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Mechanisms of Action of Drugs Used in Cardiac Arrhythmias

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Annotation. Cardiac arrhythmia is defined as disturbance of initiation or conduction of cardiac impulse. Most of us have occasional disturbances (ripple) of cardiac rhythm which are transient and go unnoticed. Normal healthy heart, not genetically predisposed to arrhythmia, is resistant to such minor disturbances by triggers. However, sometimes arrhythmias can be symptomatic and certain arrhythmias are fatal, e.g. those following acute MI. Anti-arrhythmic drugs are the drugs used to prevent or correct cardiac arrhythmias. The antifibrillatory drugs are compounds which prevent the development of atrial and ventricular fibrillation. The antifibrillatory drugs must be differentiated from the defibrillatory drugs i.e. drugs capable of restoring normal sinus rhythm of the heart under atrial and ventricular fibrillation. Although many drugs are able to arrest rapid atrial and ventricular arrhythmias, no drug is available that can consistently restore normal rhythm to a fibrillating ventricle

Keywords: arrhythmia, irregular rhythm, ectopic areas, pacemaker, repolarization, depolarization.

Introduction

According to the present concept a triggering beat/s interact with a predisposed cardiac tissue (substrate) to initiate and perpetuate cardiac arrhythmia. They could be due to: disorders of impulse formation and disorders of impulse conduction. Tachyarrhythmias due to disturbed impulse formation are associated with spontaneous, irregular and rhythmic discharge from ectopic pacemaker activity from areas other than the SA node. Production of such ectopic impulse involves an abnormality of the spontaneous diastolic depolarisation (Phases 3 and 4), leading to ectopic areas of automaticity. The differences among various atrial arrhythmias could be explained on the basis of the rate of discharge of the ectopic focus. Thus, an ectopic pacemaker with a rate 160- 180/min. causes atrial tachycardia. If the ectopic rate becomes more rapid, 220-300/min., it produces atrial flutter, while very rapid rates over 350/min results in atrial fibrillation (AF).

Disorders of impulse conduction, commonly referred to as re-entry disturbances, are the commoner of the two mechanisms of arrhythmias. According to this theory, the affected myocardium has areas of depressed function with prolonged refractory period. Due to that, an impulse approaching such an area would be diverted to adjacent excitable tissue. It is possible that the same impulse, after taking a circuitous route through normal tissue, will again reach the depressed area which by then becomes excitable. Upon traversing it, the excitatory process is free to re-enter normal regions and restimulate the chamber or entire heart. Repetition of this cycle would produce an ectopic tachycardia. The presence of a single re-entry mechanism within the ventricle may account for ventricular premature systoles, ventricular tachycardia (VT) and ventricular fibrillations (VF). The presence of a similar mechanism within the atria could cause atrial flutter. Atrial and ventricular fibrillation are caused by the fragmentation of single re-entrant path into multiple smaller cycles. In arrhythmias of the re-entrant type, conduction velocity and duration of RP are the two most critical electrophysiological properties which could be altered by drugs. Clinically, it is usually not possible to determine whether an arrhythmia represents a disorder of impulse formation or impulse

conduction. Identical arrhythmias on the ECG may result from disparate mechanisms in different patients, or even in the same individual at different times. Hence, except in a few cases, an antiarrhythmic drug cannot be selected simply on the basis of its effect on electrophysiological properties.

Not all arrhythmias need the same aggressive drug therapy. If an arrhythmia is precipitated by hypotension, restitution of BP by vasopressor agents like DA or NA may reestablish normal sinus rhythm. Further, sinus tachycardia and sinus bradycardia generally need no treatment other than that of the underlying cause. Only those which are lethal (VF), herald more dangerous rhythm (ventricular premature beats in acute MI) or seriously compromise cardiac output (AF with fast ventricular rate) require rapid and effective therapy.

Apart from common risk factors such as smoking, hypertension, metabolic diseases (diabetes), genetic predisposition seems to be important. The presence of long QT syndrome phenotype has been associated with sudden death. Blacks have higher prevalence of high BP and metabolic disease but lower incidence of atrial fibrillation compared to white population. Familial occurrence of atrial fibrillation is well known. Every patient with an arrhythmia should be evaluated for a possible underlying cause such as : a cardiovascular disorder; pulmonary disease; autonomic disorders; electrolyte disturbances; systemic disease; and drug induced toxicity. Correction of an identifiable factor, when possible should precede the administration of an anti-arrhythmic drug. In many situations, arrhythmias tend to be benign. Their treatment should be expectant, and potentially toxic drugs should be avoided.

The basic electrophysiological actions of antiarrhythmic drugs are:

Decreasing the slope of Phase 4 (diastolic depolarisation) of the action potential in the excitable cardiac tissues. This action is possessed by all antiarrhythmic drugs and suppresses the enhanced automaticity of ectopic foci.

Shifting the threshold potential towards zero (i.e., making it less negative). This again suppresses the automaticity of ectopic foci. Quinidine, Procainamide, Propranolol and Potassium possess this action.

Shifting the resting potential away from zero (i.e. making it more negative), which also slows the rate of diastolic depolarisation and suppressing automaticity. Lignocaine and Phenytoin possess this action.

Increase in the duration of the action potential, thus increasing the effective refractory period (ERP) and blocking re-entrant impulses. Quinidine, Procainamide, Propranolol and Potassium possess this action.

Shortening of the duration of action potential by Lignocaine and Phenytoin, on the other hand, reduces the refractoriness of the AV junctional tissue.

Decreasing the slope of Phase 0 of the action potential and slowing the conduction velocity of a propagated impulse. This blocks the re-entrant impulses responsible for an arrhythmia. Quinidine, Procainamide, Disopyramide, Lignocaine (in large doses) and Verapamil possess this action. Antiarrhythmic drugs, classification: They are generally classified according to their mechanism of action as:

Class I: Fast sodium channel blockers: Which predominantly block open and/or inactivated sodium channels rather than resting sodium channels. In higher concentrations, they also block nerve conduction. With the usual doses, most drugs, other than group IC, have little effect on the normal conduction system. They impede the initial rapid depolarisation and slow the phase 0 depolarisation rate, without altering the resting potential and are sometimes called membrane stabilisers. They are further subdivided into 3 groups:

(IA) Those which cause moderate phase O depression. and hence, moderately suppress conduction. They prolong repolarisation (refractoriness, phase 3) and prolong the action potential duration, in addition to suppression of automaticity e.g. Quinidine, Procainamide, Disopyramide;

(IB) Those which are weak phase O depressants and have little influence on conduction velocity. They shorten repolarisation (refractoriness, phase 3) and action potential duration. They suppress automaticity e.g. Lignocaine, Phenytoin, Mexiletine, Tocainide.

(IC) Those which cause marked phase O depression; they markedly slow conduction. They have no effect on action potential duration and repolarisation. e.g., Flecainide, Propafenone.

Class II: Beta adrenergic blockers which block the beta-1 cardiac receptors and mainly suppress automatic

discharge (phase 4 depolarisation). They do not prolong repolarisation (phase 3).

Class III: Potassium channel blockers: They markedly prolong repolarisation (phase 3) and increase action potential duration without affecting the conduction velocity. They increase RP e.g. Amiodarone, Sotalol, Ibutilide, Vernakalant, Sotalol is a noncardioselective beta blocker with additional class II activity.

Class IV: Calcium channel blockers (CCB: Verapamil but not Nifedipine) which shorten the action potential duration and depress the slow inward Ca ++ current (phase 2). Their action is mostly limited to SA and AV node where they suppress automaticity in pacemaker cells and slow conduction and increase ERP.

Class V: Miscellaneous: (a) Those which do not cause prolongation of repolarisation, e.g. Adenosine. (b) Digitalis, Potassium, Magnesium. Most of the antiarrhythmic drugs have multiple actions. Further, the metabolites of some of these drugs contribute to or even are primarily responsible for the action. For example:

QUINIDINE: This first antiarrhythmic agent used to treat both atrial and ventricular arrhythmias, is an isomer of the antimalarial drug quinine, one of the alkaloids occurring in the cinchona bark. The beneficial effect of quinine on AF was first noted by a Dutch colonial with atrial fibrillation, when he took quinine for malaria. Later, Wenckebach, an Austrian cardiologist confirmed this observation and introduced quinine as an antiarrhythmic drug. Pharmacological actions: These are: cardiac actions and extracardiac actions. The cardiac actions are due to its direct myocardiac depressant properties, and to a smaller extent due to its vagolytic (antimuscarinic) action. It blocks the sodium channels. It also inhibits potassium channels in the cardiac cells.

Automaticity: Quinidine depresses diastolic depolarisation and hence, automaticity in all tissues, especially the ectopic pacemaker. This action helps to suppress the arrhythmias due to enhanced impulse formation. Quinidine does not suppress the automaticity of the normal SA node.

Excitability: Quinidine depresses the excitability of the cardiac tissue and hence a weak ectopic impulse becomes ineffective.

Conduction velocity: Quinidine slows the conduction velocity in all the cardiac tissues. This property, along with the increased RP and decreased excitability, contributes to a decreased cardiac rate in arrhythmias due to the presence of an ectopic focus.

Refractory period: Quinidine blocks delayed rectifier potassium current, thus depressing the potassium efflux during repolarisation. Thus, it prolongs (by a direct action) repolarisation and hence, the RP. However, its vagolytic action (indirect action) increases the atrial RP, shortens that of the AV node while leaving that of the ventricles unaltered. The overall action of quinidine is: (a) To prolong the RP markedly in the atria, (b) To increase RP in the ventricles to a smaller extent and (c) To decrease RP in the AV node. Simple prolongation of RP prevents the heart from responding to premature or rapid stimulation. Re-entrant impulse finds the originally depolarised tissue still inexcitable. Quinidine thus abolishes the arrhythmias due to re-entrant circuits.

AV conduction: Quinidine depresses conduction predominantly within the atria and the His-Purkinje system. However, its vagolytic effect permits or even enhances conduction in the AV node, causing tachycardia.

Contractility: Quinidine exerts a negative inotropic action on the heart. This obviously is a disadvantage. Hyperkalemia enhances the depressant effects of quinidine.

Effects on ECG: Early changes comprise increase in Q-T interval. Decrease in amplitude or inversion of T wave and depression of S-T segment may also occur. Later changes include widening and frequent notching of the P wave, and prolonged P-R interval. Widening of the QRS complex signifies reduction of conduction velocity, and if accompanied by a considerable increase in the RP of the ventricle, might lead to the development of VT and eventually to VF. When, the QRS complex is widened by 25 to 50% or above 0.12 to 0.14 second, quinidine should be withheld. Quinidine is known to cause unpredictable abnormalities of

rhythm in digitalised heart. Extracardiac actions:
Blood pressure: Quinidine lowers BP in most patients. In patients with low cardiac output, quinidine may shift it towards normal. This is accomplished by a reduction in BP which reduces the left ventricular load, permitting a more complete emptying of the ventricle.
Miscellaneous actions: Quinidine depresses the skeletal muscle and like quinine, shows antimalarial, antipyretic and weak oxytocic activities. Absorption, fate and excretion: Quinidine is almost completely absorbed from the gut. Following a single oral dose, the peak effects are reached within 2 to 3 hours and persist for 6 to 8 hours. About 80% is bound to plasma albumin. It is primarily metabolised (75%) in the liver with half life of 4-8 hours. One metabolite 3-hydroxyquinidine is as potent as quinidine. About 25% of the drug is excreted in the urine unchanged. With the same quinidine regimen, there are wide differences in the serum quinidine levels in different persons. Electrophysiological and toxic effects correlate better with serum levels than with dosage. Hence, frequent clinical and ECG monitoring is mandatory.

All in all, the management of Cardiac arrhythmia, perhaps the most common sustained cardiac rhythm disorder, has undergone considerable changes during the last decade. Many patients of cardiac arrhythmia are asymptomatic; often they present themselves with complication such as stroke as first manifestation. The predisposing risk factors for cardiac arrhythmia include cardiovascular (hypertension, CHF, diabetes mellitus etc.) and non- cardiovascular (smoking, chest diseases, infections etc). Cardiac arrhythmia often coexists with other comorbid conditions such as hypertension and heart diseases..

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