Review

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The Changing Facade of Anti-arrhythmics

Pharmacology Section

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INTRODUCTION

There has been an overwhelming rise in the number of cardio-vascular diseases over the past few decades. In the nineties, it was found that there were around 50 million deaths world wide, of which 14 million were contributed by heart diseases alone. Since then, the number of cardiovascular diseases have not dwindled. Ischaemic heart disease is estimated to become the top ranked cause of worldwide deaths by the year 2020. The mortality and the morbidity which is caused by this disease is due to its complications. Arrhythmias have been attributed to be a major cause of death following myocardial infarction and stroke.

Over the years, cardiac arrhythmias have been one of the major health problems which were extensively studied upon, in terms of their mechanism and treatment. Ironically, they are one of the medical problems which has been very difficult to fathom. Many drugs have been approved for their treatment, but yet a large group of people who were suffering from them never responded as expected or they had side effects of the drug. The symptomatic limitations and the mortality which are connected to this condition has led researchers to push themselves to find new drugs with a robust treatment mechanism and lesser side effects. The growing financial burden which was indirectly caused by their morbidity and mortality could be eased by defining a new anti-arrhythmic with lesser side effects.

Atrial fibrillation is the most common type of arrhythmia. Inspite of ablation being effective in atrial fibrillation, it is pharmacotherapy that holds the mainstay. Researchers are working hard to unravel drugs which are more selective in their actions. The reputation of anti-arrhythmics as pro-arrhythmics should be contained. To reduce their side effects, the pursuit of multi-channel blockers would be promising. All in all, pharmacotherapy has been the mainstay in the treatment of cardiac arrhythmias. The fact that these drugs themselves caused life threatening arrhythmias and extra cardiac side effects, has led to the generation of an interest among scientists to come up with novel drugs.

THE MECHANISM OF ARRHYTHMOGENESIS [TABLE/FIG-2]

Arrhythmias occur either due to disorders of the impulse initiation or conduction of the cardiac impulses, which are characterized below:

I) Disorder Of Impulse Initiation [Table/Fig-3]

a) Abnormal Automaticity: The spontaneous cardiac rhythmicity involves slow depolarization of the trans-membrane voltage during diastole till the threshold potential is attained and an action potential is triggered. This faster paced action potential will take over as the pace maker. This phenomenon may be accelerated by changing the threshold potential or by increasing the rate of the diastolic depolarization. Such a change can be affected in any part of the cardiac tissue. Abnormal automaticity is believed to be the cause of sinus tachycardia, escape rhythms and accelerated junctional rhythms.

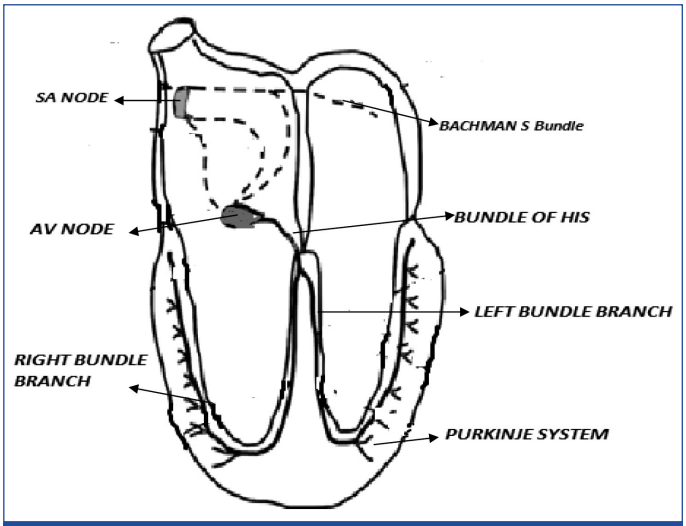
II) Disorders of Impulse Conduction

a) Triggered activity: This is due to oscillations of the trans-membrane potential at the end of the action potential which is called depolarization. These may reach a threshold potential and cause arrhythmias. It is known as early depolarization if the trans-membrane potential reaches its threshold. When the after depolarization develops after the trans-membrane potential has been reached, then it is called as delayed after depolarization. Such after depolarizations may occur in cardiac tissues, which may follow myocardial ischaemia or myocardial infarction.

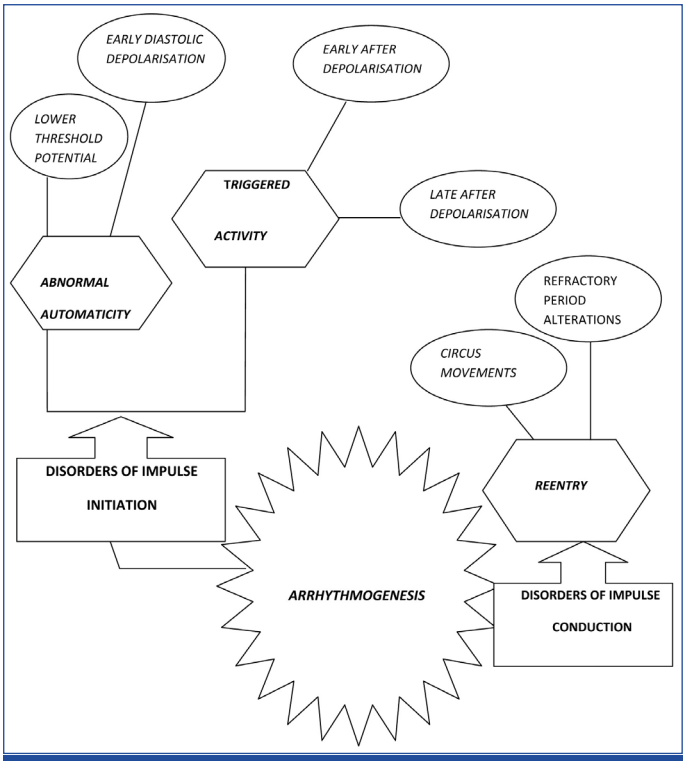
b) Re-entry or circus movement: This occurs when a ring of cardiac tissue surrounds an inexcitable core. Most of the paroxysmal tachycardias are produced by this mechanism. An arrhythmia is initiated if an ectopic beat finds one limb refractory and the other excitable but slow enough, that a re-entry circuit may be formed when the earlier refractory limb becomes excitable.

ARRHYTHMIAS

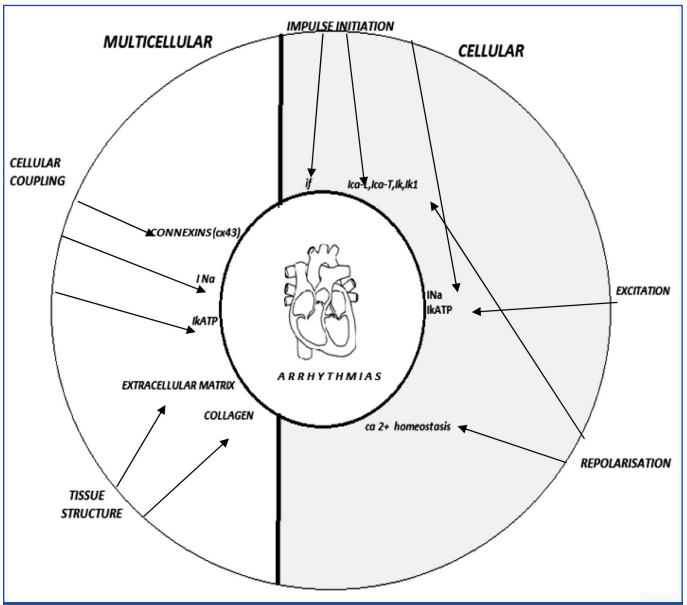
Cardiac arrhythmia is a phenomenon where there is an abnormality in the cardiac rhythm. Arrhythmia may be broadly classified into bradyarrhythmias and tachyarrhythmias.



[Table/Fig-1]: Conduction Pathway in Normal Heart



[Table/Fig-2]: Mechanism of Arrhythmias



[Table/Fig-3]: Electrophysiology and the Main Molecular Components Involved in Arrhythmogenesis

I) Bradyarrhythmias

These may be further classified into:

a) Sinus Bradycardia: Sinus bradycardia can be caused due to extrinsic or intrinsic factors. External factors affect the normal sinus node functionally, which are commonly drug induced – beta blockers, digitalis, syndromes such as the neurocardiogenic syndrome, the carotid sinus syndrome, etc. Intrinsic factors – these are associated with a sinus node that has a degenerative or a non degenerative disease eg: the Sick Sinus Syndrome, ischaemic heart disease, cardiomyopathy, myocarditis, etc.

Sinus bradycardia is characterized by a decreased heart rate, sinus arrest and syncope.

b) Heart Block: Any hindrance in the conduction of an impulse anywhere in the conductive system is referred to as a heart block.

i) Atrioventricular Block: In this type of block, there is a failure in the conduction of an impulse to the level of the Bundle of His.

ii) Bundle branch block: There is a block in the conduction of an impulse below the level of the Bundle of His.

II) Tachyarrhythmias

a) Supraventricular Tachycardias: These arise from the atrio-ventricular junction or the atrium.

b) Atrial tachyarrhythmias: They include atrial fibrillation, atrial flutter, atria ectopic beats and atrial tachycardia.

c) Ventricular Tachyarrhythmias: These include sustained ventricular tachycardia, ventricular fibrillation, non-sustained ventricular tachycardia and ventricular premature beats.

ANTI-ARRHYTHMIC DRUGS

The therapy of arrhythmia is based on the acuteness in its onset, the type of arrhythmia, and the effective interventions [Table/Fig-4]. Drugs are the mainstay in the prophylaxis and the treatment of arrhythmias [Table/Fig-5]

CLASS 1. SODIUM CHANNEL BLOCKERS

The drugs of this class mainly affect the phase 0 of the action potential. These drugs bind to the alpha units of the sodium channels and inhibit the propagation of the action potential in a majority of the excitable cells. The sodium channel blocking drugs are further divided into 1A, 1B and 1C according to the electrophysiologic difference in the type of block that these drugs exhibit.

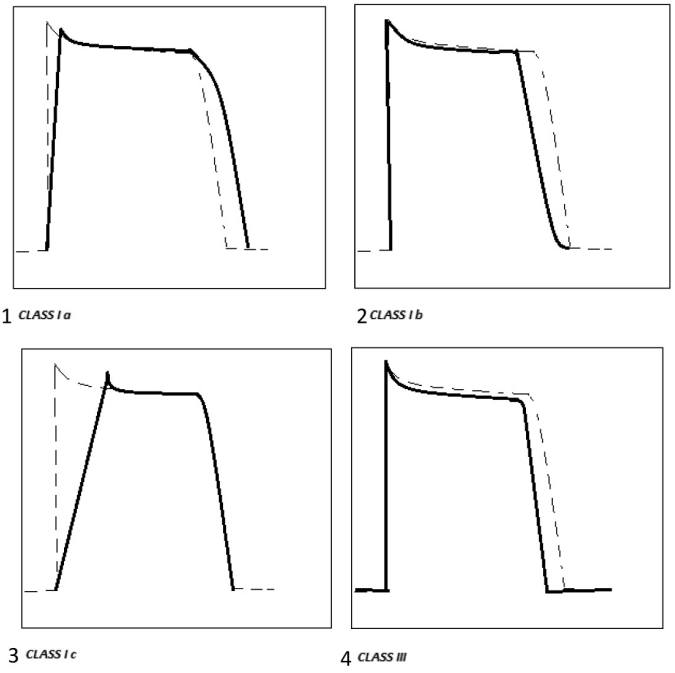
CLASS 1A: It is the oldest group among the anti-arrhythmic drugs. They depress the phase 0 of the cardiac action potential [Table/Fig-6]. In addition to sodium channel blocking, these drugs also block the potassium channels, thus causing the prolongation of the repolarisation phase of the action potential.

Arrhythmia	Drug of Choice
Atrial Fibrillation	Amiodarone Quinidine Digoxine
Atrial Flutter	Esmolol Amiodarone Quinidine Digoxin
Paroxysmal Supraventricular Tachycardia	Digoxin Verapamil Propranolol
Ventricular Extrasystoles	Lidocaine Potassium Chloride Amidarone Mexiletine
Ventricular Tachycardia	Lidocaine Amiodarone Dofetilide
Torsades De Pointes	Propranolol Isoprenaline Magnesium
Ventricular Fibrillation	Amiodarone Lidocaine
Wolff Parkinson White Syndrome	Amiodarone Propranolol Propafenone

[Table/Fig-4]: Arrhythmias and Their Drugs of Choice

Class 1 Sodium Channel Blockers	
Class 1 A Class 1 B Class 1 C	Quinidine, Procainamide, Diisopyramide,Morcizine Lignocaine, Mixeletine, Phenytoin Propafenone, Encainide, Flecainide
Class 2 Beta- Blockers	Propranolol, Metaprolol, Atenolol, Sotalol ,Esmolol
Class 3 Potassium Channel Blockers	Amiodarone, Dofetilide,Ibutelide
Class 4 Calcium Channel Blockers	Verapamil, Diltiazem
Miscellaneous	Adenosine, Magnesium
Newer Antiarrhythmics Class 1 C Agent Class 3 Agents Gap Junction Modifiers Adenosine A1 RecEptor Agonist Stretch Receptor Antagonist Angiotensin System Inhibitor Potential Investigational Drugs	 Pilscainide Niferidil Dronaderone Vernakalant Nifekalant Rotagaptide Tecadenoson Selodenoson Gadolinium, Gsmtx-4 Gap 134 , Pirfenidone, Ati 2042, Ranolazine, Chloride Channel Blockers , Gene Therapy

[Table/Fig-5]: Comprehensive classification of presently available antiarrhythmic agents



[Table/Fig-6]: Action of Antiarrhythmic Drugs on Action Potential

Quinidine: Quinidine is a D isomer which is extracted from the Cinchona bark. Quinidine depresses the propagation of the action potential and it causes depression of all the cardiac properties.

The treatment with quinidines should be well monitored as they themselves are highly pro-arrhythmic. They can cause torsade de pointes, sudden cardiac arrest, ventricular fibrillation and angio-oedema. Their alpha 2 blocking properties cause hypotension and vascular collapse.

Procainamide: it has cardio electrophysiological properties which are similar to those of quinidine and it differs from it in terms of being less potent than quinidine.

Procainamide causes CNS effects such as hallucination and mental confusion. It can cause cardiac adverse effects which are similar to those which are caused by quinidine, such as fever, rash and angio-oedema.

Diisopyramide: this drug has anti-cholinergic and cardiac depressant activities and unlike quinidine, it has no alpha adrenergic blocking property.

The anti-cholinergic side effects are dry mouth, constipation and blurring of vision. It is contraindicated in patients with the sick sinus syndrome. It causes hypotension and cardiac depression in patients with a decompensated heart.

Morcizine: It belongs to a group of phenothiazine derivatives. The Na^+ channel recovery is delayed in its case as compared to the other drugs. The CNS effects are less marked with the use of this drug, but the CAST 2 studies have found the drug to have increased the mortality in post MI patients [1].

CLASS 1B: These drugs bind to the open sodium channels during phase 0 of the action potential [Table/Fig-6]. They block many of the channels by the time the action potential would have reached its peak. They block the refractory channels, preferentially the cardiac cells which are depolarized.

Lignocaine: The selective action of this drug is seen on partially depolarized cells and damaged ventricular fibres as opposed to the normal ventricular fibres. It reduces after depolarization and automaticity in ectopic foci. Lignocaine is a popular anti-arrhythmic in intensive care units . It is used in post surgical or post-myocardial arrhythmia. Lignocaine is not effective in atrial arrhythmias as the atrial action potentials are short and as there is a lack of the lignocaine effect on the channel recovery. Lidocaine has a very low tendency to be a pro-arrhythmic. It is used in emergency situations because of its rapid and titratable action. It is useful in digitalis induced arrhythmias.

The side effects include paresthaesias, blurring of vision, disorientation, nystagmus and seizures.

Mixeletine: It is an anti-arrhythmic which is pharmacologically similar to lidocaine. It is used in post-infarction ventricular arrhythmias, extra systoles and tachycardia.

Its parenteral administration can cause hypotension and bradycardia. It can also cause blurring of vision, dizziness, ataxia, tremor and gastrointestinal discomfort.

Phenytoin: It is an anti-epileptic which has anti-arrhythmic properties. It can be used in ventricular arrhythmias, but it is not usually used due to its side effects.

Aprinidine: it is useful in controlling refractory ventricular tachyarrhythmias . It is electrophysiologically similar to quinidine.

CLASS 1C: They include the most potent sodium channel blockers. They are usually used in resistant cases. They have their effects on the sodium channels along with a long recovery period [Table /Fig 6]. Propafenone is used as a reserve drug for ventricular arrhythmia and reentrant tachycardias. Other class 1C drugs include encainide and flecainide which have an action which is similar to that of propafenone. These drugs can increase the mortality in patients with underlying myocardial infarction.

Pilscainide: Pilscainide has selectiveness for the sodium channels, especially in its inactivated state. It was found to be useful in recent onset atrial fibrillation as compared to the earlier drugs of this class

which were used. Pilscainide has preference for the fast sodium channels which affect phase 0 of the cardiac potential. It decreases the rate of depolarization and the amplitude of the action potential without affecting the timing of the action potential. In randomized multicentric trials, it was found that pilscainide achieved more numbers in the restoration of the sinus rhythm in patients with atrial fibrillation than in those who received the placebo. A single dose of oral pilscainide is capable of the restoration of the normal rhythm in recent onset atrial fibrillation [2].

It showed no superiority in terms of the long term treatment of atrial fibrillation and it exhibited adverse effects which were similar to those which were produced by other class 1 agents .

CLASS 2: BETA BLOCKERS

An increased sympathetic activity is said to be the cause for ventricular dysarrhythmias following myocardial infarction. Thus, adrenoreceptor antagonists play major roles as an anti-arrhythmics.

Propranolol: In addition to its beta blocking property, it has a class 1 activity which contributes to it being an antidysrhythmic drug. It is useful in treating arrhythmias which are induced by emotion, exercise, pheochromocytoma and anaesthetics. It can be used in post myocardial infarction patients as a prophylactic measure against arrhythmias.

Bronchospasm is its major side effect, followed by a negative ionotropic effect.

Metaprolol and Atenolol are beta 1 selective drugs which help in avoiding the risk of bronchospasms, but their selectivity is not as much as was anticipated in the clinical practice. Still these drugs are in common usage due to their once a day regimen.

Esmolol: This is a fast and short acting beta 1 blocker drug which is useful for arrhythmias following the use of anaesthetics and against supraventricular tachycardia.

CLASS 3: POTASSIUM CHANNEL BLOCKERS

They have the unique action of prolonging the action potential. This process is not really understood, but they block the potassium channels which are involved in the phase of repolarization [Table /Fig-6].

They have a tendency to be pro arrhythmic and they also lead to torsade de pointes.

Amiodarone: It is a long acting anti-arrhythmic which is highly lipophilic and it is structurally related to thyroxine. It acts by blocking the k+ channels. It preferentially blocks the inactivated Na^+ channels and it also inhibits the myocardial action of the calcium channels. Amiodarone is useful in ventricular and supra ventricular arrhythmias. It is also useful in resistant and recurrent arrhythmias. Amiodarone as an intravenous injection helps in the termination of ventricular and supraventricular arrhythmias rapidly. It is useful in patients with sustained ventricular tachycardia.

Amiodarone can cause gastro-intestinal discomfort, photosensitisation, pulmonary alveolitis and peripheral neuropathy as it contains iodine and can cause disorders of the thyroid function.

Sotalol: It is a non-selective beta blocker with a class 3 anti-arrhythmic activity. Sotalol is effective in polymorphic ventricular tachycardia and for maintaining the sinus rhythm in atrial fibrillation. Sotalol can cause dose dependant torsade de pointes.

Dofetilide: It selectively blocks the rapid component of the delayed rectifier k+ current. Its primary indication is to maintain a sinus rhythm . Even though this drug has shown a tendency of producing torsades des pointes, it has shown less mortality in patients with the risk of sudden cardiac death and myocardial infarction.

Ibutilide: is a drug which is similar to dofetilide which is used for the conversion of atrial fibrillation to a sinus rhythm.

Dronederone: Dronedarone is a benzofuran derivative which is closely related to amiodarone. In this drug, the iodine entity is replaced by a methane sulfonyl group, thus eliminating the probable neurotoxic effects. In experimental studies which were conducted on human atrial myocytes by the whole cell patch clamp technique, dronaderone was observed to inhibit the transmembrane potassium currents like the ultra rapid- delayed rectifier (*I*kur), the delayed rectifier(*I*ks and *I*kr), the transient outward (*Ito)* and the inward rectifier (*I*k1) [3]. Studies have shown dronaderone to be effective in the treatment of atrial fibrillation and in controlling the ventricular rates [4].

In January 2011, the FDA had cautioned about cases of rare but severe liver injury with the usage of dronaderone [5].The drug should be immediately stopped if a hepatic injury is suspected. Dronaderone is contraindicated in patients with NYHA class 4 heart failure or NYHA class 2-3 heart failure with a recent decompensation which requires hospitalization. Dronadarone was approved with a Risk Evaluation and Mitigation Strategy (REMS), with the goal of preventing its use in severe heart failure [5].

Vernakalant: Vernakalant is an atrial selective anti-arrhythmic drug and an amino hexyl ether which is used in atrial fibrillation. It selectively blocks the ultra rapid delayed rectifier current (I Kur). Vernakalant causes effective prolongation of the effective refractory period of the atria, with no effect on the ventricles and so, it is less pro-arrhythmic. Vernakalant was found to show better effectiveness than placebo and amiodarone in the rapid conversion of atrial fibrillation [6].

Through the ACT studies, transient adverse effects such as dysguaesia, parasthaesia, nausea and hypotension were demonstrated by this drug [7].

Nifekalant: Its action is similar to the action of Vernakalant. Nifekelant has been observed to be effective in atrial fibrillation which was caused by a prolonged atrial effective refractory period. Nifekalant has been shown to be effective in supraventricular tachycardias. The survival was higher in patients with ischaemic heart disease and ventricular tachycardia, who were resistant to the first shock of Nifekalant [8].
Unfortunately, Nifekalant causes QT prolongation and torsades des pointes [9]

Niferidil: Niferidil causes blockage of the postassium channels which are involved in the phase of repolarization. It markedly influences the atrial refractoriness and not the ventricular refractoriness.

Sinus bradycardia was seen with the usage of Niferidil in some patients.

CLASS 4: CALCIUM CHANNEL BLOCKERS

These drugs act by blocking the L-type calcium channels.

Verapamil: This drug has the most prominent action among the class 4 drugs. It blocks the L type calcium channels and delays their recovery. It is the drug of choice in paroxysmal supraventricular tachycardia. It can be administered by the intravenous route or orally.

Verapamil is not used in reentrant supraventricular tachycardia and in the Wolff Parkinson white syndrome due to the risk of ventricular tachycardia which is caused by a reflex sympathetic stimulation.

Diltiazem: Its actions are similar to those of Verapamil, but it is less effective. It is preferred over Verapamil in atrial fibrillation to control the ventricular rate, as it can be easily titrated to the required heart rate.

MISCELLANEOUS DRUGS

Adenosine: This is a naturally occurring purine nucleoside which is released during myocardial ischaemia. It activates the Ach sensitive K^+ channels and causes membrane hyperpolarization through its interaction with the A1 type of G protein coupled adenosine receptors on the SA node, the AV node, and the atrium. It decreases the Ca^{2+} current in the AV node indirectly. All these actions lead to the slowing of the action potentials, bradycardia, reduced excitability and slowing of the conduction. Adenosine is at present preferred by many cardiologists for the termination of paroxysmal supraventricular tachycardia.

Adenosine can cause dyspnoea, headache, flushing and bradycardia.

Digoxin: Reduces the ventricular rate. It is indicated in atrial fibrillation with a rapid ventricular rate or in atrial fibrillation with cardiac failure. Digoxin decreases the conduction through the A-V bundle and the A-V node. The rate cannot be brought down in the presence of fever, sepsis and hyperthyroidism and attempts to do so, can lead to toxicity.

Digoxin causes multi-focal extra-systoles, sinoatrial arrest, ventricular fibrillation, gastro-intestinal and neurological toxicity.

NEWER ANTIARRHYTHMICS

Gap Junction Modifiers: Gap junctions connect the cytoplasmic compartments of two adjacent cells and bring about an inter-cellular communication. The electrical syncytial properties and the propagation of the action potential is dependant on the gap junctions [10]. Mutations in the genes which encode for the connexins which are components of the gap junctions, may predispose the patient to the development of arrhythmias.

Rotagaptide: Rotagaptide is a gap junction modifier , which is also known as a connexin modifier. Studies in dog models have shown the significant use of rotagaptide in reverting atrial fibrillation. Rotagaptide treatment has shown activation of the protein kinase C isoforms, which in turn, could cause the phosphorylation of Cx43, which in turn could cause the proper functioning of the connexins [11]. The smoother conductions which are caused by this, leads to a more synchronous contraction of the cardiac musculature.

Adenosine A1 Receptor Agonists: Adenosine A1 Receptor agonists are highly selective, new anti-arrhythmics which eliminate the non selective effects of adenosine.

Tecadenoson: It is an adenosine derivative with a high specificity to the A1 receptors. It has a tendency to prolong the atrioventricular node conduction. This action is possible without triggering a reduction in the blood pressure or bronchospasm through the stimulation of the A2 receptors. It may prove to be a potent drug for the urgent rate control and the possible cardioversion of atrial fibrillation. It has been found that Tecadenoson is effective in the rapid conversion of paroxysmal supraventricular tachycardia to a sinus rhythm [12].

Paraesthaesia was experienced by some patients with the usage of Tecadenason. Its other side effects included tachycardia, headache and flushing [13].

Selodenoson: This drug is similar to Tecadenoson. Its half life duration is longer than that of Tecadenosone and it is more suitable for oral usage. The intravenous and oral sustained usage of this drug form is under study for chronic management on an outpatient basis [14].

Ranolazine: This is an anti-anginal agent which has the property of blocking the late and peak /Na , Na^+ /K^+ , /Kr ,/Ks currents. Ischaemia and oxidative injury may be caused by the increased atrial rates, which in turn cause augmentation of the /Na currents by causing an intra-cellular increase in the Na^+ ions and activation of the Na^+/Ca^{2+} exchangers, causing it to work in reverse mode, bringing calcium into the cell [15]. This augmentation of /Na+ leads to the promotion of the reentrant arrhythmias. Ranolazine is a potent inhibitor of the late /Na current. It has been found to prevent early depolarizations by preventing the calcium and sodium overload in animal models.

Atrial Stretch Receptor Antagonists[16]: Studies have shown that atrial stretch which is caused by dilatation may lead to activation of the stretch receptor channels ,which in turn would lead to electro-physiological effects such as the slowing down and the shortening of the refractory period [17].

Gadolinium is a drug which is a non specific stretch receptor antagonist which was found to prevent atrial fibrillation in isolated rabbit hearts. Unfortunately, Gadolinium could not be used in physiological conditions [18].

GSMTX-4: This is an agent in the experimental phase, which is a 35 amino acid peptide toxin which is isolated from the venom of the Chilean Rose tarantula. It selectively blocks the cationic stretch activated channels. It was found to prevent the induction of atrial fibrillation without any effect on the duration and the shape of the atrial action potential. Even though this agent is selective in blocking the stretch activated channels, it are not atrial specific [19]. Altering the membrane fluidity- PUFA- The activation of the stretch activated channels depend upon the membrane fluidity. The membrane fluidity can be altered by PUFA. It was found that in rabbits which were PUFA fed, their hearts demonstrated an increased resistance to the stretch mediated changes in the electrophysiological activities. Further studies are required to prove its potential [20].

Renin Angiotensin System Inhibitors: Following the atrial stretch, it has been found that there is a release of angiotensin 2, which in turn would lead to the activation of mitogen activated protein kinases. The mitogen activated protein kinases lead to fibroblast proliferation and I nterstitial fibrosis, which can cause conduction defects. Angiotensin 2 leads to an increased calcium influx and inflammation and it also causes gap junction remodelling, leading to arrhythmias. The superlative effectiveness of the ACE inhibitors in cardiac failure could be because of their proposed anti-arrhythmic effects via angiotensin 2 mediated arrhythmias.

POTENTIAL ANTI-ARRHYTMICS FOR THE FUTURE

GAP134: GAP 134 is a dipeptide gap junction modifier [21]. GAP 134 prevents the decrease in the velocity of the conduction of an impulse. It was found that pericarditis models were protected from atrial fibrillation by GAP 134 [21]. The limitations of this drug are the doubts about its action on chronically remodeled atria and its proarrhythmic property.

PIRFENIDONE

Pirfenidone is an antifibrotic agent. It acts by downregulating the profibrotic cytokines [22], thus inhibiting collagen synthesis. Pirefenidone has been found to have an anti arrhythmic potential through studies on canine models. Pirefenidone, on oral administration, was found to decrease the atrial fibrosis, which led to beneficial electro-physiological effects such as prolongation of the effective atrial refractory period and a decrease in the atrial fibrillation vulnerability [22].

ATI 2042 (budiodarone): ATI 2042 is a chemical analogue of amiodarone. It has a half life of 7 hours and it is thought to have an efficacy which is in par with amiodarone. It contains iodine, which is hypothesized to be the cause of the similarity in its efficacy with amiodarone. Unlike amiodarone, its side effect profile is better with regards to long term treatment and tissue accumulation. ATI2042 reduces the time in which the patient was in AF [23]. This drug is under the study and it has been focused upon as a future drug in AF.

Chloride Channel Blockers [24]: Ion channels such as the L-type Ca^{2+} channels, the delayed rectifier K^{+} channels and the Na+ channels are regulated by cAMP dependant protein kinase.These chloride channels which are activated by protein kinase A, have been identified in guinea pigs and the heart chloride channel shows a lot of similarity with the cystic fibrosis trans-membrane conductance regulator chloride channels. Diphenylamine -2carboxylate, anthracene 9 carboxylate, 44'dinitrostilbene-22'-disulfonicacid, indanyloxyaceticacid, p-chlorophenoxypropionic acid and gemfibrozil have been shown to prolong the action potential of the heart by its action on the CFTR chloride channels, thus showing an antiarrhythmic effect.

GENE THERAPY

New strategies are being looked upon for modulating the atrioventricular conduction by the introduction of genetic calcium channel blockers. Adenoviral vectors are being used to carry the inhibitory $G\alpha_{i2}$ protein or by the targeted transfer of the Ras-related small G protein, which in turn, regulates the activity of the $I_{CaL}\alpha$ subunit to sarcolemma [25]. Gene therapy is still under study for future use.

CONCLUSION

Despite having four classes of anti-arrhythmic agents, the arrhythmias are unhindered, as yet. Newer class 3 agents like Dronaderone and Vernakalant seem to hold a lot of promise without the antecedent adverse effects. Gap junction modifiers, adenosine receptor agonists and ranolazine act on new targets that could have a tolerable safety profile and an enhanced efficacy .

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