Setting the membrane potential

Nernst

\[ E_{eq} = -61 \log \left( \frac{[S]_i}{[S]_o} \right) \]

Goldman Hodgkin Katz

\[ E_m = \frac{RT}{F} \ln \left( \frac{P_K[K]_o + P_{Na}[Na]_o}{P_K[K]_i + P_{Na}[Na]_i} \right) \]

<table>
<thead>
<tr>
<th>Current</th>
<th>Equil. Pot.</th>
<th>Effect on ( E_m )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( I_{Na} )</td>
<td>+60 mV</td>
<td>Depolarize</td>
</tr>
<tr>
<td>( I_K )</td>
<td>-100 mV</td>
<td>Repolarize</td>
</tr>
<tr>
<td>( I_{Ca} )</td>
<td>+120 mV</td>
<td>Depolarize</td>
</tr>
</tbody>
</table>
How ion channels work

Closed ➔ Open ➔ Inactivated

Activation gate

Inactivation gate

$\text{Na}^+$
Ionic Basis of the Action Potential

Current drugs work by blocking channels

Na^+
Effects of Na\(^+\) channel blockade

- **↓ Conduction velocity (CV) - main effect**
- **↑ AP threshold = ↓ automaticity = ↑ pacing and defibrillation thresholds.**
- Slight decrease in action potential duration
- **Negative inotropy - Lower Na\(^+\) permeability through the channel means less Na\(^+\) in the cell. Less Na\(^+\) in the cell means more driving force for the Na/Ca exchanger. More Na/Ca exchange means less intracellular Ca\(^{2+}\) and less contractility.**
Use dependence or why drugs work better in tachycardia
Details of use dependence

% available

Beats
Effects of $K^+$ channel block

- ↑ Action potential duration (APD) = ↑ refractoriness - main effect
- ↑ Positive inotropy - The longer the action potential is the more $Ca^{2+}$ enters the cell. Unfortunately, this effect generally is not seen clinically.
Ca\textsuperscript{2+} channel effects

- Inhibit the SA node, AV node, and some tissue with abnormal automaticity dependent on Ca\textsuperscript{2+} channels (e.g. right ventricular outflow tachycardia) - main effect
- Generally little effect on the APD
- Stops triggered activity - EADs depend on Ca\textsuperscript{2+} channels to open to depolarize the cell. DADs result from Ca\textsuperscript{2+} overload of the cell. In either case, Ca\textsuperscript{2+} channel blockers improve the situation.
Mechanisms of arrhythmia

- Automaticity
  - Normal (e.g. sinus tachycardia)
  - Abnormal (e.g. reperfusion arrhythmias)

- Triggered activity
  - Early afterdepolarizations associated with QT prolongation (torsades de pointes)
  - Delayed afterdepolarizations associated with Ca\(^{2+}\) overload (e.g. digoxin)

- Reentry
  - Fixed obstruction (e.g. atrial flutter)
  - Leading circle (e.g. ventricular fibrillation)
Getting rid of reentry

The critical wavelength is $\text{APD} \times \text{CV}$

- $\text{K}^+ \text{ channel block}$
- Prolong the refractory period
- $\text{Na}^+ \text{ channel block}$
- Critically slow conduction
Vaughan Williams classification of antiarrhythmic drugs

- Class I – Na⁺ channel blockers
  - Class Ia - Decrease conduction velocity and increase APD. Used most frequently for conversion of atrial flutter/fibrillation and maintenance of sinus rhythm.
  - Class Ib - Minimal change in conduction velocity and a slight decrease in action potential duration. Not useful for atrial arrhythmias. Used for ventricular arrhythmias, especially those associated with myocardial infarction/ischemia but not for prophylaxis.
  - Class Ic - Marked prolongation of CV. Used for atrial flutter/fibrillation in patients with structurally normal hearts.
 Vaughan Williams classification (continued)

- Class II - β blockers
- Class III - Prolong APD - used in atrial and ventricular arrhythmias
- Class IV – Ca^{2+} channel blockers. Dihydropyridines are not effective antiarrhythmic drugs because they have little effect on cardiac Ca^{2+} channels.
- Others
  - Adenosine
    - Potentiated by dipyridamole, an adenosine uptake inhibitor
    - Inhibited by methylxanthines (e.g. caffeine) which block the receptor
    - Use with care in cardiac transplant recipients because of hypersensitivity
Quinidine – class Ia

- Diastereomer of quinine from the cinchona plant
- $\alpha$ Adrenergic block and vagolytic - results in hypotension when given IV and acceleration in AV conduction if used alone.
- Hepatic metabolism
- Inhibits CYP450 2D6 and raises digoxin levels
- Side effects
  - diarrhea (25-50%)
  - reversible thrombocytopenia
  - cinchonism (headache and tinnitus)
  - hepatitis
  - bone marrow suppression
  - lupus-like syndrome
Procainamide – class Ia

- Metabolite, N-acetyl procainamide (NAPA), blocks K⁺ channels
- Marked variations in metabolism based on acetylation rates
- Better tolerated IV than quinidine
- May cause lupus-like syndrome when given long term (30%). Most (70%) get antinuclear antibodies, especially slow acetylators.
- Renal excretion

Procanbid, Pronestyl
Disopyramide - Ia

- Rarely used except for hypertrophic cardiomyopathy and neurocardiogenic syncope
- Prominent anticholinergic effects
- Significantly negatively inotropic

Norpace
Lidocaine – class Ib

- Given IV because of hepatic first pass metabolism
- Toxicity is neurological such as tremor, nystagmus, or delirium
Other class Ib drugs

- Mexiletine
  - Equivalent to oral lidocaine
  - Hepatic metabolism
  - GI symptoms; take with food

- Phenytoin (Dilantin)
  - Not frequently used
  - Liver metabolized

- Tocainide (Tonocard) - not frequently used because of potential bone marrow suppression and pulmonary fibrosis
Class Ic

- Flecainide (Tambocor)
  - increased mortality after MI in CAST
  - has minor K\(^+\) channel blocking properties
  - common side effect is blurred vision

- Propafenone (Rythmol)
  - S-(+)-enantiomer is a β blocker
  - metabolized by CYP450 2D6 - 5-hydroxy propafenone blocks Na\(^+\) channels but not β receptors
  - increases digoxin (83%), warfarin, metoprolol
  - Renal and liver dose adjustments

- Moricizine
  - phenothiazine derivative
  - increased mortality after MI in CAST-II
Amiodarone (Cordarone)– class III

- Most effective drug for maintenance of sinus rhythm in patients with atrial fibrillation and for decreasing risk of ventricular tachyarrhythmias
- Has little effect on contractility and is one of the best drugs to use in heart failure
- Shown to improve mortality in nonischemic cardiomyopathy patients at risk of sudden death, possible advantageous after MI
- Has properties of all four classes (i.e. Na\(^+\), K\(^+\), Ca\(^{2+}\) channel blocker and noncompetitive \(\alpha,\beta\) blocker)
- Can be given IV or oral
- Lipophilic - requires a loading dose and has a half life of weeks (800-1600 mg/day for 1-3 weeks, 600-800 mg for 1 month)
- Can be used in renal failure
- Onset of action 2 days – 2 weeks even with loading
- CAMIAT (arrhythmia), EMIAT (EF<40%) showed safety in structural heart disease
- Get baseline CXR, PFTs, LFTs, TFTs
Amiodarone side effects

- A thyroxine analog containing iodine that can give hypothyroid or hyperthyroid symptoms
- Nausea
- Pulmonary fibrosis that can be irreversible and life threatening - unusual at doses used for atrial fibrillation (200 mg/day)
  - gallium scan and DLCO reduction of 30% are helpful
  - 10% fatal, most reversible
- Hepatitis
- Corneal deposits - usually clinically unimportant and reversible
- Myopathy
- Skin deposit that leads to photosensitivity and bluish tint
- Neuropathy
- Raise levels of digoxin (50-75%), warfarin (50-100%), diltiazem, cyclosporin

N Engl J Med 1997; 337:1814
Other class III agents

- **d,l – Sotalol (Betapace)**
  - *l*-Enantiomer is a non selective β blocker and K⁺ channel blocker; *d*-enantiomer is a pure K⁺ channel blocker
  - *d*-Sotatol increased mortality in the SWORD trial
  - Renal dose adjustments required
  - Do not start if QTc >450 ms, stop if QTc >520 ms

- **Bretylium**
  - Generally used in ACLS protocols only
  - Causes degranulation of sympathetic neurons and prevents reuptake
  - Causes orthostasis, nausea

- **Ibutilide (Covert)**
  - Used IV for acute conversion of atrial flutter/fibrillation
  - About 40% effective (atrial flutter > atrial fibrillation) with about <10% incidence of torsades (>in low EF)
  - Activates a prolonged Na⁺ current
  - Similar structurally to sotalol
  - t½ = 6-9 hours, liver metabolism
Other class III agents (cont.)

- Dofetilide (Tikosyn)
  - Renal excretion
  - DIAMOND CHF and MI showed safety in structural heart disease
  - Avoid verapamil, cimetidine, trimethoprim, prochlorperazine, megestrol, or ketoconazole, which alter renal excretion
  - Do not start if QTc >440 ms, stop if QTc >500 ms

- Azimilide
  - Not approved yet
  - Blocks a new class of $K^+$ channels
  - Probably safe in low EF structural heart disease
  - Being developed for atrial arrhythmias
  - No renal dose adjustments necessary
Proarrhythmia

- Class I proarrhythmia may be drug induced Brugada syndrome
- Class III proarrhythmia is related to QT prolongation
Drugs, ablation, or devices?

- **Common drug uses**
  - Supraventricular rhythms not curable by other means, such as atrial fibrillation. Since atrial fibrillation is present in up to 10% of the elderly population, this is the major use of antiarrhythmic drugs.
  - Termination of hemodynamically stable rhythms including VT or SVT.
  - Treatment of hemodynamically stable rhythms, especially if they occur frequently. For example, treating a hemodynamically stable but incessant VT with an ICD would result in multiple shocks and rapid depletion of the ICD battery.
  - Combination therapy with ICDs to decrease the shock occurrences.
  - When other methods are impossible to use. For example, the patient is a poor candidate for ablation or an ICD because of infection, coagulopathy, etc.
Pearls

- Drugs work best when the EF is high.
- Drugs have most proarrhythmia when EF is low.
- Use amiodarone, quinidine, mexiletine, moricizine, ibutilide, or lidocaine in renal failure.
- Amiodarone’s risk of torsades is poorly related to QT prolongation.
- Classes Ia, Ic, II, IV are negatively inotropic.
- Only amiodarone, sotalol, and dofetilide are known safe in low EF patients.
- Use AV blockers with class Ic drugs for PAF.
- Start everything but amiodarone in house.
- Monitor QRS duration with class Ic drugs.