ANTI-ARRHYTHMIC DRUGS

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Overview

- In a health adult with normal functioning heart, each heartbeat originates in the sinoatrial node
- The rhythm of the heartbeats is regular with the heart rate being about 70 beats /min at rest
- Arrhythmia (Dysrhythmia) is a condition where the origin, rhythm and **heart rate** are **abnormal**
- Generally, arrhythmias usually occur due to the disturbance in cardiac impulse **formation** or **conduction**
- These disturbed impulses may occur from any part of the heart

Types of arrhythmias

- The arrhythmias are classified based on **anatomic site** of the abnormality and the **type** of the abnormality in the heart rate as below;

- **Supraventricular arrhythmias** - those arising in the **atria or atrioventricular (AV)** node

- **Ventricular arrhythmias** – **those** arising from the ventricles are **ventricular arrhythmias**

- **Tachyarrhythmias** - arrhythmias presenting with very rapid heart rate

- **Bradyarrhythmias** – arrhythmias presenting with very slow heart rate

PHASES IN MYOCARDIAL CONDUCTION

Pathophysiology

- Arrhythmias can be caused by the following;
  - Coronary ischemia and tissue hypoxia
  - Electrolyte disturbances
  - Overstimulation of the sympathetic nervous system
  - General anesthetic drugs
  - Other conditions that disturb cardiac transmembrane potential which lead to abnormal impulse formation and conduction

- Generally and as highlighted earlier, most arrhythmias arise due to either of the two causes ie;

i. Aberrations in impulse generation (abnormal automaticity)

ii. Defect in impulse conduction

Pathophysiology of arrhythmias Cont'd

1. Automaticity:

- The SA node shows the fastest rate of phase 4 depolarization
- This later exhibits a higher rate of discharge than that occurring in other pacemaker cells exhibiting automaticity
- Thus, the SA node normally sets the pace of contraction for the myocardium and hence it is known a **PACE MAKER**
- If cardiac sites other than the SA node show enhanced automaticity, they may generate competing stimuli, and arrhythmias may arise

2. Abnormalities in impulse conduction:

- Impulses from higher pacemaker centers are normally conducted down pathways that bifurcate to activate the entire ventricular surface

- A phenomenon called re-entry can occur if a unidirectional block caused by myocardial injury or a prolonged refractory period results in an abnormal conduction pathway

- Re-entry is the most common cause of arrhythmias, and it can occur at any level of the cardiac conduction system

- This short-circuit pathway results in re-excitation of the ventricular muscle, causing premature contraction or sustained ventricular arrhythmia

- Antiarrhythmic agents prevent re-entry by slowing conduction (class I drugs) and/or increasing the refractory period (class III drugs), thereby converting a unidirectional block into a bidirectional block

MECHANISMS AND CLASSIFICATION OF ANTI-ARRHYTHMIC DRUGS

- Anti-arrhythmic drugs act by suppressing abnormal impulse formation or conduction
- Drugs that block sodium or calcium channels can reduce abnormal automaticity and slow conduction of the cardiac impulses
- Drugs that block potassium channels can prolong re-polarisation and the action potential duration thereby, increasing the refractory period of cardiac tissue
- Drugs that block beta adrenoceptors reduce the sympathetic stimulation of cardiac automaticity and conduction velocity thereby preventing overstimulation that contributes to some arrhythmias

Classification of Antiarrhythmic drugs

- Based on the mechanisms and their predominant effect on the predominant effect on the action
- Referring to the above stated mechanisms ,Vaughan-Williams divided antiarrhythmic drugs into different classes as follows;
- Class I - Sodium channel blockers
- Class II - Beta adrenoceptor blockers
- Class III - Potassium channel blockers
- Class IV - Calcium channel blockers
- Others – adenosine which does not belong to any of the above classes while amiodarone can belong to more than one class

CLASS I DRUGS

- These drugs bind more rapidly to open or inactivated sodium channels than to channels that are fully repolarised 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)** and it enables these drugs to block cells that are discharging at an abnormally high frequency without interfering with the normal, low-frequency beating of the heart

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

CLASS I A ANTIARRHYTHMIC DRUGS

- Example – Quinidine, procainamide and disopyramide
- Quinidine is the prototype in this group
- These drugs can precipitate arrhythmias that can progress to ventricular fibrillation because of their ability to solicit activities of Class III anti-arrhythmic medicines

Mechanism of group IA anti-arrhythmic drugs

- Quinidine binds to open and inactivated sodium channels and prevents sodium influx which leads to slowing the rapid upstroke during phase o
- It decreases the slope of phase 4 spontaneous depolarization through inhibition of potassium channels, and blockage of calcium channels
- Because of these actions, it slows conduction velocity and increases refractoriness

Mechanism of group IA anti-arrhythmic drugs Cont'd

- Quinidine also has mild α-adrenergic blocking and anticholinergic actions
- While procainamide and disopyramide have similar actions to quinidine, less cholinergic activity is recorded with procainamide while more is recorded with disopyramide
- Neither procainamide nor disopyramide has α-blocking activity
- Disopyramide produces more negative inotropic effect than that of quinidine and procainamide
- Furthermore, disopyramide causes peripheral vasoconstriction
- The drug may produce a clinically important decrease in myocardial contractility in patients with systolic heart failure

Indications of group IA anti-arrhythmic drugs

Quinidine

- Treatment of a wide variety of arrhythmias, including atrial, AV junctional and ventricular tachyarrhythmias

Procainamide

- Available in an intravenous formulation only and may be used to treat acute atrial and ventricular arrhythmias
- It is important to mention that electrical cardioversion or defibrillation and amiodarone have mostly replaced procainamide in clinical use

Disopyramide

- Used in the treatment of ventricular arrhythmias as an alternative to procainamide or quinidine and may also be used for maintenance of sinus rhythm in atrial fibrillation or flutter

Pharmacokinetics of group IA anti-arrhythmic drugs

- Quinidine sulfate or gluconate is rapidly and almost completely absorbed after oral administration
- It undergoes extensive metabolism primarily by the hepatic cytochrome P450 3A4 (CYP_3A_4) isoenzyme, forming active metabolites
- Procainamide has a relatively short duration of action of 2 to 3 hours with a portion of procainamide, being acetylated in the liver to N-acetylprocainamide (NAPA), which prolongs the duration of the action potential
- This metabolite (NAPA) has properties and side effects of a class III drug
- NAPA is eliminated via the kidney, and dosages of procainamide may need to be adjusted in patients with renal failure
- Disopyramide is well absorbed after oral administration and is metabolized in the liver to a less active metabolite and several inactive metabolites
- Disopyramide is a substrate of CYP_3A_4 and about half of the drug is excreted unchanged by the kidneys

Side effects group IA anti-arrhythmic drugs

- Large doses of quinidine may induce the symptoms of cinchonism (blurred vision, tinnitus, headache, disorientation, and psychosis)
- Drug interactions are common with quinidine since it is an inhibitor of both CYP2D6 and P-glycoprotein
- Intravenous administration of procainamide may cause hypotension
- Disopyramide has the most anticholinergic adverse effects of the class IA drugs (for example, dry mouth, urinary retention, blurred vision, and constipation)
- Both quinidine and disopyramide should be used with caution with potent inhibitors of CYP3A4

CLASS IB ANTI-ARRHYTHMIC DRUGS

- Examples – Lidocaine, mexiletine
- 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 or firing rapidly

Mechanism of action

- In addition to sodium channel blockade, lidocaine and mexiletine shorten phase 3 repolarization

- This subsequently decreases the duration of the action potential

Indications

- Lidocaine may be useful as an alternative to amiodarone in ventricular fibrillation or pulseless ventricular tachycardia (VT)
- Lidocaine may also be used in polymorphic VT or in combination with amiodarone for VT storm
- The drug does not markedly slow conduction and, thus, has little effect on atrial or AV junction arrhythmias
- Mexiletine is used for chronic treatment of ventricular arrhythmias, often in combination with amiodarone

Pharmacodynamics

- Lidocaine is given intravenously because of extensive first-pass transformation by the liver
- The drug is dealkylated to two less active metabolites, primarily by CYP1A2 with a minor role by CYP3A4
- Lidocaine should be monitored closely when given in combination with drugs affecting these CYP isoenzymes
- As lidocaine is a high extraction drug, drugs that lower hepatic blood flow (β-blockers) may require lidocaine dose adjustment
- Mexiletine is well absorbed after oral administration and is metabolized in the liver primarily by CYP2D6 to inactive metabolites and excreted mainly via the biliary route

Side effects

- Lidocaine has a fairly wide therapeutic index, showing little impairment of left ventricular function
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- Lidocaine has no negative inotropic effect
- Central nervous system (CNS) effects include nystagmus which is an early indication of toxicity, drowsiness, slurred speech, paresthesia, agitation, confusion, and convulsions which often limit the duration of continuous infusions
- Mexiletine has a narrow therapeutic index and caution should be used when administering the drug with inhibitors of CYP2D6
- Nausea, vomiting, and dyspepsia are the most common adverse effects.

CLASS IC ANTI-ARRHYTHMIC DRUGS

- Examples – Flecainide, propafenone
- These drugs slowly dissociate from resting sodium channels and show prominent effects even at normal heart rates
- Several studies have cast serious doubts on the safety of the class IC drugs, particularly in patients with structural heart disease

Mechanism of action

- Flecainide suppresses phase o upstroke in Purkinje and myocardial fibers
- This causes marked slowing of conduction in all cardiac tissue, with a minor effect on the duration of the action potential and refractoriness
- Automaticity is reduced by an increase in the threshold potential, rather than a decrease in slope of phase 4 depolarization
- Flecainide also blocks potassium channels leading to increased action potential duration, even more so than propafenone
- Propafenone, like flecainide, slows conduction in all cardiac tissues but does not block potassium channels.

Indications

- Flecainide is useful in the maintenance of sinus rhythm in atrial flutter or fibrillation in patients without structural heart disease (left ventricular hypertrophy, heart failure, atherosclerotic heart disease)
- Flecainide is also used for treating refractory ventricular arrhythmias
- Flecainide has a negative inotropic effect and can aggravate chronic heart failure and thus caution should be taken when using the drug
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- Use of propafenone is restricted mostly to atrial arrhythmias: rhythm control of atrial fibrillation or flutter and paroxysmal supraventricular tachycardia prophylaxis in patients with AV re-entrant tachycardias
- Propafenone's use in Av re-entrant tachycardias is premised its β-blocking properties

Pharmacokinetics

- Flecainide is absorbed orally and is metabolized by CYP2D6 to multiple metabolites
- The parent drug and metabolites are mostly eliminated renally and dosage adjustment may be required in renal disease
- Propafenone is metabolized to active metabolites primarily via CYP2D6 and also by CYP1A2 and CYP3A4
- The metabolites are excreted in the urine and the feces

Side effects

- Flecainide is generally well tolerated, with blurred vision, dizziness, and nausea occurring most frequently
- Propafenone has a similar side effect profile, but it may also cause bronchospasm due to its β-blocking effects
- It should be avoided in patients with asthma. Propafenone is also an inhibitor of P-glycoprotein
- Both drugs should be used with caution with potent inhibitors of CYP2D6

CLASS II ANTI-ARRHYTHMIC DRUGS

- Examples - β-adrenergic antagonists, or β-blockers e.g. metoprolol, esmolol, atenolol
- Cardio selective β-blockers are preferred in that they reduces the risk of bronchospasms
- These drugs diminish phase 4 depolarization and thus depress automaticity, prolong AV conduction and decrease heart rate and contractility
- Class II agents are useful in treating tachyarrhythmias caused by increased sympathetic activity, atrial flutter and fibrillation and for AV nodal re-entrant tachycardia
- In addition, β-blockers prevent life-threatening ventricular arrhythmias following a myocardial infarction
- **NB**: In contrast to the sodium channel blockers, β-blockers and class III compounds, such as sotalol and amiodarone are increasing in use

Class II anti-arrhythmic drugs Cont'd

- Metoprolol is extensively metabolized in the liver primarily by CYP2D6 and has CNS penetration (less than propranolol, but more than atenolol
- Esmolol is a very-short-acting β-blocker used for intravenous administration in acute arrhythmias that occur during surgery or emergency situations
- It has a fast onset of action and a short half-life, making it ideal for acute situations and also limiting its adverse effect profile
- Esmolol is rapidly metabolized by esterases in red blood cells and hence, there are no pharmacokinetic drug interactions

CLASS III ANTI-ARRHYTHMIC DRUGS

- **Examples** – Amiodarone, dronedarone, Sotalol, dofetilide, Ibutilide

- Class III agents block potassium channels and hence diminishing the outward potassium current during repolarization of cardiac cells

- These agents prolong the duration of the action potential without altering phase o of depolarization or the resting membrane potential

- Instead, they prolong the effective refractory period, increasing refractoriness

NB:

- All class III drugs have the potential to induce arrhythmias

Amiodarone

Mechanism of action

- Amiodarone contains iodine and is related structurally to thyroxine
- It has complex effects, showing class I, II, III, and IV actions and α-blocking activity
- Its dominant effect is prolongation of the action potential duration and the refractory period by blocking K+ channels

Indications for amiodarone

- Amiodarone is effective in the treatment of;
  - Severe refractory supraventricular tacyarrhythmias
  - Severe ventricular tachyarrhythmias
  - Atrial fibrillation or flutter (mainstay treatment)

- Despite its adverse effect profile, amiodarone is the most commonly employed antiarrhythmic

NB:

- It is thought to be the least pro-arrhythmic of the class I and III antiarrhythmic drugs

Pharmacokinetics of amiodarone

- Amiodarone is incompletely absorbed after oral administration
- The drug is unusual in having a prolonged half-life of several weeks and it distributes extensively in adipose tissue
- Full clinical effects may not be achieved until months after initiation of treatment, unless loading doses are employed
- Amiodarone is subject to numerous drug interactions, since it is metabolized by CYP3A4 while it serves as an inhibitor of CYP1A2, CYP2C9, CYP2D6, and P-glycoprotein

Side effects of amiodarone

- Amiodarone shows a variety of toxic effects, including
- Pulmonary fibrosis
- Neuropathy
- Hepatotoxicity
- Corneal deposits
- Optic neuritis
- blue-gray skin discoloration
- Hypo- or hyperthyroidism

- One great thing of note that use of low doses and close monitoring reduce toxicity, while retaining clinical efficacy

CLASS IV ANTI-ARRHYTHMIC DRUGS

- Class IV drugs are the nondihydropyridine calcium channel blockers verapamil and diltiazem
- Although voltage-sensitive calcium channels occur in many different tissues, the major effect of calcium channel blockers is on vascular smooth muscle and the heart
- Verapamil shows greater action on the heart than on vascular smooth muscle while diltiazem is intermediate in its actions
- In the heart, verapamil and diltiazem bind only to open depolarized voltage-sensitive channels, thus decreasing the inward current carried by calcium
- They prevent repolarization until the drug dissociates from the channel, resulting in a decreased rate of phase 4 spontaneous depolarization
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- **These drugs are therefore use-dependent**

Class IV anti-arrhythmic drugs

- They also slow conduction in tissues that are dependent on calcium currents, such as the AV and SA nodes
- These agents are more effective against atrial than against ventricular arrhythmias
- They are useful in treating reentrant supraventricular tachycardia and in reducing the ventricular rate in atrial flutter and fibrillation
- Both drugs are metabolized in the liver by CYP3A4. Dosage adjustments may be needed in patients with hepatic dysfunction
- Both agents are also inhibitors of CYP3A4, as well as substrates and inhibitors of P-glycoprotein

OTHER ANTI-ARRHYTHMIC DRUGS

1. Digoxin

- Inhibits the Na+/K+-ATPase pump thus ultimately shortening the refractory period in atrial and ventricular myocardial cells
- This leads to the prolonging of the effective refractory period and diminishing conduction velocity in the AV node
- Digoxin is used to control ventricular response rate in atrial fibrillation and flutter; however, sympathetic stimulation easily overcomes the inhibitory effects of digoxin
- At toxic concentrations, digoxin causes ectopic ventricular beats that may result in VT and fibrillation

2. Adenosine

- Adenosine is a naturally occurring nucleoside
- The drug decreases conduction velocity and thus prolonging the refractory period and decreases automaticity in the AV node
- Intravenous adenosine is the drug of choice for abolishing acute supraventricular tachycardia
- It has low toxicity but causes flushing, chest pain, and hypotension
- Adenosine has an extremely short duration of action (approximately 10 to 15 seconds) due to rapid uptake by erythrocytes and endothelial cells

3.Magnesium sulphate

- Magnesium is necessary for the transport of sodium, calcium and potassium across cell membranes
- It slows the rate of SA node impulse formation and prolongs conduction time along the myocardial tissue
- Intravenous magnesium sulfate is the salt used to treat arrhythmias since oral magnesium is not effective in the setting of arrhythmia
- Most notably, magnesium is the drug of choice for treating the potentially fatal arrhythmia torsades de pointes and digoxin-induced arrhythmias.

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