Cardiac Arrhythmias
Anti Arrhythmic Agents

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NORMAL CARDIAC RHYTHM

A. The rhythm of a normal resting adult heart is initiated from impulses generated from the sinoatrial (SA) node with a rate varying between 60 - 100 beats per minute (bpm).

B. During sleep the rate may decrease to 30 - 50 bpm, with episodes of sinus pauses up to 3 seconds, sinoatrial block, junctional rhythms, first degree and second degree atrioventricular nodal block occurring often enough (particularly in trained athletes) to be considered normal variants.

NORMAL CARDIAC RHYTHM

C. The impulses generated from the SA node spread via specialised internodal atrial conducting pathways to the atrioventricular (AV) node, where they are delayed before they are finally distributed to the ventricular myocardium via the His-Purkinje system.

D. Normally, with exercise the heart rate increases to at least 85% of the age predicted maximum of 220 - age in years, with failure to do so being termed 'chronotropic incompetence'.

NORMAL CARDIAC RHYTHM

E. Sinus arrhythmia is defined as sinus rhythm with P-P variations of more than 10%. It is due to cyclical variations in vagal tone commonly related to respiration (the rate is faster with inspiration and slower with expiration), and is often seen in individuals with sinus bradycardia.

F. It disappears with exercise, breath holding and atropine and is more likely to be seen in individuals who do not have cardiac disease.

CARDIAC ARRHYTHMIAS

A. An arrhythmia is defined as any cardiac rhythm other than regular sinus rhythm. It is caused by a disorder of impulse generation, impulse conduction or a combination of the two, and may be life-threatening due to a reduction in cardiac output, reduction in myocardial blood flow or precipitation of a more serious arrhythmia.

B. While the term 'dysrhythmia' would appear to be better suited as a label for an abnormal cardiac rhythm (as the term arrhythmia suggests an absence of rhythm).

Diagnosis of an arrhythmia

A. The assessment of an arrhythmia requires the determination of the site of the conduction disturbance, the atrial and ventricular rhythms present and the relationship between the atrial and ventricular impulses.

B. When using the standard ECG leads, the cardiac rhythm is often best considered with maximum P and QRS wave amplitudes, to allow the supraventricular and ventricular impulse relationship to be determined.

C. In unusual circumstances, a trace of up to 60 seconds may be required.

Description of an arrhythmia

Arrhythmias may be described from their following characteristics:

Rate (e.g. tachycardia or bradycardia)

a. tachycardia is defined as three or more consecutive impulses from the same pacemaker at a rate exceeding 100 bpm in adults (i.e. > 8 years of age).

b. bradycardia is defined as three or more consecutive impulses from the same pacemaker at a rate less than 60 bpm.

Rhythm (e.g. regular or irregular)

Origin of impulse (i.e. supraventricular, ventricular, or artificial pacemaker)

Impulse conduction (i.e. atrioventricular, ventriculoatrial or block)

Ventricular rate

Special phenomena (e.g. pre-excitation)

Summary

Normal cardiac rhythm originates from impulses generated within the sinus node. These impulses are conducted to the atrioventricular node where they are delayed before they are distributed to the ventricular myocardium via the His-Purkinje system.

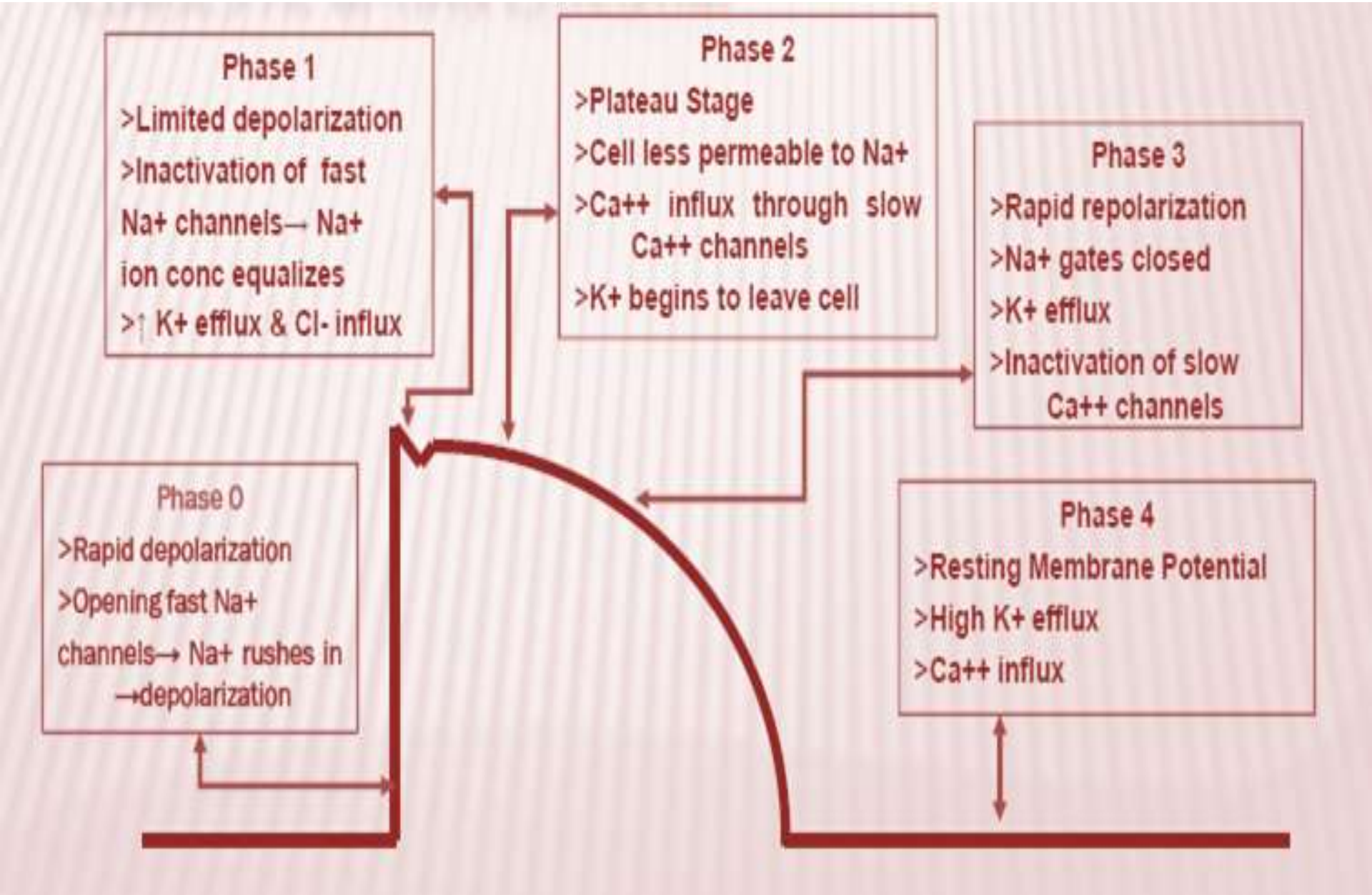
Abnormalities in cardiac rhythm are caused by disorders of impulse generation, conduction or a combination of the two and may be lifethreatening due to a reduction in cardiac output or myocardial oxygenation. Cardiac arrhythmias are commonly classified as tachycardias (supraventricular or ventricular) or bradycardias. The differentiation between supraventricular and ventricular tachycardias usually requires an assessment of atrial and ventricular rhythms and their relationship to each other. In the critically ill patient the commonest tachycardia is sinus tachycardia and treatment generally consists of management of the underlying disorder.

Action Potential

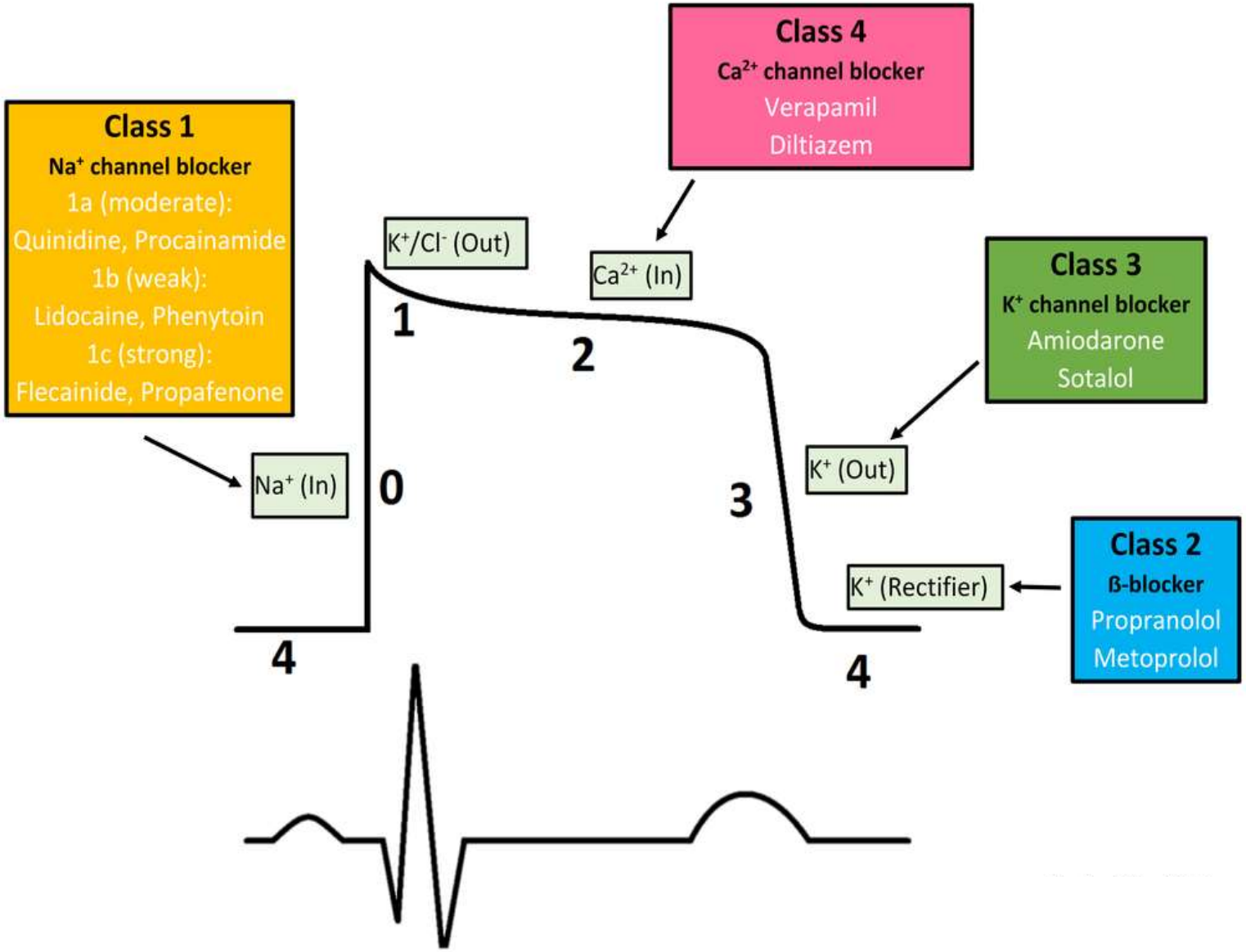
The change in electrical potential associated with the passage of an impulse along the membrane of a muscle cell or nerve cell.

A. Depolarization
B. Repolarization
C. Influx
D. Efflux

Phases of Action Potential



Drugs affecting the Cardiac Potential



Classification of Anti Arrhythmic agents

The Vaughan Williams classification was introduced in 1970 by Miles Vaughan Williams.

The five main classes in the Vaughan Williams classification of antiarrhythmic agents are:

A. Class I agents interfere with the sodium (Na^+) channel.
B. Class II agents are anti - sympathetic nervous system agents. Most agents in this class are beta blockers.
C. Class III agents affect potassium (K^+) efflux.
D. Class IV agents affect calcium channels and the AV node.
E. Class V agents work by other or unknown mechanisms.

Class 1 agents

A. The class 1 antiarrhythmic agents interfere with the sodium channel. Class 1 agents are grouped by what effect they have on the Na^+ channel, and what effect they have on cardiac action potentials.

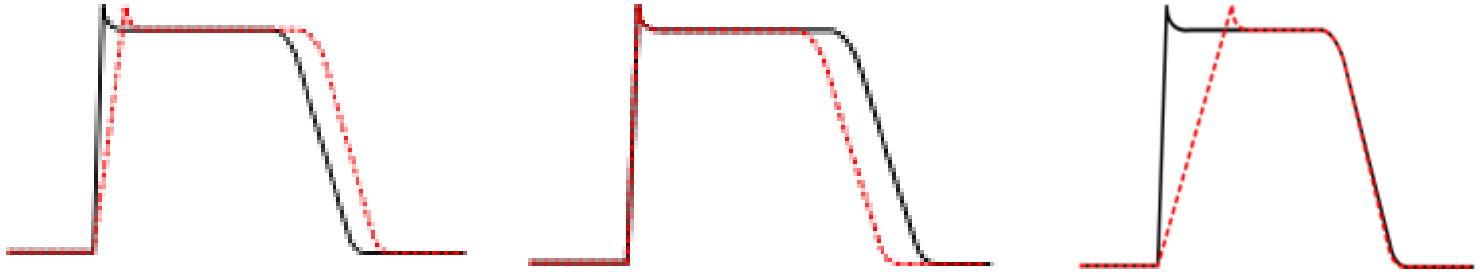
B. Class 1 agents are called membrane-stabilizing agents, "stabilizing" referring to the decrease of excitogenicity of the plasma membrane which is brought about by these agents. (Also noteworthy is that a few class 11 agents like propranolol also have a membrane stabilizing effect.)

C. Class 1 agents are divided into three groups (1a, 1b, and 1c) based upon their effect on the length of the action potential.

i. 1a lengthens the action potential (right shift)

ii. 1b shortens the action potential (left shift)

iii. 1c does not significantly affect the action potential (no shift)



Class II agents

A. Class II agents are conventional beta blockers.
B. They act by blocking the effects of catecholamines at the β_1-adrenergic receptors, thereby decreasing sympathetic activity on the heart, which reduces intracellular cAMP levels and hence reduces Ca^{2+} influx. These agents are particularly useful in the treatment of supraventricular tachycardias. They decrease conduction through the AV node.
C. Class II agents include atenolol, esmolol, propranolol, and metoprolol.

Class III agents

A. Class III agents predominantly block the potassium channels, thereby prolonging repolarization.

B. Since these agents do not affect the sodium channel, conduction velocity is not decreased. The prolongation of the action potential duration and refractory period, combined with the maintenance of normal conduction velocity, prevent re-entrant arrhythmias. (The re-entrant rhythm is less likely to interact with tissue that has become refractory).

C. The class III agents exhibit reverse-use dependence (their potency increases with slower heart rates, and therefore improves maintenance of sinus rhythm). Inhibiting potassium channels, slowing repolarization, results in slowed atrial-ventricular myocyte repolarization. Class III agents have the potential to prolong the QT interval of the EKG, and may be proarrhythmic (more associated with development of polymorphic VT).

D. Class III agents include: bretylium, amiodarone, I butilide, sotalol.

Class IV agents

A. Class IV agents are slow non-dihydropyridine calcium channel blockers. They decrease conduction through the AV node, and shorten phase two (the plateau) of the cardiac action potential.
B. They thus reduce the contractility of the heart, so may be inappropriate in heart failure. However, in contrast to beta blockers, they allow the body to retain adrenergic control of heart rate and contractility.
C. Class IV agents include verapamil and diltiazem.

Class V / other agents

Since the development of the original Vaughan Williams classification system, additional agents have been used that do not fit cleanly into categories I through IV.

Agents include:

Digoxin, which decreases conduction of electrical impulses through the AV node and increases vagal activity via its central action on the central nervous system, via indirect action, leads to an increase in acetylcholine production, stimulating M2 receptors on AV node leading to an overall decrease in speed of conduction.

Adenosine is used intravenously for terminating supraventricular tachycardias.

Magnesium sulfate, an antiarrhythmic drug, but only against very specific arrhythmias [12] which has been used for torsades de pointes.

Trimagnesium dicitrate (anhydrous) as powder or powder caps in pure condition, better bioavailability than ordinary MgO

CLASS I: SODIUM CHANNEL BLOCKING DRUGS

- IA - lengthen AP duration
  - Intermediate interaction with Na+ channels
  - *Quinidine, Procainamide, Disopyramide*
- IB - shorten AP duration
  - rapid interaction with Na+ channels
  - *Lidocaine, Mexiletene, Tocainide, Phenytoin*
- IC - no effect or minimal ↑ AP duration
  - slow interaction with Na+ channels
  - *Flecainide, Propafenone, Moricizine*

CLASS II: BETA-BLOCKING AGENTS

- Increase AV nodal conduction
- Increase PR interval
- Prolong AV refractoriness
- Reduce adrenergic activity
- *Propranolol, Esmolol, Metoprolol, Sotalol*

CLASS III: POTASSIUM CHANNEL BLOCKERS

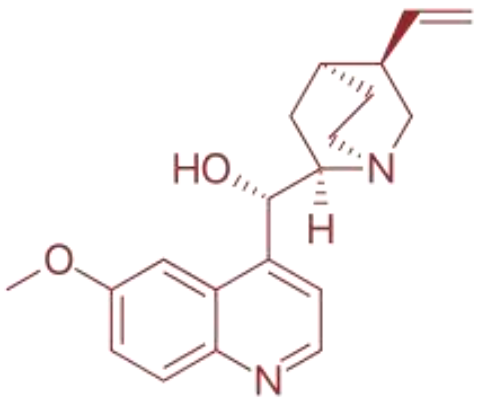
- Prolong effective refractory period by prolonging Action Potential
  - *Amiodarone*
  - *Bretylium*
  - *Sotalol*
  - *Ibutilide*
  - *Dofetilide*

CLASS IV: CALCIUM CHANNEL BLOCKERS

- **Blocks cardiac calcium currents**
  - **→ slow conduction**
  - **→ increase refractory period**
  - ***esp. in Ca++ dependent tissues (i.e. AV node)**
- ***Verapamil, Diltiazem, Bepridil***

Anti Arrhythmic Drugs

A. Quinidine sulphate (1a)
B. Procainamide hydrochloride (1a)
C. Disopyramide phosphate* (1a)
D. Phenytoin sodium (1b)
E. Lidocaine hydrochloride (1b)
F. Tocainide hydrochloride (1b)
G. Mexiletine hydrochloride (1b)
H. Lorcainide hydrochloride (1b)
I. Sotalol (II)
J. Amiodarone (III)



Quinidine sulphate

Quinidine is a medication that acts as a class 1 antiarrhythmic agent (1a) in the heart. It is a stereoisomer of quinine, originally derived from the bark of the cinchona tree. The drug causes increased action potential duration, as well as a prolonged QT interval.

MOA

A. Quinidine acts on sodium channels on the neuronal cell membrane, limiting the spread of seizure activity and reducing seizure propagation.
B. The antiarrhythmic actions are mediated through effects on sodium channels in Purkinje fibers.
C. Quinidine may also act on the slow inward calcium current (ICa), the rapid (IKr) and slow (IKs) components of the delayed potassium rectifier current, the inward potassium rectifier current (IKI), the ATP-sensitive potassium channel (IKATP) .

Uses

A. To prevent ventricular arrhythmias, particularly in Brugada Syndrome.
B. It reduces the recurrence of atrial fibrillation after patients undergo cardioversion.
C. Quinidine is also used to treat short QT syndrome.
D. A combination of dextromethorphan and quinidine alleviates symptoms of easy laughing and crying (pseudobulbar affect) in patients with amyotrophic lateral sclerosis and multiple sclerosis.

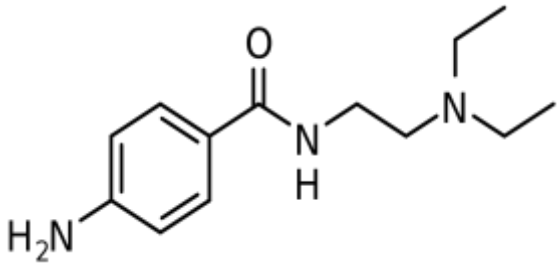
Adverse Effects

A. Quinidine is also an inhibitor of the cytochrome P450 enzyme 2D6, and can lead to increased blood levels of lidocaine, beta blockers, opioids, and some antidepressants.
B. Quinidine also inhibits the transport protein P-glycoprotein and so can cause some peripherally acting drugs such as loperamide to have central nervous system side effects, such as respiratory depression, if the two drugs are coadministered.
C. Quinidine can cause thrombocytopenia, granulomatous hepatitis, myasthenia gravis, and torsades de pointes (dangerous heart rhythm), so is not used much today.
D. Torsades can occur after the first dose. Quinidine-induced thrombocytopenia (low platelet count) is mediated by the immune system, and may lead to thrombocytic purpura.
E. Quinidine intoxication can lead to a collection of symptoms collectively known as cinchonism, with tinnitus (ringing in the ears) being among the most characteristic and common symptoms of this toxicity syndrome.

Contraindications

A. Hypersensitivity
B. Thrombocytopenic purpura
C. Myasthenia gravis
D. Intraventricular conduction defects
E. Complete AV block
F. Long QT syndrome

Procainamide hydrochloride



MOA

A. Procainamide is sodium channel blocker. It stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses thereby effecting local anesthetic action.

B. Thus it slows down the conduction rate and increases refractory period. Hence there is reduction in rate of depolarization.

Uses

A. Supraventricular Arrhythmias
B. Ventricular Tachycardia (VT)
C. Life-threatening ventricular arrhythmias
D. Pre-excited atrial fibrillation

Symptoms of overdose

A. Decrease in urination
B. Dizziness (severe) or fainting
C. Drowsiness
D. Fast or irregular heartbeat
E. Nausea and vomiting

Adverse Effects

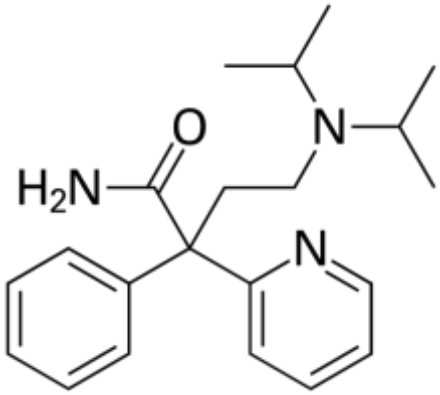
Less common

A. Fever and chills
B. Joint pain or swelling
C. Pains with breathing
D. Skin rash or itching

Rare

A. Confusion
B. Fever or sore mouth, gums, or throat
C. hallucinations
D. Mental depression
E. Unusual bleeding or bruising
F. Unusual tiredness or weakness

Disopyramide phosphate



A. A class 1 anti-arrhythmic agent (one that interferes directly with the depolarization of the cardiac membrane and thus serves as a membrane-stabilizing agent) with a depressant action on the heart similar to that of guanidine.
B. It also possesses some anticholinergic and local anesthetic properties.

MOA

A. Disopyramide phosphate exerts its actions by blocking both sodium and potassium channels in cardiac membrane during phase 0 of the action potential.
B. This slows the impulse conduction through the AV node and prolongs the duration of the action potential of normal cardiac cells in atrial and ventricular tissues.

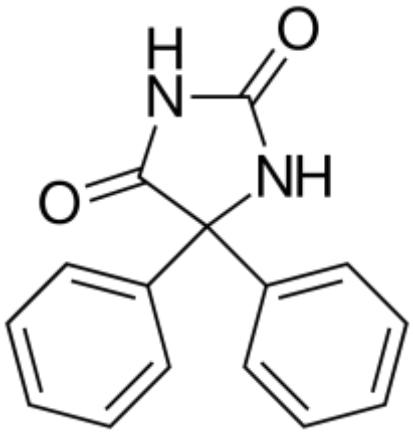
Uses

A. Certain types of serious (possibly fatal) irregular heartbeat, such as persistent ventricular tachycardia.
B. It is used to restore normal heart rhythm and maintain a regular, steady heartbeat.
C. Disopyramide is known as an anti-arrhythmic drug. It works by blocking certain electrical signals in the heart that can cause an irregular heartbeat.
D. Treating an irregular heartbeat can decrease the risk for blood clots, and this effect can reduce your risk of heart attack or stroke.

Adverse Effects

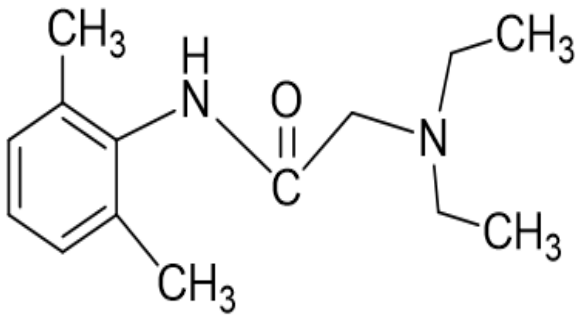
Dry mouth, constipation, nausea, abdominal pain/gas/bloating, blurred vision, dizziness, dry nose/eyes/throat, and urination problems (such as difficulty urinating or unusual frequent urge to urinate) may occur.

Phenytoin sodium



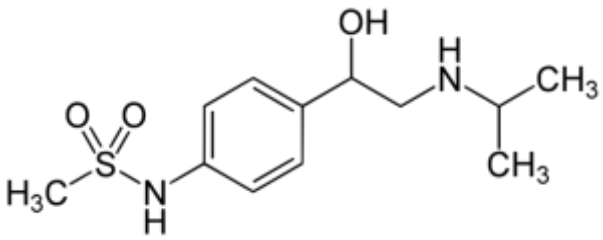
A. Phenytoin is a class 1B antiarrhythmic agent that has been successfully utilized for over half a century for treatment of ventricular arrhythmias.
B. Over the recent years it has been supplanted by newer, more effective and less toxic agents. It remains, however, a potent agent, which may be potentially useful in selected patients with antiarrhythmic intolerant and refractory arrhythmias.
C. As a class 1B drug, Phenytoin primarily shortens action potentials and inhibits rapid inward sodium currents.

Lidocaine



A. Lidocaine is a class 1B antiarrhythmic drug used in the treatment of ventricular arrhythmias, specifically ventricular tachycardia and ventricular fibrillation.
B. Lidocaine blocks cardiac sodium channels shortening the action potential and is used intravenously only for arrhythmia.
C. Lidocaine is also used as a topical anesthetic.
D. Lidocaine is not recommended for prophylactic administration to suppress premature ventricular contractions or prevent ventricular tachycardia or ventricular fibrillation after an acute coronary syndrome. Lidocaine toxicity is a concern

Sotalol



A. Sotalol inhibits beta-1 adrenoceptors in the myocardium as well as rapid potassium channels to slow repolarization, lengthen the QT interval, and slow and shorten conduction of action potentials through the atria.
B. The action of sotalol on beta adrenergic receptors lengthens the sinus node cycle, conduction time through the atrioventricular node, refractory period, and duration of action potentials.

Uses

A. Treatment of Cardiac arrhythmias
B. Hypertension
C. Angina pectoris
D. Myocardial infarction

Indications

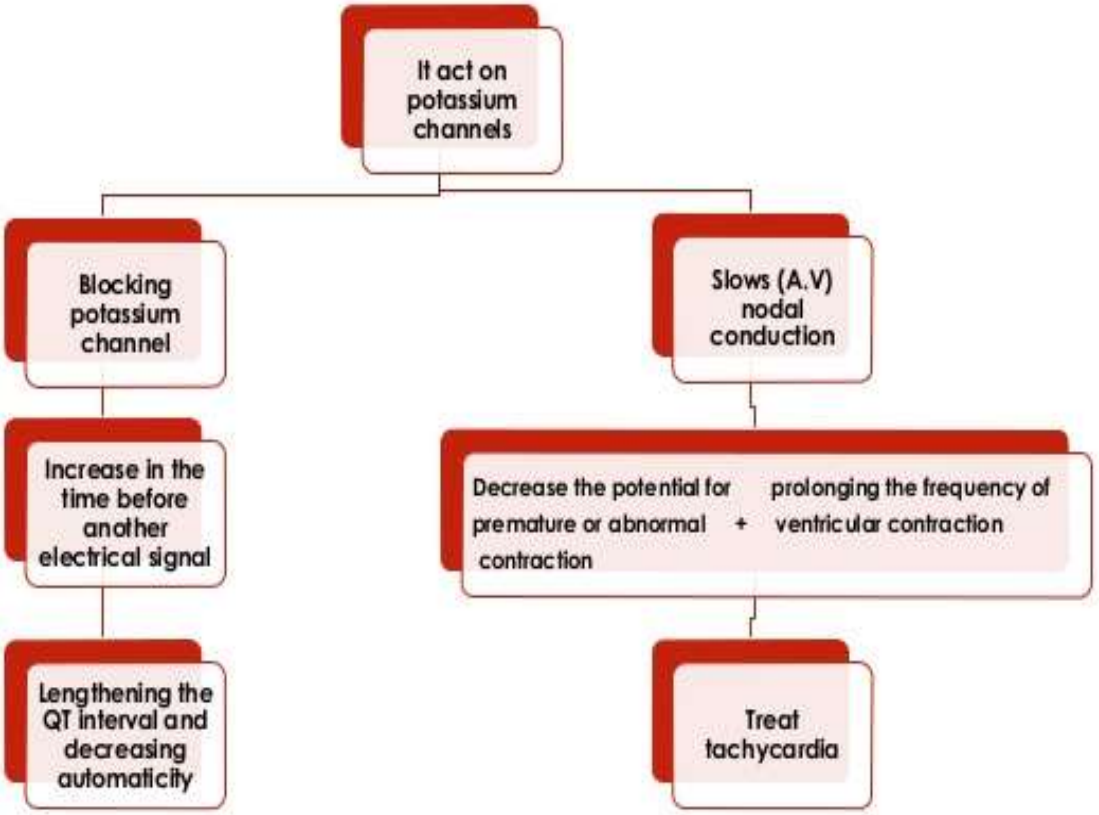
Anti-arrhythmic agent for treatment of ventricular and supraventricular arrhythmias .

Sotalol is indicated for the maintenance of normal sinus rhythm [delay in time to recurrence of atrial fibrillation/atrial flutter (AFIB/AFL)]

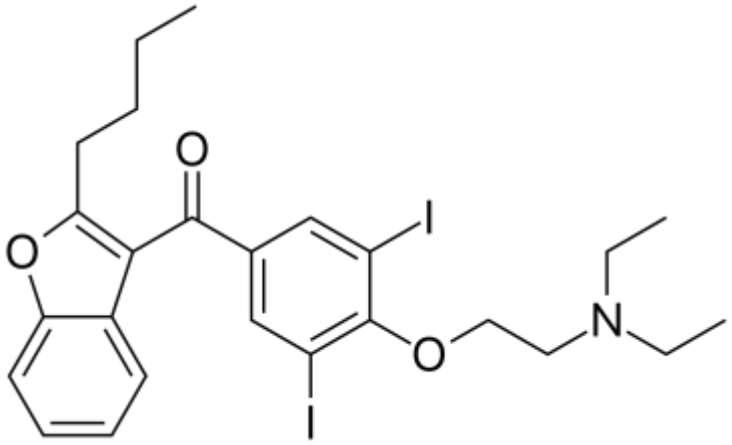
in patients with symptomatic AFIB/AFL who are currently in sinus rhythm.

Adverse Effects

1- Bradycardia
2- Congestive Heart Failure
3-Hypotension
4-Bronchospasm
5-Hypoglycaemia
6-Fatigue
7-Dizziness
8- Headache



Amiodarone



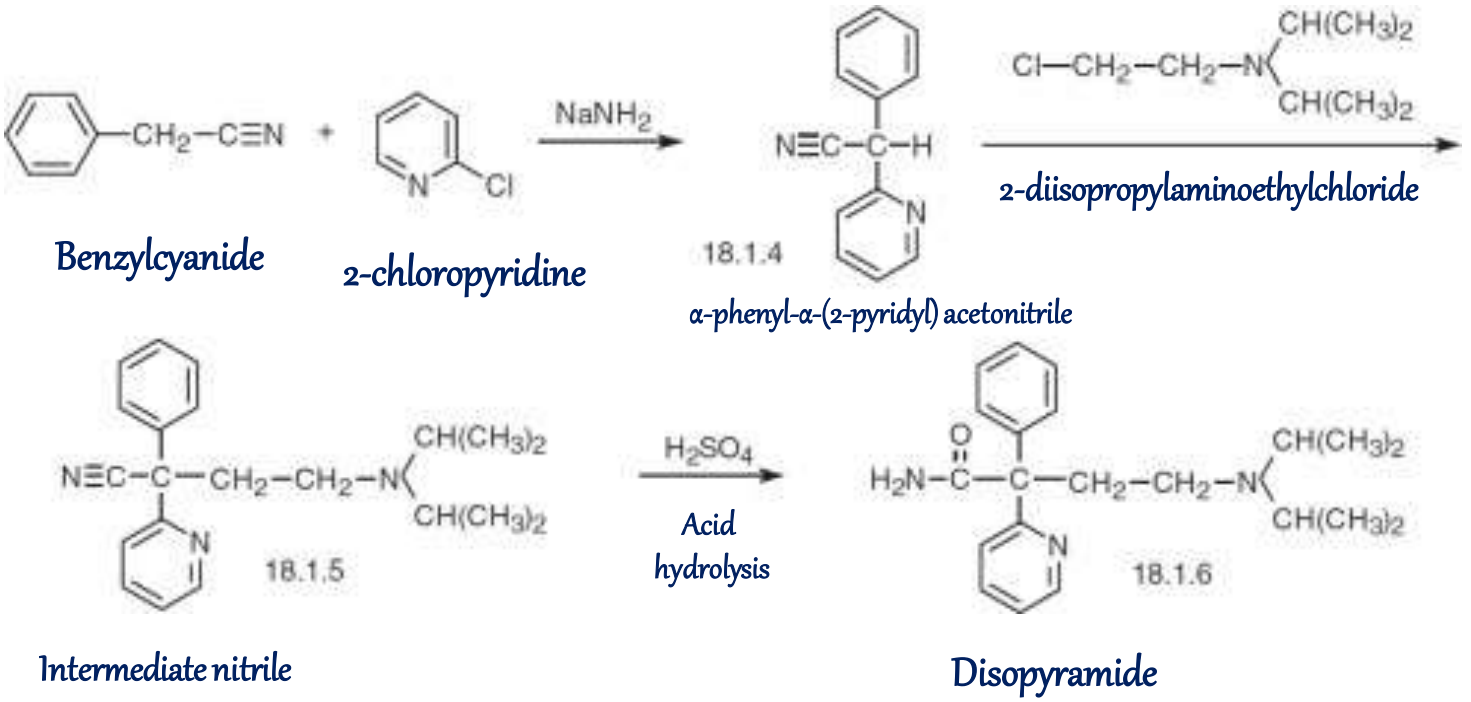
A. Amiodarone is considered a class III anti-arrhythmic drug. It blocks potassium currents that cause repolarization of the heart muscle during the third phase of the cardiac action potential.
B. As a result amiodarone increases the duration of the action potential as well as the effective refractory period for cardiac cells (myocytes). Therefore, cardiac muscle cell excitability is reduced, preventing and treating abnormal heart rhythms.
C. Unique from other members of the class III anti-arrhythmic drug class, amiodarone also interferes with the functioning of beta-adrenergic receptors, sodium channels, and calcium channels .
D. These actions, at times, can lead to undesirable effects, such as hypotension, bradycardia, and Torsades de pointes (TdP).
E. In addition to the above, amiodarone may increase activity of peroxisome proliferator-activated receptors, leading to steatogenic changes in the liver or other organs.
F. Finally, amiodarone has been found to bind to the thyroid receptor due to its iodine content, potentially leading to amiodarone induced hypothyroidism or thyrotoxicosis.

Uses

A. This medication is used to treat certain types of serious (possibly fatal) irregular heartbeat (such as persistent ventricular fibrillation/tachycardia). It is used to restore normal heart rhythm and maintain a regular, steady heartbeat.
B. Amiodarone is known as an anti-arrhythmic drug. It works by blocking certain electrical signals in the heart that can cause an irregular heartbeat.

Synthesis of Disopyramide

Disopyramide, α-(2-diisopropylaminoethyl)-α-phenyl-2-pyridineacetamide (18.1.6), is synthesized by arylating benzylcyanide with 2-chloropyridine in the presence of sodium amide and subsequent alkylation of the resulting α-phenyl-α-(2-pyridyl) acetonitrile (18.1.4) with 2-diisopropylaminoethylchloride using sodium amide. Sulfuric acid hydrolysis of the resulting nitrile (18.1.5) leads to the formation of α-(2-diisopropylaminoethyl)-α-phenyl-2-pyridineacetamide, disopyramide.



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Thank You!