \) cardiac manifestation (only propranolol)
  - panic attacks, stage fright
**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)

---

**Amiodarone (Class III)**

- Others: Ibutilide, Bretylium, Sotalol, Dofetilide

- **General**
  - a. New DOC for ventricular dysrhythmias (Lidocaine, old DOC)
  - b. Prolongs refractory period by blocking potassium channels
  - c. Also member of Classes IA,II,III,IV since blocks Na, K, Ca channels and alpha and beta adrenergic receptors
  - d. Serious side effects (cardiac depression, pulmonary fibrosis, thyroid)
  - e. Effective against atrial, A-V and ventricular dysrhythmias
  - f. Widely used, very long acting (>25 d)
AHA Guidelines for VT/VF 2000

1. Amiodarone
2. Procainamide, [Bretylium]
3. Sotalol
4. Lidocaine

AHA Guideline Prior to 2000

1. Lidocaine
2. Procainamide
3. Bretylium
4. Electrical cardioversion

Cardiac effects of Amiodarone

a. Block Na channels (1A), but low affinity for open channels; mainly blocks inactivated Na channels

b. Block is most pronounced in tissues with long action potentials, frequent spiking or more depolarized diastolic potential

c. Weak Ca channel blocker also (Class IV activity)

d. A powerful inhibitor of abnormal automaticity, decreases conduction, increases refractory period and APD.

e. Has antianginal effects (blocks alpha/beta receptors and Ca channels)

Extracardiac effects: Vasodilation via block of Ca channels and alpha receptors
Adverse effects: Amiodarone

A. Cardiac
i. Sinus bradycardia, **increase QT interval**
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. Paresthesias (tingling, pricking, or numbness)
vi. Photosensitivity
vii. Corneal microdeposits and blurred vision
viii. Ataxia, dizziness, tremor
ix. Anorexia, nausea, vomiting
Amiodarone: Pharmacokinetics and therapeutics

- **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

Bretyllium (Class III, K\(^+\) channel blockers)

- Others  Amiodarone , Ibutilide, (Sotalol, also beta-blocker)

General: originally used as an antihypertensive agent

Cardiac effects
  a. Direct antidysrhythmic action
  b. Increases ventricular APD and increases refractory period; decreases automaticity
  c. Most pronounced action in ischemic cells having short APD
  d. Initially stimulates and then blocks neuronal catecholamine release from adrenergic nerve terminals
  e. Blocks cardiac K channels to increase APD

Extracardiac effects: Hypotension (from block of NE release)

Pharmacokinetics/therapeutics
  a. iv or intramuscular
  b. Excreted mainly by the kidney
  c. Usually for emergency use only: ventricular fibrillation when lidocaine and cardioversion therapy fail. Increases threshold for fibrillation.
  d. Decreases tachycardias and early extrasystoles by increasing effective refractory period
Ibutilide (Class III).

1. Prolongs cardiac action potential without additional effects.
2. Mechanism incompletely understood but it known to increase inward Na current and decrease repolarizing K current.
3. Can be administered I-V or orally. Most effective current agent to convert atrial fibrillation and flutter of recent onset to normal rhythm. Low incidence of Torsades (about 2%), compared to other drugs.
4. More effective for flutter than fibrillation
5. Generally well tolerated

Sotalol (Class III and Class II)

1. Non-selective beta blocker, increases AP duration.
2. Dysrhythmias of supraventricular and ventricular origin

Verapamil (Class IV, Ca++ channel blockers)

Other example: Diltiazem - CCBs increasing use and importance

a. Blocks active and inactivated Ca channels, prevents Ca entry
b. More effective on depolarized tissue, tissue firing frequently or areas where activity dependent on Ca channels (SA node; A-V node)
c. Increases A-V conduction time and refractory period; directly slows SA and A-V node automaticity
d. suppresses oscillatory depolarizing after depolarizations due to digitalis
**Ca++ Channel Blockers - Actions**

**Extracardiac**
- a. Peripheral vasodilatation via effect on smooth muscle
- b. Used as antianginal / antihypertensive
- c. Hypotension may increase HR reflexively

**Toxicity**
- a. **Cardiac**
  - Too negative inotropic for damaged heart, depresses contractility
  - Can produce full A-V block
- b. **Extracardiac**
  - Hypotension
  - Constipation, nervousness
  - Gingival hyperplasia

**Pharmacokinetics/Therapeutics**
- a. $T_{1/2} = 7\text{h}$, metabolized by liver
- b. Oral administration; also available parenterally
- c. Great caution for patients with liver disease
- d. Blocks reentrant supraventricular tachycardia ("A-V nodal reentrant tachycardia"), decreases atrial flutter and fibrillation
- e. Only moderately effective against ventricular arrhythmias

---

**Dysrhythmics - Others**

1. Adenosine: i.v. (15 secs), activates P1 purinergic receptors (A1) coupled to K channels, ↓CV, ↑refractory period. SVT. Flushing, hypotension, burning sensation

2. Potassium ions (K+): Depress ectopic pacemakers

3. Digoxin: used to treat atrial flutter and fibrillation
   - AV node ↓conduction (vagal stimulation)
   - myocardium ↓refractory period
   - Purkinje fibers ↑refractory period, ↓conduction

4. Autonomic agents: used to treat A-V block
   - β-agonists (ie.EPI), anticholinergics (ie. atropine)

5. 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>APD</th>
<th>ANS effects</th>
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<tbody>
<tr>
<td>Quinidine</td>
<td>IA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑↑↓↓ M-block, α-block</td>
</tr>
<tr>
<td>Procainamide</td>
<td>IA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑↑↓↓ M-block, α-block</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>IA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑↑↓↓ M-block, α-block</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>IB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓↑↓↑↓↑</td>
</tr>
<tr>
<td>Tocainide</td>
<td>IB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓↑</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>IB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Flecaïnide</td>
<td>IC</td>
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<td></td>
<td></td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Propafenone</td>
<td>IC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑</td>
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<tr>
<td>Propranolol</td>
<td>II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓↓↓↓  β-block</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓↓↓↓  β-block</td>
</tr>
<tr>
<td>Esmolol</td>
<td>II</td>
<td></td>
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<td></td>
<td></td>
<td>↓↓↓↓  β-block</td>
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<tr>
<td>Sotalol</td>
<td>II/III</td>
<td></td>
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<td></td>
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<td>↓↓↓↓  β-block</td>
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<tr>
<td>Amiodarone</td>
<td>III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓↓↓↓ α-, β-block</td>
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<tr>
<td>Bretylium</td>
<td>III</td>
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<td></td>
<td></td>
<td></td>
<td>↑↑ 0                 Sympatholytic</td>
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<td>Verapamil</td>
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<td>Digitalis</td>
<td>Other</td>
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<td></td>
<td>↑↑↓↓                       vagal stimulation</td>
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More important agents
### Pharmacokinetic Properties of Antiarrhythmic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Plasma Binding %</th>
<th>T₁/₂ (hrs)</th>
<th>Drug Excretion Unchanged</th>
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<tbody>
<tr>
<td>Quinidine</td>
<td>IA</td>
<td>60</td>
<td>6</td>
<td>20-40%</td>
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<tr>
<td>Procarbazine</td>
<td>IA</td>
<td>95</td>
<td>10</td>
<td>&lt;1%</td>
</tr>
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<td>Disopyramide</td>
<td>IA</td>
<td>80</td>
<td>10</td>
<td>&lt;10%</td>
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<tr>
<td>Lidocaine</td>
<td>IB</td>
<td>45</td>
<td>95</td>
<td>&gt;25 days</td>
</tr>
<tr>
<td>Tocainide</td>
<td>IB</td>
<td>40</td>
<td>12</td>
<td>10%</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>IB</td>
<td>45</td>
<td>15</td>
<td>40%</td>
</tr>
<tr>
<td>Flecaïnide</td>
<td>IC</td>
<td>40</td>
<td>4</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Propranolol</td>
<td>II</td>
<td>90</td>
<td>15</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>III</td>
<td>15</td>
<td>4</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Esmolol</td>
<td>II (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>9</td>
<td>80%</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>II</td>
<td>95</td>
<td>&gt;25 days</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Bretylium</td>
<td>III</td>
<td>5</td>
<td>9</td>
<td>80%</td>
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<tr>
<td>Verapamil</td>
<td>IV</td>
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<td>5</td>
<td>2%</td>
</tr>
<tr>
<td>Adenosine</td>
<td>Misc (other)</td>
<td>15 sec</td>
<td>0%</td>
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</tbody>
</table>

**Drug Excretion:**
- Unchanged

**Key:**
- Class I: High degree of AV nodal block
- Class II: Moderate degree of AV nodal block
- Class III: No AV nodal block
- Class IV: Positive dromotropic and inotropic effects

**Site:**
- Ventricular vs Supraventricular

**Dysrhythmia Treatment:**
- Treatment: Acute vs Chronic

**Lipincott's Illustrated Reviews: Pharmacology, 4th Ed**

**Note:**
- This page contains information on the pharmacokinetic properties of antiarrhythmic drugs, including their plasma binding percentages, half-lives, and drug excretion. The table outlines the characteristics of various drugs and their effects on different cardiac rhythms, emphasizing the importance of understanding these properties in the context of treating dysrhythmias.