Drugs used in treatment of Cardiovascular System

Antiarrhythmic drugs

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Cardiac arrhythmia

- Are abnormalities in the rate, regularity or site of origin of cardiac impulse, or disturbance in conduction of the impulse such that normal sequence of activation of the atria & ventricles is altered.

- Arrhythmia may result from:

1. Disturbances in impulse formation.
2. Disturbance in impulse conduction.
3. Both.

Cardiac electrophysiology

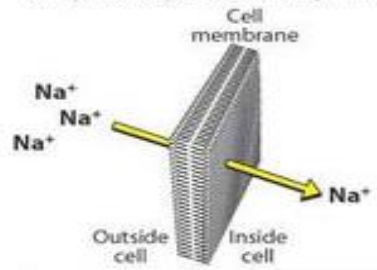
- The heart contain specialized tissue that exhibit automaticity (can generate A.P. in the absence of external stimulation).

- These pacemaker cells differs from other myocardial cells in showing a slow spontaneous depolarization during diastole (phase 4) caused by the inward current carried by sodium & calcium.

- The depolarization is fastest in the SA node (normal pacemaker) beating at frequency 60-100 beat/min then impulse spreads rapidly to the atria & enters the AV node(which is normally the only conductive pathway between the atria & ventricles), conduction through the AV node is slow (0.15 sec.) then the impulse propagates over the His-Purkinji system & invades all parts of the ventricles. Ventricles activation is complete in less than 0.1 sec.

PHASE 0: FAST UPSTROKE

- Na^+ channels open ("fast channels") resulting in a fast inward current.
- Upstroke ends as Na^+ channels are rapidly inactivated.
- Sodium current is blocked by anti-arrhythmic agents, such as *quinidine*.

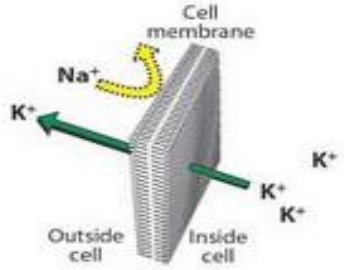


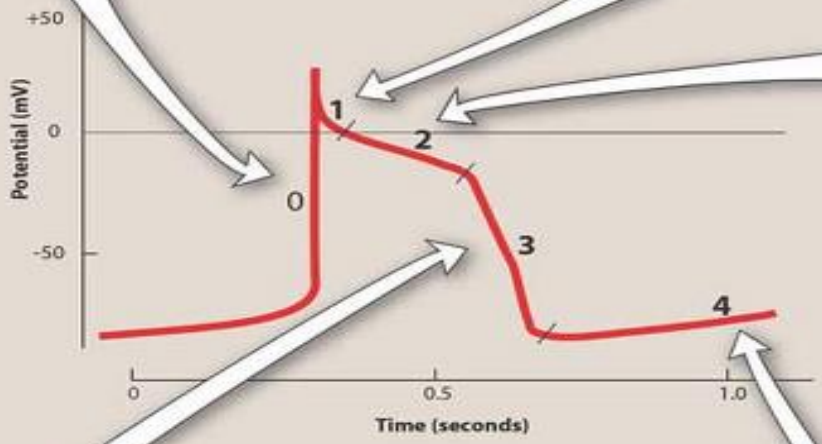
PHASE 1: PARTIAL REPOLARIZATION

- The initial rapid phase of repolarization is due to:

  1) inactivation of Na^+ channels.

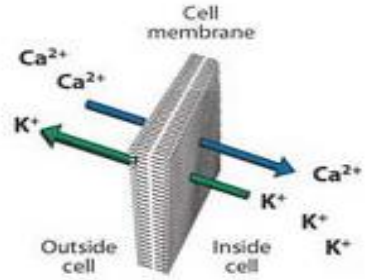
  2) K^+ channels that rapidly open and close, causing a transient outward current.





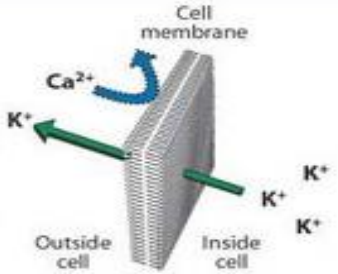
PHASE 2: PLATEAU

- Voltage-sensitive Ca^{2+} channels open, resulting in a slow inward (depolarizing) current that balances the slow outward (polarizing) leak of K^+.



PHASE 3: REPOLARIZATION

- Ca^{2+} channels close.
- K^+ channels open, resulting in an outward current that leads to membrane repolarization.
- The net result of the action to this point is a net gain of Na^+ and loss of K^+. This imbalance is corrected by Na^+/K^+-ATPase.



PHASE 4: FORWARD CURRENT

- Increasing depolarization results from gradual increase in sodium permeability.
- The spontaneous depolarization automatically brings the cell to the threshold of the next action potential.

Classification of Antiarrhythmic drugs

- Class I: (Na-channel blockers)

✓IA: lengthen the duration of AP.

✓IB: shorten the duration of AP.

✓IC: no effect on duration of AP.

- Class II: are sympathoplegic drugs. i.e. BB

- Class III: prolong the AP duration by prolonging phase 3 repolarization (K-channel blockers).

- Class IV: block the cardiac Ca^{2+} current (CCB).

- Miscellaneous antiarrhythmic: digoxine, adenosine, magnesium.

Class I

- Class I antiarrhythmic drugs act by blocking voltage-sensitive sodium channels.

- The decreased rate of entry of sodium slows the rate of rise of Phase 0 of the action potential. Therefore, generally cause a decrease in excitability and conduction velocity.

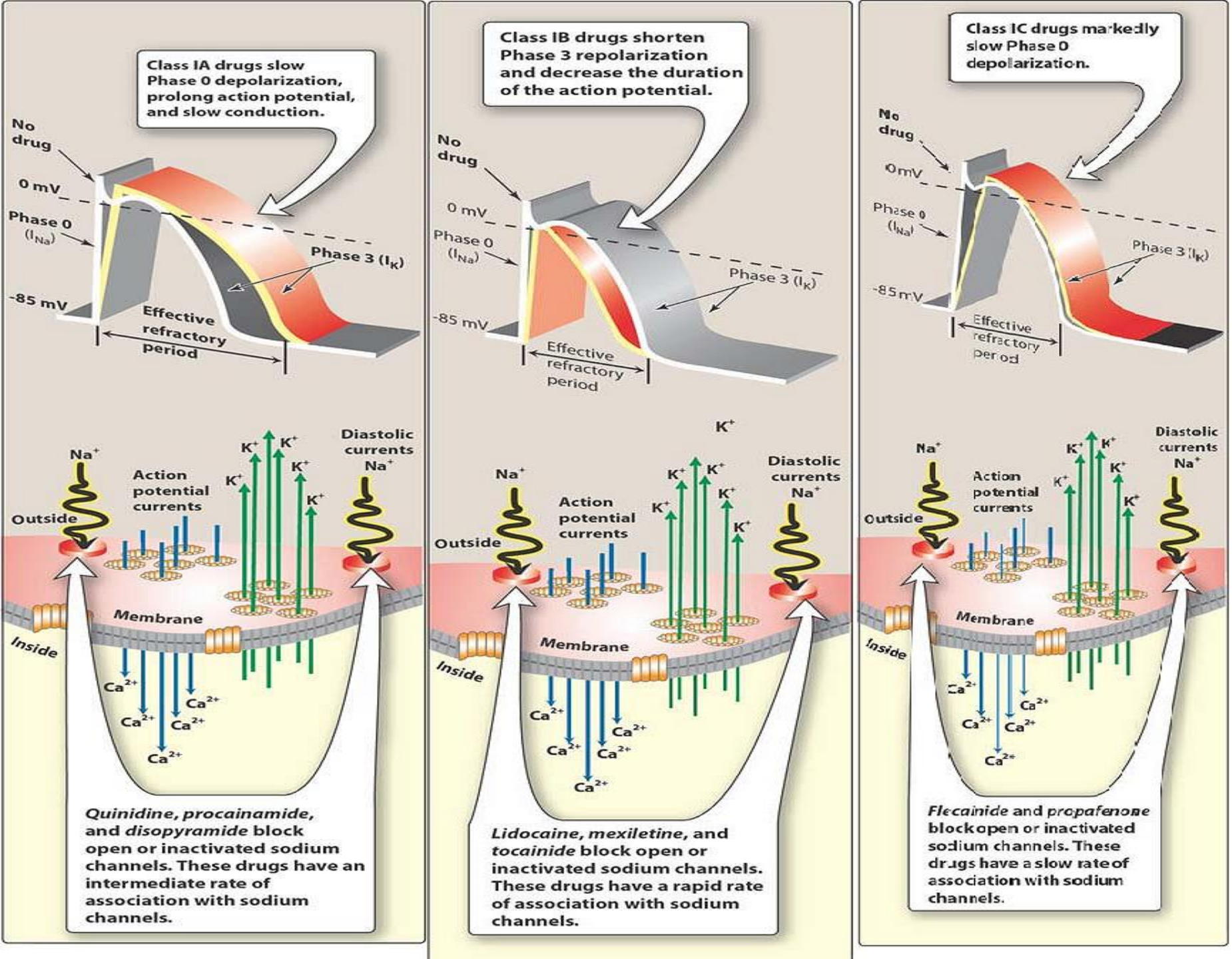
- Class I drugs bind more rapidly to open or inactivated sodium channels than to channels that are fully repolarized following recovery from the previous depolarization cycle. Therefore, these drugs show a greater degree of blockade in tissues that are frequently depolarizing. This property is called use-dependence (or state-dependence)

- The Class I drugs have been subdivided into three groups according to their effect on the duration of the action potential:

- Class IA agents slow the rate of rise of the action potential (thus slowing conduction), prolong the action potential, and increase the ventricular effective refractory period. They have an intermediate speed of association with activated/inactivated sodium-channels and an intermediate rate of dissociation from resting channels. Prolongation of duration of the action potential and increased ventricular effective period are due to concomitant Class III activity.

- Class IB drugs have little effect on the rate of depolarization; rather, they decrease the duration of the action potential by shortening repolarization. They rapidly interact with sodium channels.

- Class IC agents markedly depress the rate of rise of the membrane action potential. Therefore, they cause marked slowing of conduction but have little effect on the duration of the membrane action potential or the ventricular effective refractory period. They bind slowly to sodium channels.


Class IA drugs slow Phase 0 depolarization, prolong action potential, and slow conduction.
No drug
0 mV
Phase 0 (I_{Na})
Phase 3 (I_K)
-85 mV
Effective refractory period
Na+
Action potential currents
K+
Diastolic currents Na+
Outside
Membrane
Inside
Ca2+
Quinidine, procainamide, and disopyramide block open or inactivated sodium channels. These drugs have an intermediate rate of association with sodium channels.
Class IB drugs shorten Phase 3 repolarization and decrease the duration of the action potential.
No drug
0 mV
Phase 0 (I_{Na})
Phase 3 (I_K)
-85 mV
Effective refractory period
K+
Na+
Action potential currents
Diastolic currents Na+
Outside
Membrane
Inside
Ca2+
Lidocaine, mexiletine, and tocainide block open or inactivated sodium channels. These drugs have a rapid rate of association with sodium channels.
Class IC drugs markedly slow Phase 0 depolarization.
No drug
0 mV
Phase 0 (I_{Na})
Phase 3 (I_K)
-85 mV
Effective refractory period
Na+
Action potential currents
K+
Diastolic currents Na+
Outside
Membrane
Inside
Ca2+
Flecainide and propafenone block open or inactivated sodium channels. These drugs have a slow rate of association with sodium channels.

Quinidine

- Quinidine is the prototype Class IA drug. Because of its concomitant Class III activity, it can actually precipitate arrhythmias such as polymorphic ventricular tachycardia (torsades de pointes), which can degenerate into ventricular fibrillation.
- Because of the toxic potential of quinidine, calcium antagonists, such as amiodarone and verapamil, are increasingly replacing this drug in clinical use.

- <u>Mechanism of action:</u>

Quinidine binds to open and inactivated sodium channels and prevents sodium influx, thus slowing the rapid upstroke during Phase 0. It also decreases the slope of Phase 4 spontaneous depolarization and inhibits potassium channels.

- <u>Therapeutic uses:</u>

1. SVA (supraventricular arrhythmia): prevent recurrence of paroxyzmal SVT due to AV nodal or Wolff-Parkinson-White (WPW) syndrome.
2. Convert atrial flutter or AF to normal sinus rhythm and prevent recurrence of flutter and AF. Quinidine should not be used without prior digitalization because of its vagolatic action (i.e. cause tachycardia).
3. Ventricular arrhythmia, PVC (premature ventricular contraction) to prevent VT after cardioconversion of the arrhythmia.

- **Adverse effects:**

1. Cardiac toxicity: which include:

A- AV block, SA block and even asystole.

B- exacerbation of the arrhythmia.

C- myocardial depression.

2. GIT: Nausea, vomiting, anorexia, and diarrhea are commonly observed.

3. CNS-Cinchonism

- **Contraindications:**

1. Previous allergy, heart failure, hypotension, AV block & sick sinus syndrome.
2. Poisoning with digitalis.
3. Myasthenia gravis, it cause muscular weakness because it blocks Na entry to the muscle.

Procainamide

- Pharmacologic effect: is similar to quinidine.

- Extracardial effect: when given I.V. it may cause a drop in BP due to peripheral vasodilation.:

- Therapeutic uses: same as quinidine (SAV, convert AF or flutter to normal sinus rhythm, VA).

- Pharmacokinetics: can be gien orally, I.V., I.M.

- Peak effect in one hour.
- After oral adm, t1/2 = 3 hrs.
- Elimination by hepatic metabolism and renal excretion.
- Renal failure might produce toxicity.

- Adverse effect

1. Acute procainamide toxicity can produce ventricular arrhythmia, VF and cardiac depression.
2. Nausea, vomiting, diarrhea, and anorexia are common but less than quinidine.
3. Mental convulsion has be reported but less than procaine.
4. Hypersensitivity reaction are much more common than quinidine, it includes: A- fever, joint and muscular pain, and skin rash. (B) fetal agranulocytosis.

Disopyramide

- Actions:

This Class IA drug shows actions similar to those of quinidine.

Disopyramide produces a negative inotropic effect that is greater than the weak effect exerted by quinidine and procainamide, and unlike the latter drugs, disopyramide causes peripheral vasoconstriction. The drug may produce a clinically important decrease in myocardial contractility in patients with preexisting impairment of left ventricular function.

Disopyramide is used in the treatment of ventricular arrhythmias as an alternative to procainamide or quinidine. Like procainamide and quinidine, it also has Class III activity.

- Pharmacokinetics: Approximately half of the orally ingested drug is excreted unchanged by the kidneys. Approximately 30 percent of the drug is converted by the liver to the less active mono-N-dealkylated metabolite.

- Adverse effects: Disopyramide shows effects of anticholinergic activity (for example, dry mouth, urinary retention, blurred vision, and constipation).

Class IB drugs:

- Lidocaine

The Class IB agents rapidly associate and dissociate from sodium channels. Thus, the actions of Class IB agents are manifested when the cardiac cell is depolarized rapidly.

- Class IB drugs are particularly useful in treating ventricular arrhythmias.

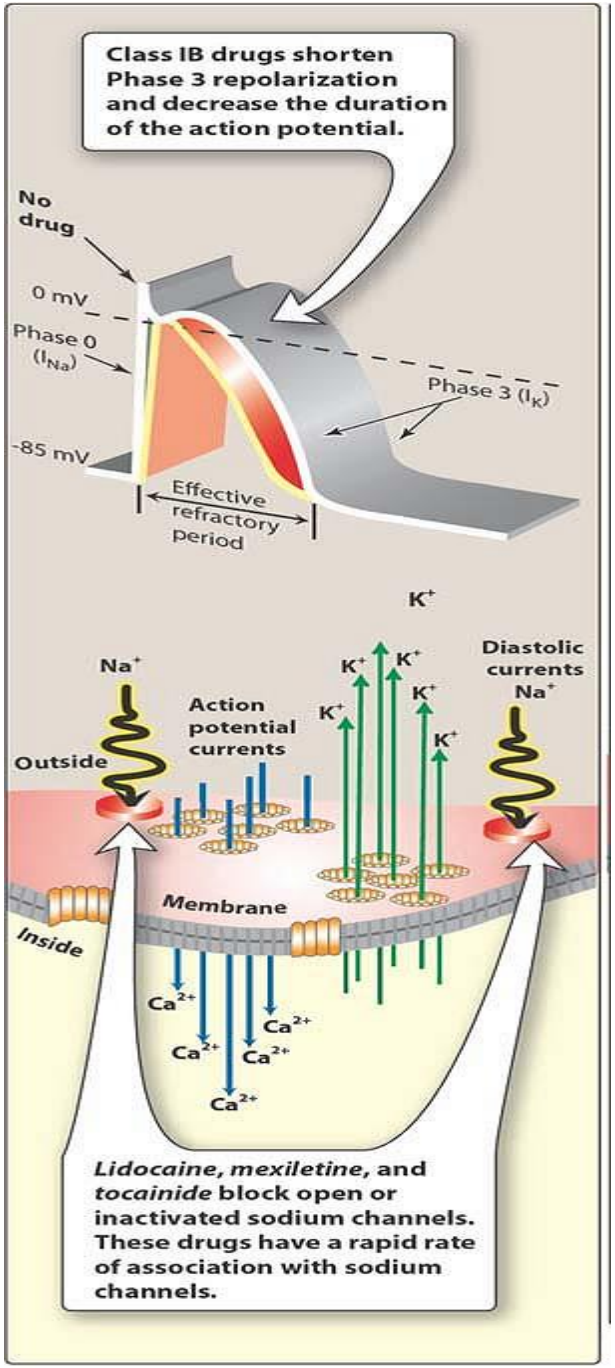
Lidocaine was the drug of choice for emergency treatment of cardiac arrhythmias.

- <u>Actions:</u>

Lidocaine, a local anesthetic, shortens Phase 3 repolarization and decreases the duration of the action potential.

- <u>Therapeutic uses:</u>

Lidocaine is useful in treating ventricular arrhythmias arising during myocardial ischemia, such as that experienced during a myocardial infarction. The drug does not markedly slow conduction and, thus, has little effect on atrial or AV junction arrhythmias.



Mexiletine and tocainide

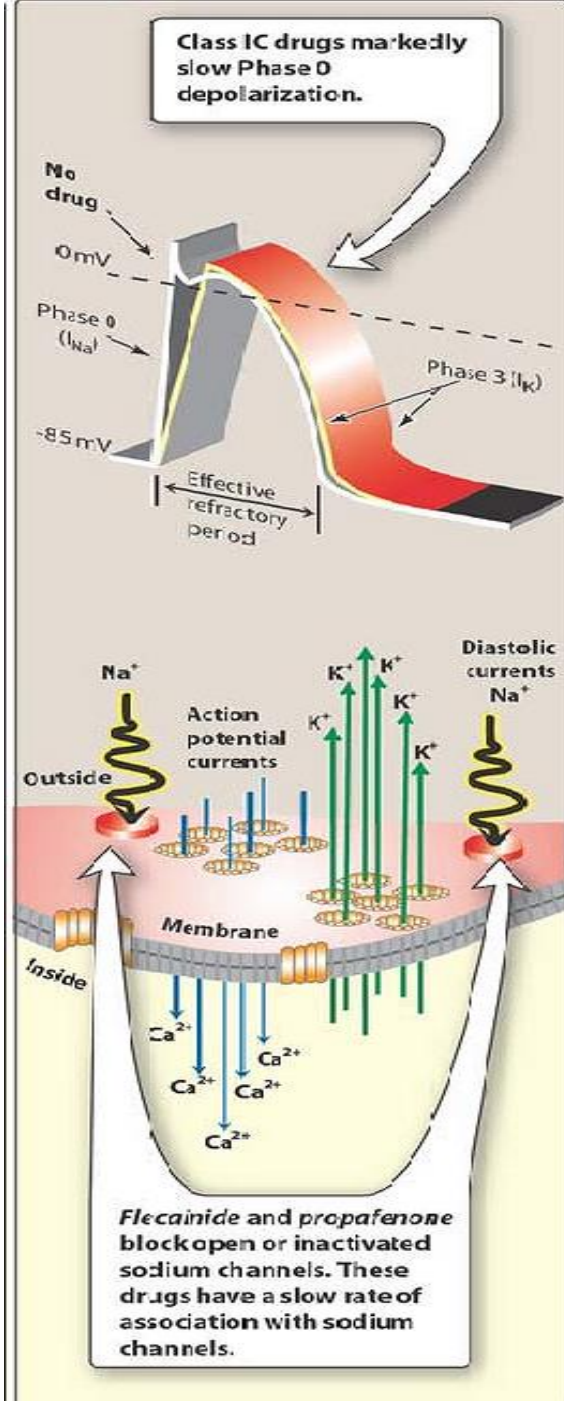
- These Class IB drugs have actions similar to those of lidocaine, and they can be administered orally.

- Mexiletine is used for chronic treatment of ventricular arrhythmias associated with previous myocardial infarction.

- Tocainide is used for treatment of ventricular tachyarrhythmias. Tocainide has pulmonary toxicity, which may lead to pulmonary fibrosis.

Class IC drugs:
Flecainide, Moricizine, Propafenone

- These drugs slowly dissociate from Na channels and show prominent effect even at normal heart rate.
- They markedly slow phase 0 depolarization causing marked conduction slowing, but only little effect on AP duration or ventricular ERP.
- They are proved only for refractory arrhythmia (ventricular). They have negative inotropic effects and can aggrevate CHF. They can ppt cardiac arrest.
- Also approved for AV node tachy in WPW syndrome.



Class II drugs:

- Class II agents are B-adrenergic antagonists. These drugs diminish Phase 4 depolarization, thus depressing automaticity, prolonging AV conduction, and decreasing heart rate and contractility.
- Class II agents are useful in treating tachyarrhythmias caused by increased sympathetic activity. They are also used for atrial flutter and fibrillation and for AV-nodal reentrant tachycardia.

- A. Propranolol

reduces the incidence of sudden arrhythmic death after myocardial infarction (the most common cause of death in this group of patients). The mortality rate in the first year after a heart attack is significantly reduced by propranolol, partly because of its ability to prevent ventricular arrhythmias.

- B. Metoprolol

most widely used in the treatment of cardiac arrhythmias. Compared to propranolol, it reduces the risk of bronchospasm.

- C. Esmolol

is a very short-acting B-blocker used for intravenous administration in acute arrhythmias that occur during surgery or emergency situations.

Class III Antiarrhythmic Drugs

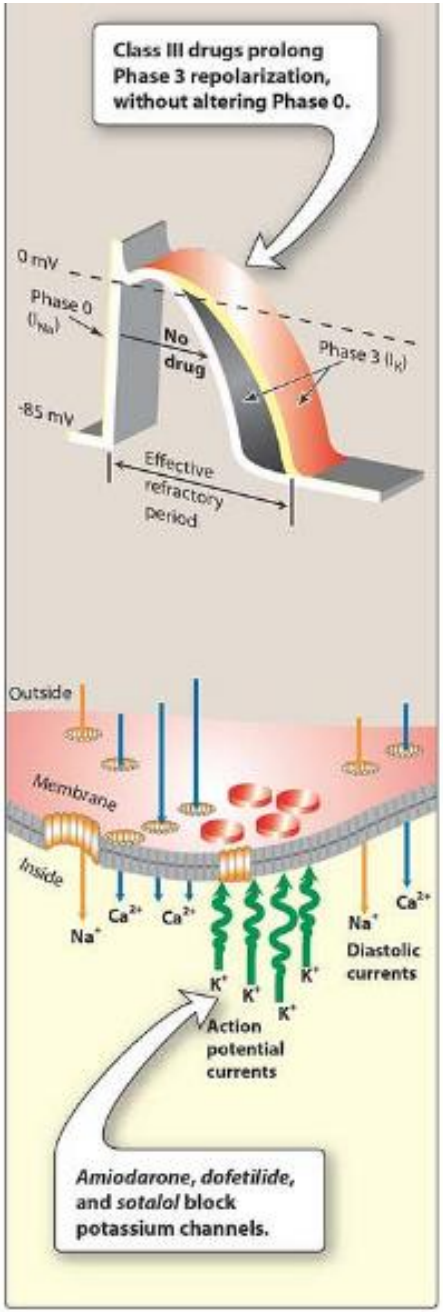
- They block potassium channels, thus, prolong the duration of the action potential and prolong the effective refractory period.
- All Class III drugs have the potential to induce arrhythmias.

- A. Amiodarone

It has complex effects, showing Class I, II, III, and IV actions.

- Therapeutic uses:

- Amiodarone has antianginal activity.
- It is effective in the treatment of severe refractory supraventricular and ventricular tachyarrhythmias.
- It is DOC in WPW syndrome.



- Adverse effects:

Amiodarone shows a variety of toxic effects. After long-term use, more than half of patients receiving the drug show side effects that are severe enough to prompt its discontinuation. However, use of low doses reduces toxicity, while retaining clinical efficacy. Some of the more common effects include

- interstitial pulmonary fibrosis,
- gastrointestinal tract intolerance, tremor, ataxia, dizziness,
- hyper- or hypothyroidism,
- liver toxicity,
- photosensitivity,
- neuropathy, muscle weakness, and blue skin discoloration caused by iodine accumulation in the skin.

B- Sotalol

- it has potent nonselective B-blocker activity.

- Therapeutic uses:

1. used for long-term therapy to decrease the rate of sudden death following an acute myocardial infarction.
2. B-Blockers have a modest ability to suppress ectopic beats and to reduce myocardial oxygen demand.
3. They have strong anti-fibrillatory effects, particularly in the ischemic myocardium.
4. Sotalol was more effective in preventing recurrence of arrhythmia and in decreasing mortality than imipramine, mexiletine, procainamide, propafenone, and quinidine in patients with sustained ventricular tachycardia.

- Adverse effects:

This drug also has the lowest rate of acute or long-term adverse effects. As with all drugs that prolong the QT interval, the syndrome of (torsade de pointes) is a serious potential adverse effect, typically seen in three to four percent of patients.

C. Dofetilide

- Dofetilide can be used as a first-line antiarrhythmic agent in patients with persistent atrial fibrillation and heart failure or in those with coronary artery disease with impaired left ventricular function.

- Because of the risk of proarrhythmia, dofetilide initiation is limited to the inpatient setting and is restricted to prescribers who have completed a specific manufacturer's training session.

- Along with amiodarone and B-blockers, dofetilide is the only antiarrhythmic drug that is recommended by experts for the treatment of atrial fibrillation in a wide range of patients.

Class IV Antiarrhythmic Drugs

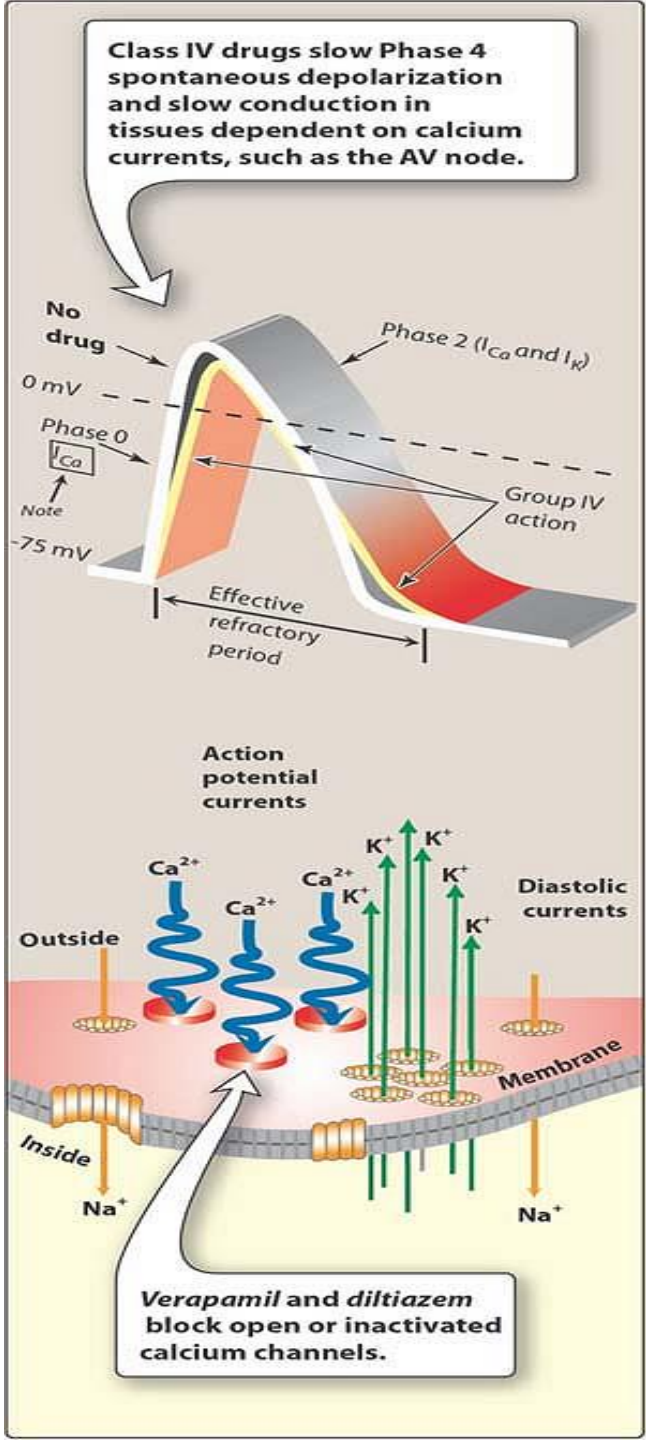
- **A. Verapamil and Diltiazem**

These drugs are *use-dependent* as they block most effectively when the heart is beating rapidly.

- By decreasing the inward current carried by calcium, they slow conduction and prolong the effective refractory period in the AV node.

- Therapeutic uses:

1. More effective against atrial than against ventricular arrhythmias.
2. They are useful in treating reentrant supraventricular tachycardia and in reducing the ventricular rate in atrial flutter and fibrillation.



Other Antiarrhythmic Drugs

A. Digoxin:

- Digoxin shortens the refractory period in atrial and ventricular myocardial cells while prolonging the effective refractory period and diminishing conduction velocity in the AV node.
- Digoxin is used to control the ventricular response rate in atrial fibrillation and flutter.

B. Adenosine:

- is a naturally occurring nucleoside, but at high doses, the drug decreases conduction velocity, prolongs the refractory period, and decreases automaticity in the AV node.
- Intravenous adenosine is the DOC for abolishing acute SVT.

End of Antiarrhythmic drugs

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