

Antiarrhythmic drug pharmacology

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Setting the membrane potential

Nernst

$$E_{eq} = -61 \log \frac{[S]_i}{[S]_o}$$

Goldman Hodgkin Katz

$$E_m = \frac{RT}{F} \ln \frac{P_K [K]_o + P_{Na} [Na]_o}{P_K [K]_i + P_{Na} [Na]_i}$$

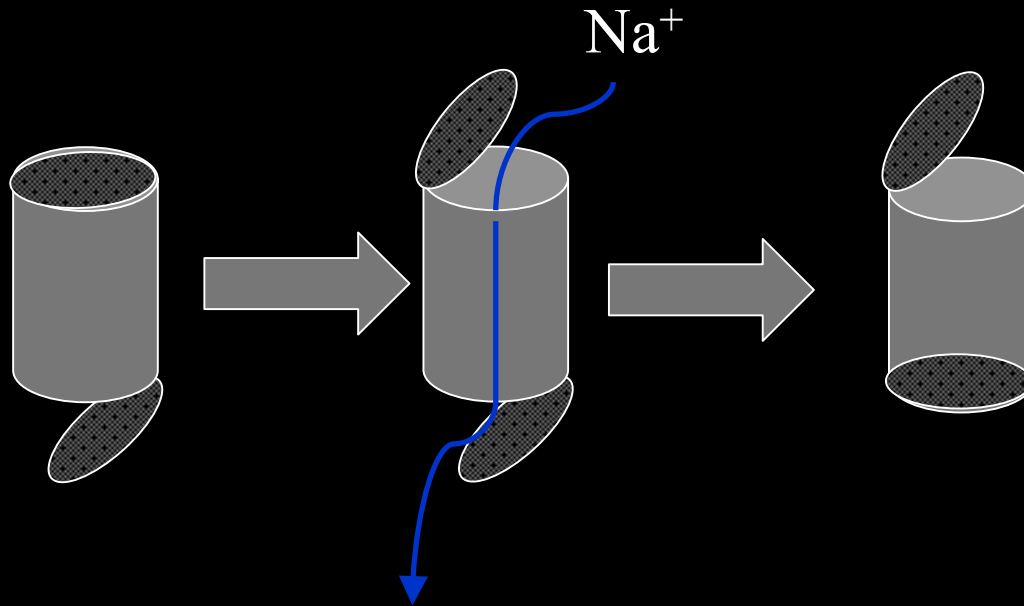
Current	Equil. Pot.	Effect on E_m
I_{Na}	+60 mV	Depolarize
I_K	-100 mV	Repolarize
I_{Ca}	+120 mV	Depolarize

How ion channels work

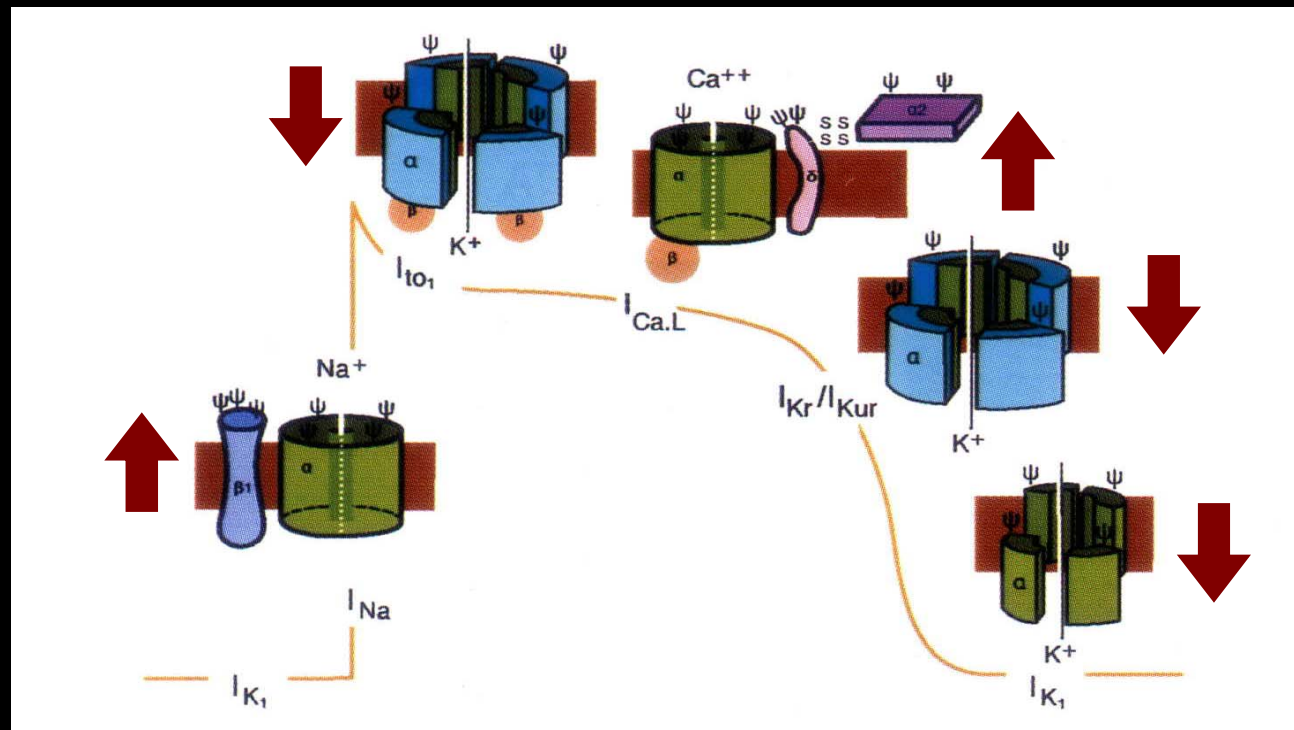
Closed \longrightarrow Open \longrightarrow Inactivated

Activation gate

Inactivation gate

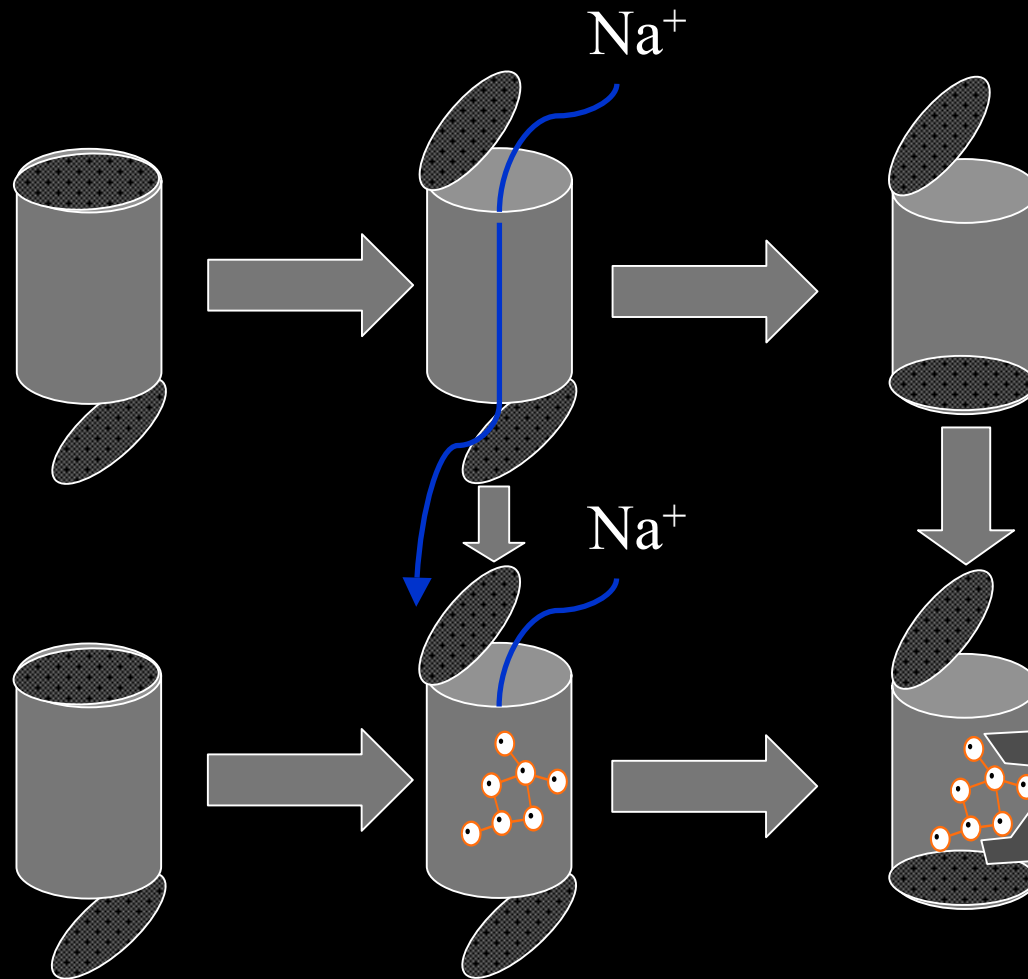


Ionic Basis of the Action Potential



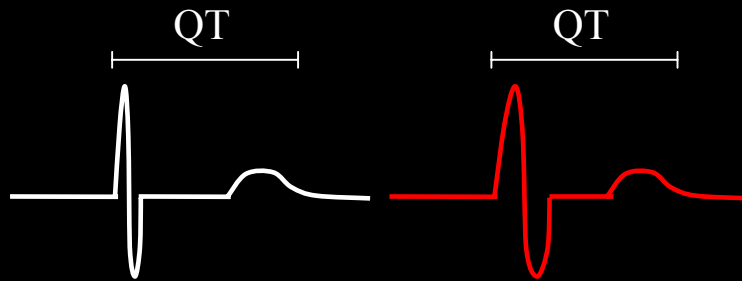
Ackerman and Clapham. 1999. In *Mol. Basis of Cardiovascular Disease*. Ed. Chien. 284.

Current drugs work by blocking channels

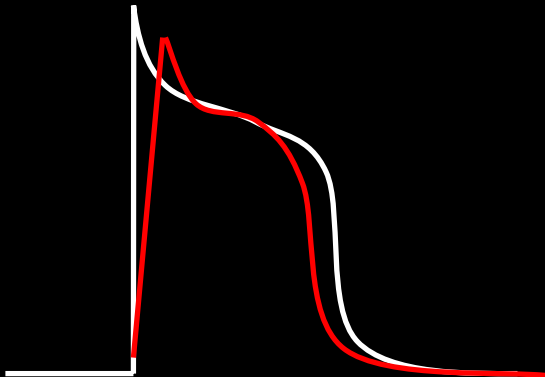


Effects of Na⁺ channel blockade

EKG

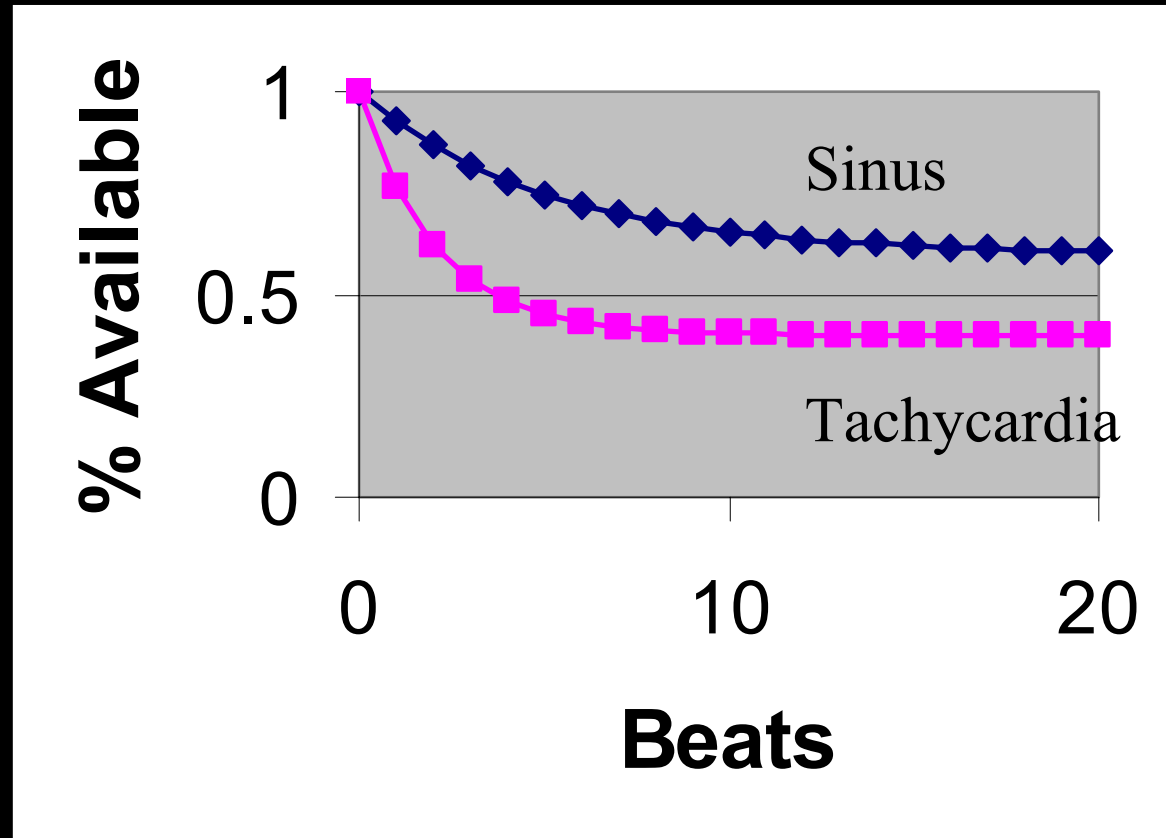


AP

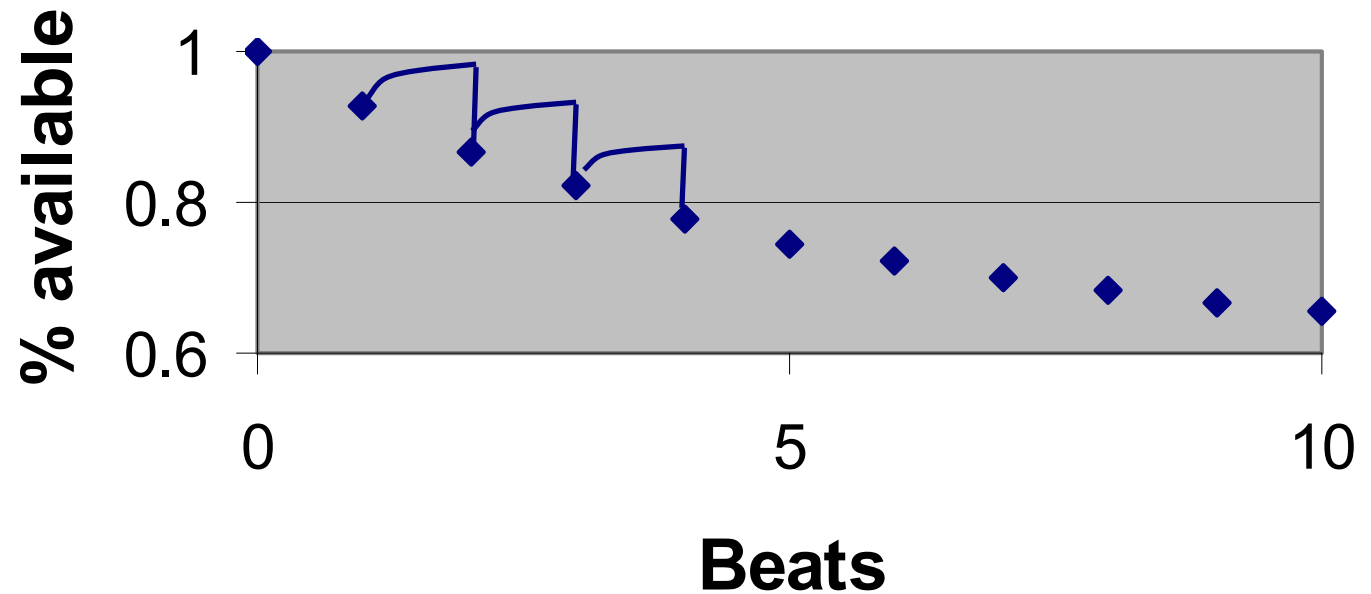


- ↓ Conduction velocity (CV) - main effect
- ↑ AP threshold = ↓ automaticity = ↑ pacing and defibrillation thresholds.
- Slight decrease in action potential duration
- Negative inotropy - Lower Na⁺ permeability through the channel means less Na⁺ in the cell. Less Na⁺ in the cell means more driving force for the Na/Ca exchanger. More Na/Ca exchange means less intracellular Ca²⁺ and less contractility.

Use dependence or why drugs work better in tachycardia

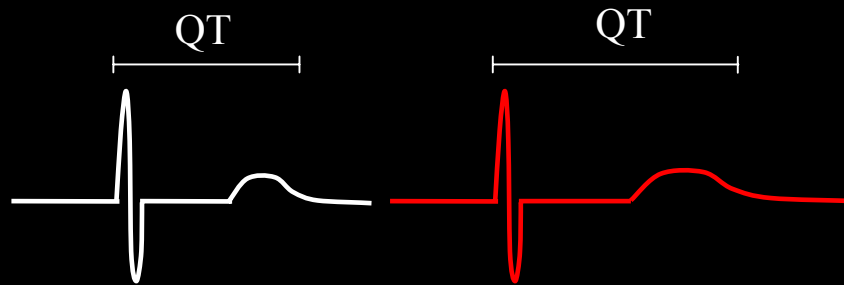


Details of use dependence

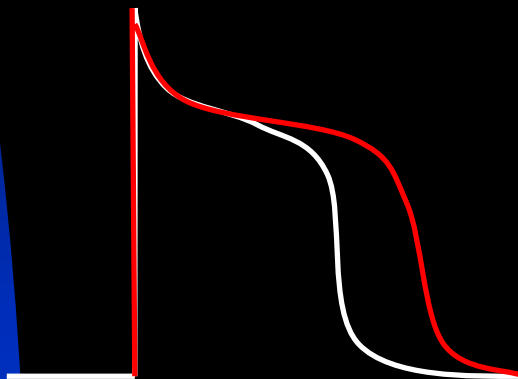


Effects of K⁺ channel block

EKG

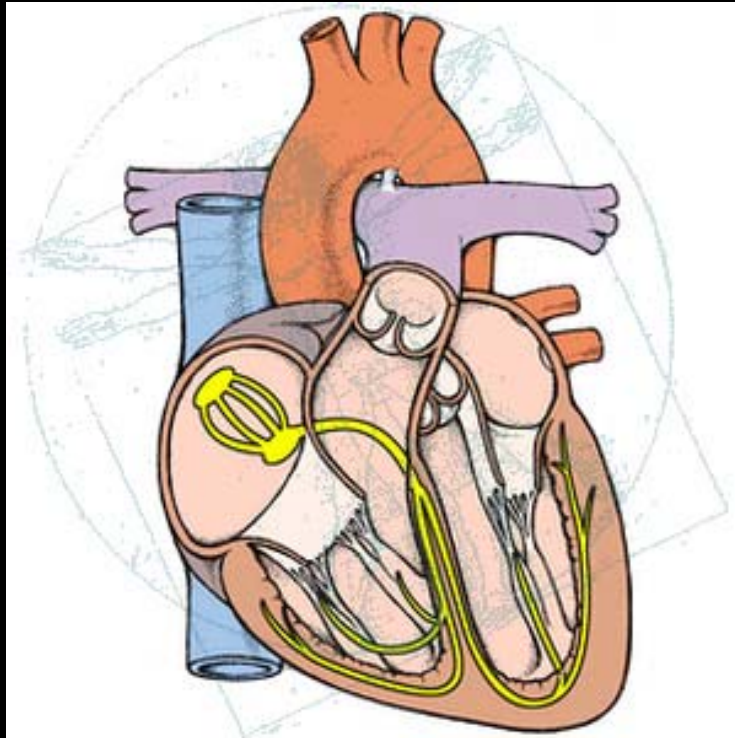


AP



- ↑ Action potential duration (APD) = ↑ refractoriness - main effect
- ↑ Positive inotropy - The longer the action potential is the more Ca²⁺ enters the cell. Unfortunately, this effect generally is not seen clinically.

Ca²⁺ channel effects

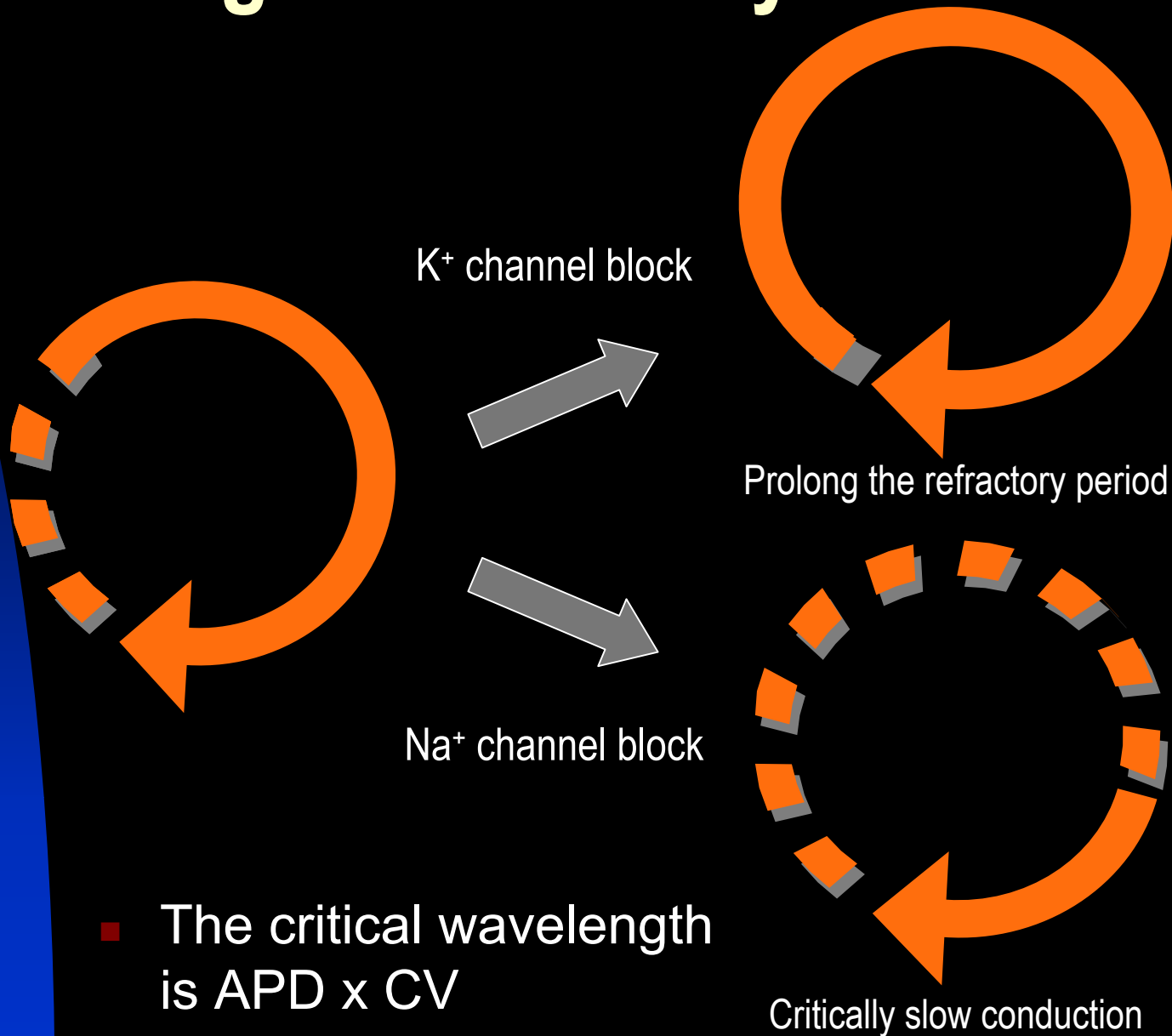


- Inhibit the SA node, AV node, and some tissue with abnormal automaticity dependent on Ca²⁺ channels (e.g. right ventricular outflow tachycardia) - main effect
- Generally little effect on the APD
- Stops triggered activity - EADs depend on Ca²⁺ channels to open to depolarize the cell. DADs result from Ca²⁺ overload of the cell. In either case, Ca²⁺ 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



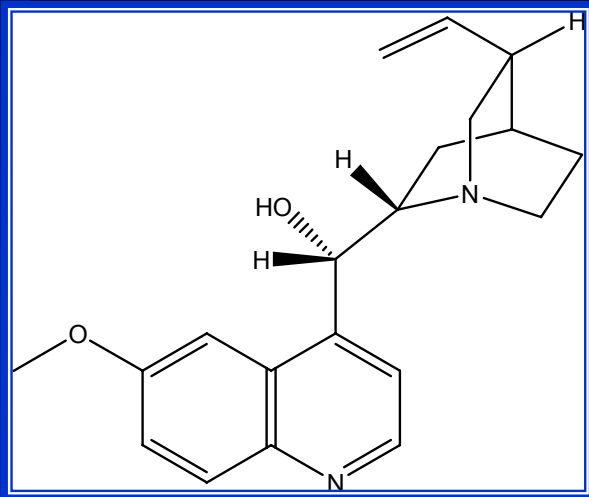
Vaughan Williams classification of antiarrhythmic drugs

- 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

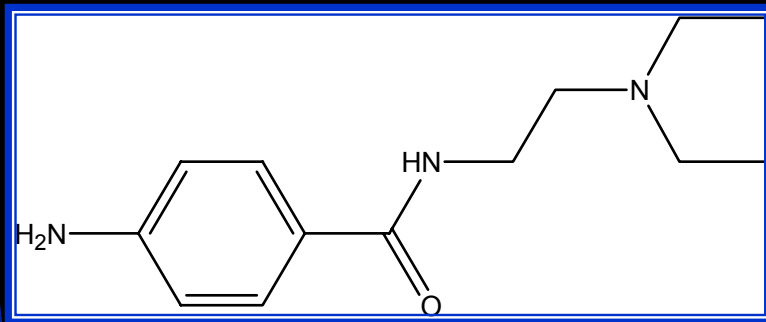
Quinidine – class Ia



Quinaglute, Quinidex

- Diastereomer of quinine from the cinchona plant
- α 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

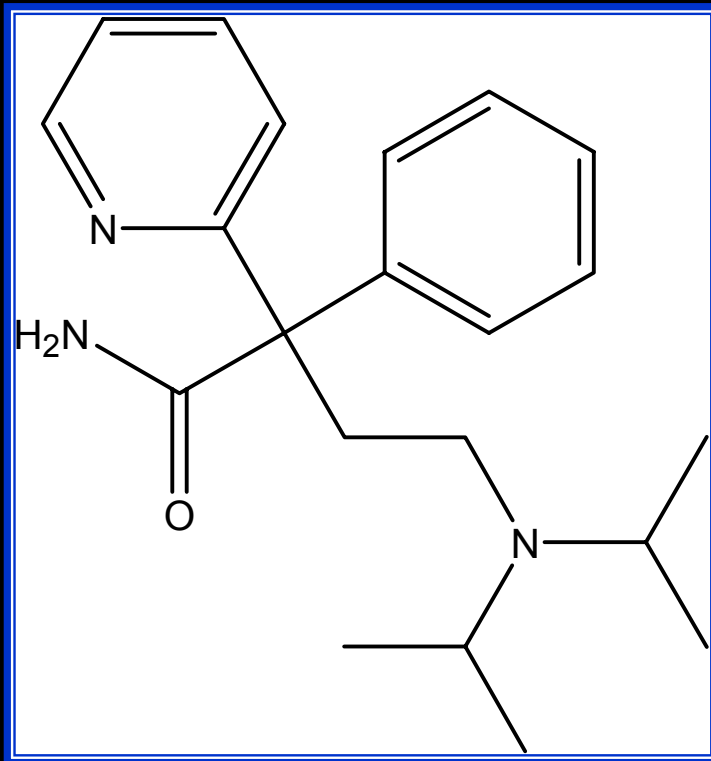
Procainamide – class Ia



Procanbid, Pronestyl

- 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

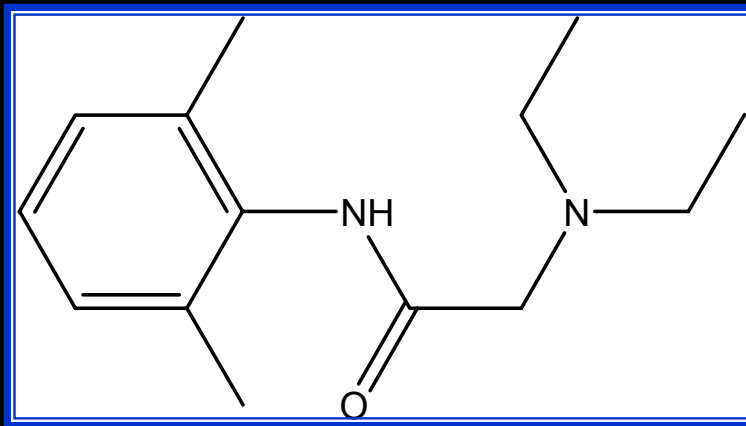
Disopyramide - Ia



Norpace

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

Lidocaine – class Ib

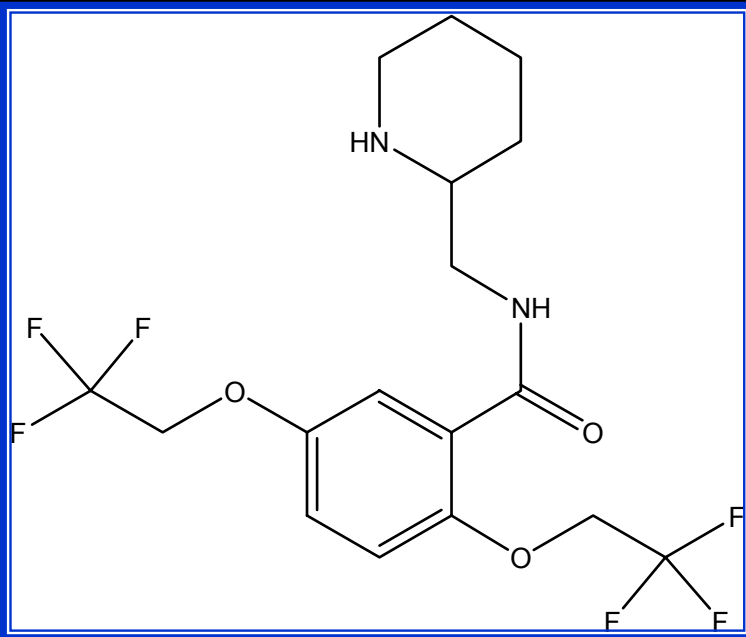


- Given IV because of hepatic first pass metabolism
- Toxicity is neurological such as tremor, nystagmus, or delirium

Other class Ib drugs

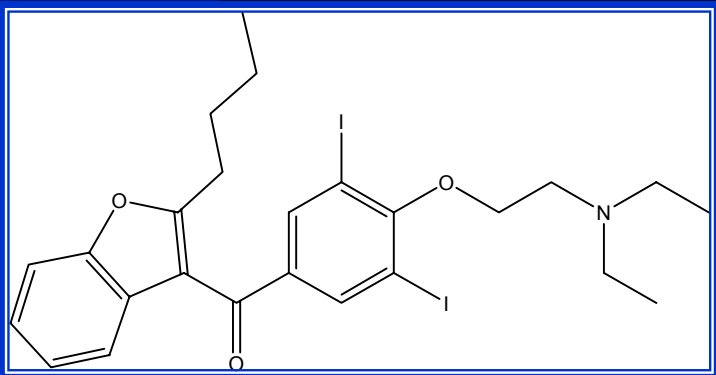
- Mexiletine
 - ◆ Equivalent to oral lidocaine
 - ◆ Hepatic metabolism
 - ◆ GI symptoms; take with food
- Phenytoin (Dilantin)
 - ◆ Not frequently used
 - ◆ Liver metabolized
- Tocainide (Tonocard) - not frequently used because of potential bone marrow suppression and pulmonary fibrosis

Class Ic



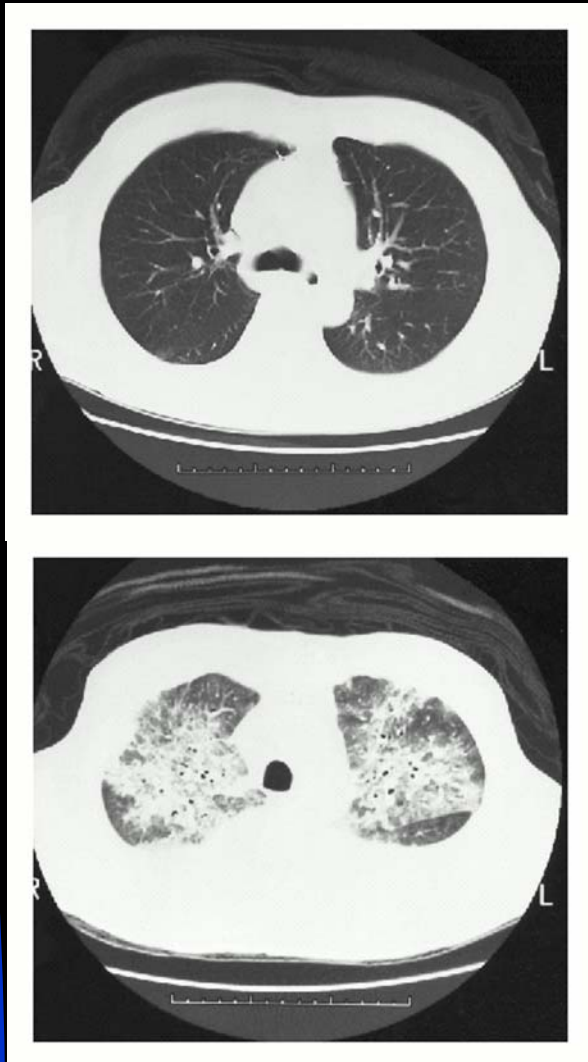
- Flecainide (Tambocor)
 - ◆ increased mortality after MI in CAST
 - ◆ has minor K⁺ channel blocking properties
 - ◆ common side effect is blurred vision
- Propafenone (Rythmol)
 - ◆ S-(+) enantiomer is a β blocker
 - ◆ metabolized by CYP450 2D6 - 5-hydroxy propafenone blocks Na⁺ channels but not β receptors
 - ◆ 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⁺, Ca²⁺ channel blocker and noncompetitive α , β 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

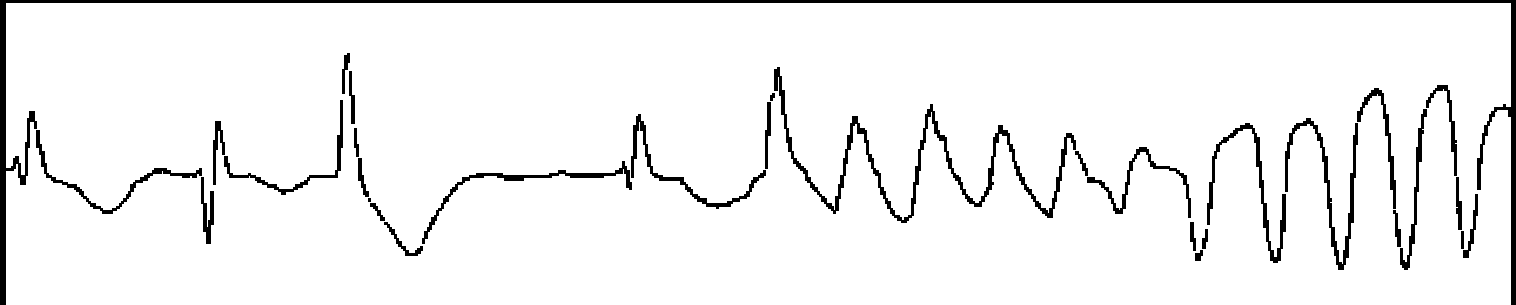
Other class III agents

- *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*-Sotalol 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
 - ◆ $t_{1/2}$ = 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.