

PHARMACOLOGY

Drugs Acting on Cardiovascular System: Antiarrhythmic Drugs

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Key words

Adenosine, Amiodarone, Atrial fibrillation, Digoxin, Lidocaine, Mexiletine, Paroxysmal atrial tachycardia, Procainamide, Propranolol, Quinidine, Ventricular premature beats, Verapamil, Ventricular tachycardia.

Introduction

Cardiac rhythm disturbance (cardiac arrhythmia) occurs due to a number of causes such as ischemia, catecholamine excess, anatomical or functional abnormality of impulse conduction and drugs. Cardiac rhythm disturbance is of two types. Abnormally slow heart beats or rhythms (the bradyarrhythmias) and abnormally fast rhythms (the tachyarrhythmias). Both of these arrhythmias require urgent medical attention because they reduce cardiac output, cause palpitations and have a potential to cause hypotension and shock. Occasionally sudden death is due to cardiac asystole or ventricular fibrillation.

In order to understand the pharmacology of antiarrhythmic drugs it is important to understand the cardiac electrophysiology and ionic movements across the excitable cell membrane of conducting and contractile myocardial tissues.

Cardiac Action Potential

Just like other excitable tissues, the cardiac action potential (AP) consists of a rapid upstroke followed by a gradual decline to normal. The characteristic AP of ventricular myocardium (also Purkinje's fibers-PF) is shown in Fig-1.

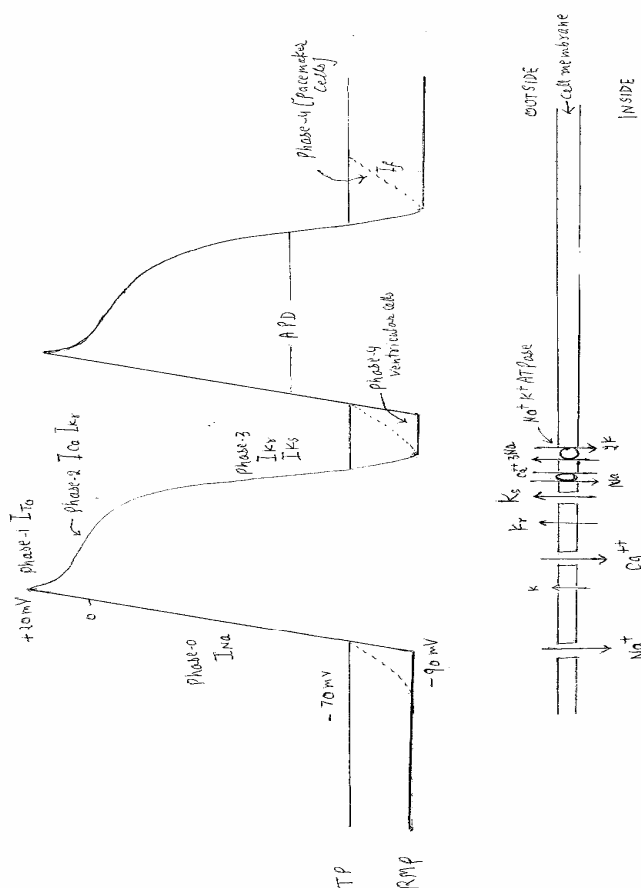


Fig. 1: Diagrammatic representation of Cardiac Action Potential (AP)

TP = Threshold potential; RMP = Resting membrane potential; APD = Duration of action potential
Phase-0: rapid influx of Na^+ produced sodium current (I_{Na}) and depolarization.

Phase-1: There is transient outward K^+ current (I_{to}), causing a notch.
 Phase-2: Influx of Ca^{++} (I_{Ca}) maintains plateau of AP
 Phase-3: Efflux of K^+ (repolarization current- I_k). I_k consists of rapid component (I_{ks}) and delayed rectifier component (I_{kr}).
 Phase-4: AP returns back to RMP. In pacemaker cells of SA and AV nodes, phase 4 is unstable. There is spontaneous depolarization (diastolic depolarization). Normal ventricular myocardium does not show diastolic depolarizations (straight dashed black line).
 Ionic rearrangement during repolarization phase occurs due to electrogenic $3Na^+/Ca^{++}$ exchange and $3Na^+/2K^{++}$ ATPase pump activity.

The components are:

Phase-0: Due to entry of sodium inside the cell by opening of sodium channels (sodium current, I_{Na}).

Phase-1: Due to reduction in sodium movement and more importantly due to transient efflux of Potassium ion by opening of K^+ channels (this potassium current is called as I_{TO})

Phase-2: Predominantly due to inward calcium current ($I_{Ca^{++}}$) by opening of L-type of voltage operated calcium channels and also due to continuous leak of K^+ ion outside cell.

Phase-3: Due to activation of delayed rectifier K current through opening of K^+ channels (rapid component of delayed rectifier current- I_{kr} and slow component of delayed rectifier current- I_{ks}). This is also known as repolarization phase and corresponds with the QT or heart rate corrected QT interval (QTc) of ECG .

Phase-4: It is isoelectric in PF and ventricular fibers but is unstable in automatic pacemaker cells. There is spontaneous depolarization (also called as diastolic depolarization) so that once threshold potential is achieved and a subsequent depolarization and action potential is generated. There is movement of calcium along with sodium to generate this pacemaker current I_f (f stands for funny!) in SA node.

It is to be noted that the APs of PF and ventricular myocardial tissues (fast fibres) are wider (250-300 m seconds), make a sharp peak at about +20 to +30 mV, threshold potential (TP) is -60 to -75 mV and are mainly due to sodium current. Whereas, APs of SA and AV node occur early, do not show sharp peak , are smaller in height with RMP of about -50 mV, show unstable diastolic phase and are mainly due to calcium current (slow fibers). Because of slow recovery the effective refractory period (ERP) may extend beyond full depolarization. This is unlike fast fibers which achieve rapid recovery and are fully excitable immediately at the end of RP (Fig-2)

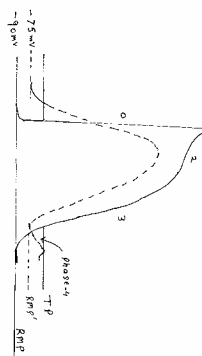
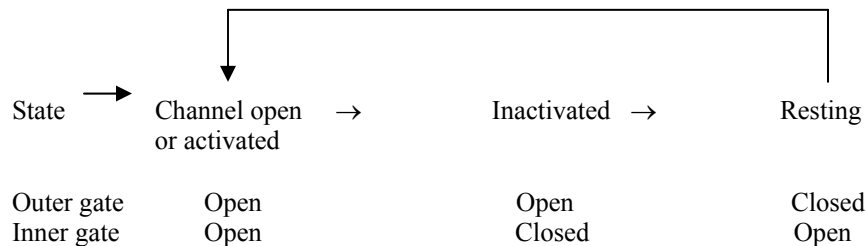


Fig 2: Action potentials of Pacemakers (SA node) and ventricular myocardium

The curve with dashed lines indicates SA nodal AP; the main ion involved is Ca^{++} . Note the prominent and unstable phase-4. The AP of ventricular myocardium is steeper and phase-4 is stable.

Rapid movement of cations across excitable cell membranes is through selective ion channels, which undergo cyclic changes as given below



The rate of channel opening (frequency dependence) and open/inactive state (state dependence) determine the selectivity of antiarrhythmic action of certain drugs (vide infra).

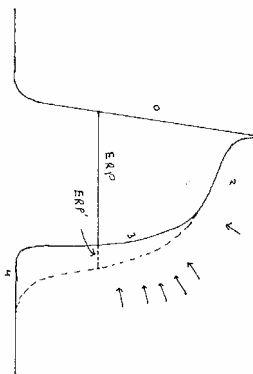


Fig 3: Activation cycle of sodium channels

Activation cycle of sodium channels in fast conducting ventricular fibers. The depolarized fibers will remain refractory unless sufficient number of sodium channels recovers back to resting state for further reactivation

Note: ↙ Arrow indicates recovery of Na^+ channels from inactive to resting state.

Fig-3 shows that sodium channels begin to inactivate just after phase-0 and as the curve goes down more and more channels are inactive and finally attain resting state so that they can reopen again. This is called as channel-recovery. Different antiarrhythmics produce different recovery rates: Lidocaine-blocked channels recover rapidly whereas flecainide-blocked channels recover slowly.

Refractory period: It is the time interval during which cardiac tissue is inexcitable. Absolute refractory period (ARP) is the period during which stimulus of any strength fails to elicit response and it extends upto half of phase-3 of AP. The relative refractory period (RRR) is the period after ARP during which a suprathreshold stimulus can evoke response/ and is propagated. A clinically useful term is Effective refractory period (ERP) during which only a local

nonconducted response can be evoked by a stimulus. This period intervenes between ARP and RRP and roughly corresponds with action potential duration (APD). In fast conducting fibers ERP is determined by voltage dependent recovery of Sodium channels from inactivation. In slow fibers recovery of calcium channels is slow (time dependence), therefore, a strong stimulus can evoke a full response only after repolarization is complete i.e., *ERP may extend beyond APD*. Refractoriness can be prolonged by two ways.

1. Prolongation of APD by blocking K⁺ efflux (K⁺ channel blockers)
2. Delay in the recovery of Na⁺ channels i.e., remain in inactivated state for a longer time.

Automaticity: Ability to generate action potential resides in SA and AV nodes normally. Abnormal impulse generation can also occur in atrial or ventricular myocardium in the event of ischemia and digoxin overdose and is termed as Ectopy, premature depolarizations or extrasystoles

Mechanisms of Cardiac Arrhythmia

Broadly speaking bradyarrhythmias and tachyarrhythmias occur due to disorders of impulse generation (Altered automaticity) or/and impulse conduction (conduction disturbance-reentry or block)

Disorders of impulse generation (Disturbed automaticity): The four determinants of automaticity are **i**-Resting membrane potential, **ii**-Slope of phase-4, **iii**-Threshold potential and **iv**-Duration of AP or ERP. Abnormalities of pacemakers (SA arrest, SA block, Sinus tachycardia, AV nodal tachycardia,) and atrial or ventricular fibers (Premature depolarizations or extrasystoles) are due to altered slope of Phase-4, triggered activity or afterdepolarizations. A less negative RMP favours ectopic impulse generation and a more negative RMP (e.g., vagal stimulation) stabilizes cell membrane and reduces excitability. Ischemia activates latent pacemakers and thus favours ectopic rhythms. Phase-4 is slowed by vagal stimulation, β -blockers and hyperkalemia while it is accelerated by β_1 -stimulation (adrenaline), ischaemia, acidosis and hypokalemia.

Triggered activity: It is an important cause of tachyarrhythmias and is seen in the form of afterdepolarizations (Fig-4). These are of two types:

a. Early afterdepolarizations(EADs): Occur at *slower heart rates* during phase 3 down slope of AP and are precipitated by hypokalemia. They prolong APD and QT interval and can be blocked by shortening of APD (Magnesium & electrical overdrive). Torsades de pointes (TDP) is due to EADs.

b. Delayed afterdepolarizations(DADs): These occur at the end of phase-3 or during phase -4, are caused by digitalis overdose, catecholamines and ischemia. These usually occur at *faster heart rates*. The common denominator is Ca⁺⁺ overload, which cause oscillations in phase-4. One of the oscillations may achieve threshold limit and thus is conducted as premature depolarization.

Disorders of impulse conduction: Failure of impulse conduction through AV node produces first and second degree heart blocks . Another important conduction disturbance is *Reentry*, which may be through an anatomical or functional pathway (Fig-5). Reentry can be around a macro-reentrant pathway and is seen in WPW syndrome, atrial flutter and AV nodal reentrant

tachycardia (Fig-6). The functional reentrant pathway is established in ischaemia of localized area which differ in refractoriness from a normal myocardial tissue thus a core of inexcitable tissue is formed which favors a round movement (Circus pathway). There may be more than one such circus pathways. This mechanism is operative in genesis of atrial and ventricular fibrillations.

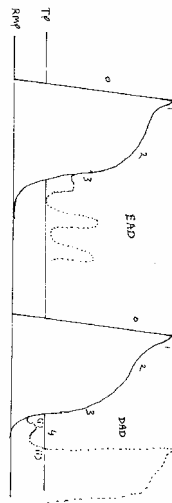


Fig 4: Early and delayed afterdepolarizations in Purkinje's fibers

A. EADs favour triggered activity and cause Torsades de pointes
 B. DADs (i and ii). The ii is capable of evoking a propagated AP.
 The atrial and ventricular extrasystoles occur by this mechanism.

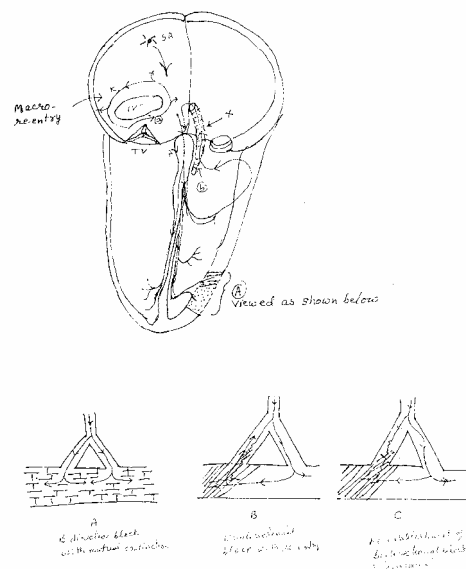


Fig 5: Examples of re-entry

Note: x = Accessory pathway; SA = SA node; TV = tricuspid valve

M= Portion of Purkinje fiber-myocardial tissue involved in ischaemia or infarction.

Anatomical micro-entry occurs at the His bundle-myocardial junctions (Fig-5,A-C) and is responsible for ventricular tachycardia (VT). It is to be noted that both mechanisms (disordered impulse formation and generation) operate in many arrhythmic disorders.

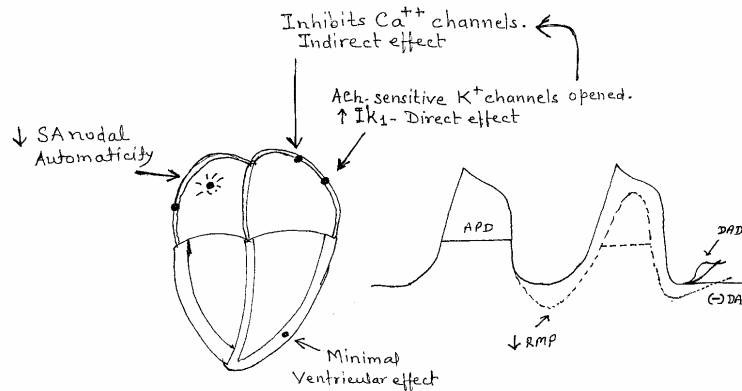


Fig 6: Normal AV nodal conduction and tachycardia due to preexcitation in WPW syndrome.

X = Accessary pathway bypassing AV node

Normal beats(A) are fusion beats due to δ -wave in Wolff-Parkinson-White syndrome (WPW syndrome). This δ -wave is due to a faster conducting fiber-tract (accessory pathway)) which bypasses AV node and it does not have AV nodal delay. Note the short PR interval and apparent widening of QRS complexes (B).

When tachycardia occurs in WPW syndrome, the impulse may pass through AV node and may find accessory pathway (curved blue line) excitable. So it re-enters for upwards (retrograde) conduction and results in orthodromic tachycardia (C).

Less commonly downgrade (anterograde) conduction through accessory pathway leads to antidromic tachycardia (D) in which heart rate is faster than orthodromic tachycardia.

Drugs such as quinidine and ibutilide increase refractoriness in accessory pathway and thus terminate wide complex tachycardia.

General mechanism of action of antiarrhythmic drugs

Drugs slow automaticity (Fig-7): Automaticity is reduced by:

1. Elevation of threshold potential- (less negative) Quinidine, propranolol, verapamil, diltiazem, potassium
2. Reducing RMP (More negative)- Adenosine, lidocaine, phenytoin
3. Prolonging APD (ERP) - Quinidine, amiodarone (Class Ia & III)
4. Reducing slope of phase-4. - Class IV drugs, propranolol

Drugs reduce afterdepolarizations: EADs and DADs are inhibited by:

1. Inhibiting upstroke of AP (Na^{+} or Ca^{++} currents in fast and slow fibers respectively)-Verapamil and phenytoin inhibit DADs.
2. Shortening of APD-Isoprenaline inhibits EADs -Magnesium acts by blocking triggered beats and reduce EADs induced heterogeneity in ventricular cells.

Drugs affect conduction and reentry by:

1. Slowing anterograde (upside down) conduction in AV node: Digoxin, propranolol and verapamil. Paroxysmal supraventricular tachycardia (PSVT) is terminated in this way. Rate reduction in atrial fibrillation also occurs by this mechanism.
2. Prolongation of refractoriness (& thus retrograde or downside-up conduction) in accessory pathways by Na⁺ channel block. Example is use of Class-Ia drugs to terminate PSVT in WPW syndrome.
3. Converting unidirectional block into bi-directional block by facilitating conduction in slow conducting pathway. Lidocaine blocks extrasystoles in myocardial infarction by this mechanism (Fig-5 C). Facilitated conduction through AV node by phenytoin makes it a useful drug in digoxin induced atrial tachycardia with varying AV nodal block.
4. Reduction in the dispersion (variability) of refractoriness by lengthening of ERP also blocks reentry by quinidine.

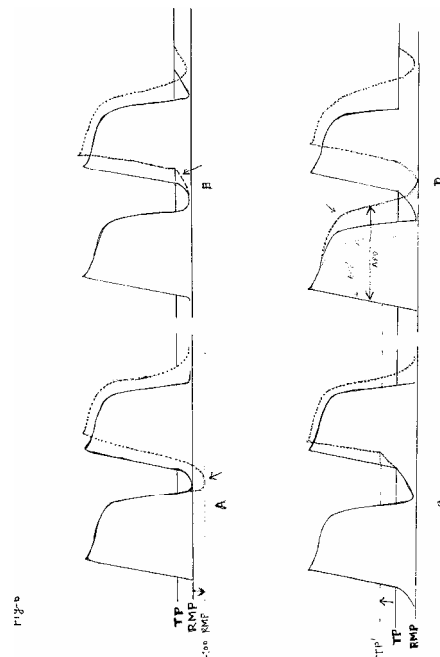


Fig 7: Some mechanisms by which arrhythmias are terminated or controlled
(indicated by arrows)

- A. Resting membrane potential more negative. The maximum diastolic potential needs to increase for generation of AP. Examples : Acetylcholine, adenosine, Lidocaine, potassium.
- B. Reduced slope of Phase-4. Examples: Adenosine, amiodarone, β -blockers.
- C. Elevation of threshold potential. Examples: Class-I drugs, lidocaine, verapamil.
- D. Prolongation of ERP (APD). Examples: Class-Ia, Class-III drugs.
- E. Shortening of atrial ERP. Examples: Adenosine and lidocaine (blue dashed line).

Individual Drugs

I. Class-Ia Antiarrhythmic Drugs

These drugs slow the rate of rise of action potential and prolong duration of action potential. They block Na^+ channels and prolong repolarisation time

1. Quinidine

The bark of Cinchona tree yields quinine alkaloid which apart from its antimalarial activity was also found to quieten palpitations. The dextro (diastereo-) isomer of quinine (quinidine) has prominent antiarrhythmic actions. Quinidine has cardiac and extracardiac actions

Cardiac actions of quinidine: It depresses cardiac contractility by direct action. It also has important electrophysiological (suppressant) effects on automaticity, refractoriness and excitability of cardiac tissues.

Quinidine blocks Na^+ channels in open state and the recovery from block is moderately slower. This results in reduced rate of rise of AP (Class-I effect) and reduced height of AP (Fig-8 A). Quinidine also blocks K^+ channels; in low doses rapid component I_{K_r} and in high doses slow component I_{K_s} of delayed rectifier current; resulting in prolongation of APD (Class-Ia effect). This effect is prominent at low heart rates (therefore more likely to cause TDP. Quinidine raises threshold of excitation and prolongs refractoriness in most of the tissues. Disparity of refractoriness is reduced. One unwanted action of these changes is that quinidine evokes EADs when serum potassium is low, this predisposes to TDP. It slows conduction in retrograde pathway and converts one way block to two way block, thereby terminate reentry.

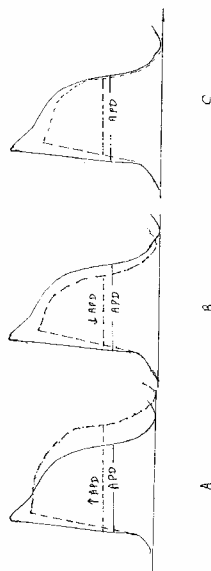


Fig 8: Effects of class-I drugs on cardiac action potential

Common class-I action: Slow rate of rise of action potential

Class-Ia action: Prolongation of APD

Class-Ib action: Shortening of APD

Class-Ic action: No change in APD.

Note: Class-Ia drugs have class-III action.

Antivagal action on AV node: While quinidine directly suppresses AV node but antimuscarinic action is dominant so there is facilitation of conduction of impulses arising above in atria.

Paradoxical tachycardia(↑HR) in Atrial flutter/fibrillation: When quinidine is used alone in the treatment of atrial flutter or fibrillation, it suppresses flutter/fibrillation rates of atria but allows more of the impulses to pass downgrade through AV node by facilitating conduction. (Remember that in Atrial Flutter /fibrillation decremental conduction in AV node establishes certain degree of AV block). This can be avoided by prior digitalization. Digitalis prolongs AV nodal conduction and refractoriness and simultaneous improves cardiac contractility (Table-1).

Table 1: Classification of Antiarrhythmic Drugs

Class	Effect on channel Or current	Effect on Phase-0 (rate of rise of AP)	Effect on APD	Drug
I	Na ⁺ channel blocked	Slowed	-	
Ia	„	„	Prolonged	Quinidine Disopyramide Procainamide
Ib	„	„	Decreased	Lidocaine Mexiletine Phenytoin Tocainide*
Ic	„	„	Unchanged	Flecainide Propafenone Moricizine**
II	I _f -pacemaker current↓ (β-blockers)	-	-	Propranolol Metoprolol Esmolol Sotalol
III	K ⁺ channel blockers Pure class-III drugs	-	Prolonged	Ibutilide Dofetilide Amiodarone Sotalol Bretium Azilimide Dronadarone (amiodarone- like but has no iodine)
	Mixed class-III drugs			
	Newer class-III drugs			
IV	Ca ⁺⁺ channel blockers*** (Non-DHPs)	-	unchanged	Verapamil Diltiazem Bepridil
IV-like	K ⁺ channel openers	-	unchanged Or shortened	Adenosine ATP

Unclassified drugs: Atropine, digoxin, isoprenaline and magnesium.)

* Withdrawn because of fatal marrow suppression/pulmonary fibrosis.

** Has class-Ib effect also

*** Nifedipine and other DHPs do not have antiarrhythmic effects

Many other drugs prolong APD (QTc interval): Astemizole, terfenadine, halofantrine, imipramine, phenothiazines, sparfloxacin, gatifloxacin, moxifloxacin, cisapride.

Effects on ECG: Prolongation of PR & QTc intervals, broadening of QRS duration and T wave inversion occur in dose dependent manner.

Extracardiac action: It has α -blocking action that contributes to hypotension. Higher doses have direct vasodilating action also. It is depressant of skeletal muscle membrane thus reduces contractions and muscle power so is contraindicated in myasthenia gravis. It stimulates uterus (Not to be used in pregnancy) and causes GIT irritation. Like quinine, it has antimalarial action.

Pharmacokinetics: About 70% of oral dose is absorbed. It has a half-life of 7-9 hours which increases with age (so dose reduction is required in elderly). Quinidine is bound to albumin and α_1 globulin (90%) and is metabolized by hydroxylation in liver (reduce dose in liver disease) forming 3-hydroxyquinidine. About 20% is excreted unchanged in urine.

Therapeutic uses: It has broad spectrum of antiarrhythmic effects in reentrant and ectopic tachycardias arising from atrium, AV node or ventricular myocardium.

1. Quinidine is used to convert atrial flutter and fibrillation to normal sinus rhythm (NSR) but now a days ibutilide, amiodarone and dofetilide are preferred.
2. It is useful to maintain NSR once atrial flutter & atrial fibrillation is reverted back to NSR by electrical cardioversion.
3. Quinidine also prevents recurrence of ventricular tachycardia (VT)

Doses: Traditionally a test dose of 200 mg is given to check idiosyncratic reactions and then 300-400 mg given 4 times daily. A longer acting preparation needs to be given twice a day. Instead of these high doses now a days, smaller doses of 100-200 mg TDS are used for maintenance therapy.

Adverse effects (ADRs): Nausea, vomiting, diarrhea are common. In higher doses, cinchonism characterized by tinnitus, deafness, vertigo, headache, delirium and visual disturbances is observed. Idiosyncratic reactions include fever, angioedema, bronchospasm, hypotension & syncope (on IV use) and rarely thrombocytopenia. Quinidine worsens CHF or precipitates it. Problem of paradoxical tachycardia is discussed above. Quinidine is an important cause of TDP.

Precautions and contraindications: It should be given with caution in occult CHF. If QRS broadens > 50% of baseline, then the drug should be discontinued. Prior anticoagulation is needed when quinidine is used for pharmaco-conversion of atrial flutter or fibrillation, because poorly contracting atria lodge thrombi, which get dislodged into circulation when atria start contracting following quinidine cardioversion. It should be avoided in QT prolongation, sick sinus syndrome, bundle branch blocks, idiosyncrasy and myasthenia.

Drug interactions.

1. *Digoxin quinidine interaction:* Quinidine roughly doubles plasma digoxin levels by reducing renal and biliary clearance, displacing tissue-bound digoxin into blood and inhibiting p-glycoprotein transporter in tissues.

2. Diuretics: Hypokemia caused by kaluretic agents predisposes to TDP.
3. Verapamil: Increases quinidine effect by inhibiting inactivation and has additive cardiac depressant action
4. Phenytoin/Rifampicin reduce quinidine effect by induction of metabolism.
5. Warfarin: anticoagulant effect is increased.

Place of quinidine: Overall, despite having a broad spectrum of antiarrhythmic actions, quinidine use is declining because of frequent administration, ADRs and availability of safer drugs. It does not reduce mortality (may increase) on long-term use.

2. Procainamide

Procainamide is an amide derivative of local anesthetic procaine and is effective orally.

Antiarrhythmic actions: Procainamide has quinidine like class-Ia effects such as depression of automaticity, slowing of conduction and prolongation of APD but there are some differences.

1. It does not have antivagal and α -blocking actions but has ganglionic blocking activity which contributes to its hypotensive effects.
2. Depression of cardiac contractility is less as compared to quinidine.
3. It is better tolerated by IV route but oral tolerance is same as for quinidine.
4. It forms active metabolite N-acetyl procainamide (NAPA) which has class-3 antiarrhythmic action. NAPA does not block Na^+ channels.
5. Sodium channels are blocked in open state and channel recovery rate is intermediate.

Pharmacokinetics: Oral bioavailability is reduced by first pass effect (>80%). It is acetylated into N-acetyl procainamide (NAPA) which has a longer $t_{1/2}$ (6-10 hrs) than procainamide (3-4 hrs). The rate of acetylation is variable. In slow acetylators, systemic lupus erythematosus (SLE) occurs earlier and rapidly. Oral loading dose is 250-750 mg every 3 hours & then 500 mg 6 hourly. An IV loading dose is given for rapid termination and is 12 mg/kg given at a rate of 0.3 mg/kg/min followed by 2-5 mg/min.

Therapeutic uses: Procainamide can be given in place of quinidine as it is better tolerated in the treatment of atrial fibrillation & flutter. It is an alternative to lidocaine in prevention and treatment of frequent VPBs and sustained tachycardia after MI. Its use is also declining because of frequent dosing and unacceptable adverse effects.

Adverse effects: Nausea and vomiting are common and diarrhea may occur. Hypotension can occur on rapid IV use. There is risk of development of TDP more so in those who metabolize it to NAPA to a greater extent. A major problem with procainamide is drug induced SLE. It occurs in about 1/3rd users who are slow metabolizers. Serum shows positive ANA and there are joint pains, arthritis, pleuritis, pericarditis, and nephropathy. The drug itself or an oxidative metabolite, but not the NAPA, is responsible for SLE. Higher doses can cause confusion and hallucinations. Marrow aplasia may occur rarely.

3. Disopyramide

Disopyramide is another class-Ia drug whose antiarrhythmic effects are similar to those of quinidine. Some differences are-

1. It has greater anticholinergic (antimuscarinic) effects than quinidine so chances of paradoxical tachycardia are more. The direct depressant effects on SA and AV node are offset by marked antivasal actions.
2. It has been found to be useful in maintenance therapy of VT in a dose of 150 mg three times a day. The dose is reduced in renal disease.

As such the adverse effects of drug are like quinine but peripheral atropine like effects (dry mouth, blurred vision, constipation, precipitation of urinary retention & glaucoma in elderly) preclude its use in elderly. It may worsen CHF.

II. Class-Ib Antiarrhythmics

The characteristic class Ib effects are reduced rate of rise of action potential and reduced or unchanged APD (Fig-8 B).

1. Lidocaine (Lignocaine, Xylocaine): Lidocaine is a local anesthetic but i.v. lidocaine without a preservative produces characteristic electrophysiological changes, which are useful in a variety of cardiac arrhythmias. Lidocaine blocks Na⁺ channels in open and importantly in inactivated state. APs of PF and ventricular tissue is longer than in atrial tissue so the Na⁺ channels remain in inactive state longer in PF & ventricular tissues. Therefore, lidocaine is more effective in ventricular than in atrial arrhythmias (in other words, because of short atrial APs Na⁺ channels remain in inactive state for a brief interval only and recovery time is longer than the time spent in active/inactive state). The recovery of lidocaine-blocked channels is rapid in PF/Ventricular tissues. Lidocaine blocks abnormal automaticity by

- i. Reducing slope of phase-4 and
- ii. Elevating TP.
- iii. The APD of atrial and ventricular tissues is reduced because of blocking of those Na⁺ channels that inactivate late during AP (Figs 7, 8 B).

Special role of Lidocaine in ischemia induced arrhythmias:

1. Ischaemic tissue is partially depolarized. In partially depolarized tissues Na⁺ channels are in inactive state for a longer period hence lidocaine is more effective in ischemia induced ventricular extrasystoles and VT.
2. Lidocaine, which is bound on inactivated Na⁺ channels of ischemic fibers, dissociates slowly (recovery delayed), thus it selectively slows conduction in ischemic fibers. Lidocaine hyperpolarizes PFs and suppresses automaticity thereby preventing impulses to be formed and abnormally conducted.
3. Conversely, it increases conduction velocity in slow ischemic limbs, converting a unidirectional block into bi-directional block and terminating reentrant arrhythmias (Fig-5 B).

Other actions: The blood pressure and pulse rate are unaffected and uncommonly cardiac contractility is depressed

Pharmacokinetics of lidocaine: Lidocaine is absorbed orally but undergoes extensive presystemic elimination so it is always given i.v. for antiarrhythmic therapy. On i.v. administration, it shows biexponential clearance (Fig-9). The initial decline in plasma levels is due to distribution ($t_{1/2}$ of 8 minutes) in peripheral tissues and terminal decline is due to metabolism ($t_{1/2}$ 100-120 min). A loading dose is needed to attain therapeutic plasma concentration (2-6 μ g/ml). The loading dose is 3-4 mg/Kg to be given as 100 mg stat, 50 mg every 8 minutes-3 times to achieve desired levels in the central compartment. A maintenance dose is needed at a rate 1-4 mg/min for 24-48 hours.

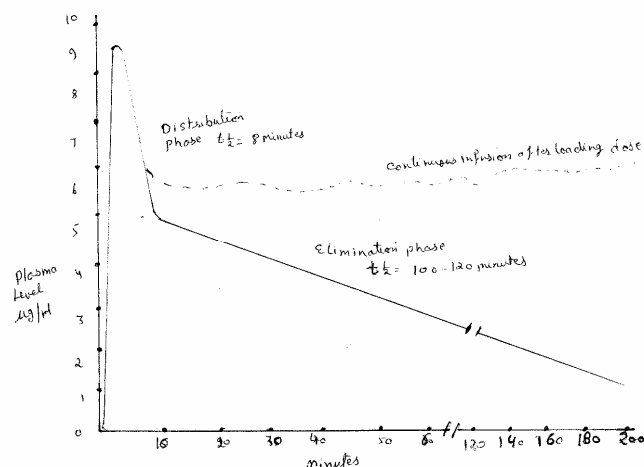


Fig 9: Diagrammatic presentation of biexponential kinetics of lidocaine

Single dose given IV shows rapid distribution and elimination phases. Therefore, it is given as a bolus (in 3 divided doses) which is followed by a continuous infusion or a bolus intramuscular dose (400 mg) followed by continuous infusion.

Dashed lines indicate bolus followed by infusion to achieve a plasma level of 5-6 μ g/ml.

Dose adjustments: In congestive heart failure (CHF) lidocaine loading and maintenance dose is reduced. In liver disease, lidocaine clearance is reduced so maintenance dose is reduced. Liver metabolizes it to inactive deethyl derivatives glycine xylidide(GX) and monoethyl-GX. The GX competes with lidocaine binding on Na^+ channels thus on continuous administration its efficacy is reduced. It also competes with lidocaine for hepatic metabolism, reducing its clearance. Renal disease has no major influence on lidocaine kinetics. In acute myocardial infarction (MI), there is a rise in α_1 -glycoprotein(acute phase reactant). This increases bound fraction of lidocaine and this may explain why some patients with acute MI require higher doses of lidocaine.

Drug interactions: Beta-blockers, cimetidine & halothane reduce hepatic blood flow and thus inhibit lidocaine metabolism. Enzyme inducers (barbiturates, carbamazepine, rifampicin) increase hepatic metabolism and reduce antiarrhythmic action. Hypokalemia causes lidocaine failure and its efficacy is increased by potassium supplementation.

Therapeutic uses of Lidocaine:

1. It is the drug of choice for suppression of serious ventricular tachyarrhythmia such as frequent VPBs and VT occurring during acute MI, general anesthesia and cardiac surgery.

2. It is also used to prevent recurrence of ventricular fibrillation following DC cardioversion.
3. It was used routinely as a prophylactic agent in acute MI. However routine use is not recommended now because some increase in mortality is reported due to lidocaine induced severe bradycardia and asystole .
4. Occasionally lidocaine is used to treat digoxin induced tachyarrhythmia because it does not slow AV conduction.

Adverse effects: Cardiac and CNS manifestations occur in higher doses. SA nodal arrest and hypotension may occur. Paresthesia, tremor (facial twitchings), central vomiting, light headedness, slurred speech and convulsions.

2. Phenytoin

Diphenyl hydantoin or phenytoin is an antiepileptic drug used in the treatment of tonic-clonic seizures. It has unique cardiac electrophysiological effects which make it useful agent in digoxin induced arrhythmias.

Electrophysiological effects: Phenytoin blocks sodium channels in inactivated state from which recovery is rapid. It depresses automaticity in ventricular tissues and PF, thus suppresses DADs. *The most important aspect is that it does not prolong APD and is devoid of autonomic effects (no anticholinergic action). It may facilitate AV nodal conduction.* SA node is not depressed. Therefore, phenytoin is a suitable agent in supraventricular arrhythmia associated with AV blocks such as digitalis induced atrial tachycardia with varying AV block and digoxin induced VT. It is also effective in VT in children with congenital heart disease and congenital prolonged QT syndrome. A central action may contribute to its antiarrhythmic effects. As such it has only modest antiarrhythmic efficacy. Usual dose is 100-200 mg 3-4 times a day. IV dose is 100 mg slowly, repeated every 10 min till 600-1000 mgs have been infused, then shifted to oral route.

Limitations of Phenytoin:

- i. It is an enzyme inducer so is likely to interact with concurrently used medications.
- ii. Its solution is highly alkaline so extravasation may cause phlebitis and sloughing of tissues.
- iv. It is less effective in arrhythmias not caused by digitalis.
- v. Rapid IV injection may cause hypotension (solvent may be responsible)
Longer use may cause gum hypertrophy, coarsening of facial features (females), osteomalacia, ataxia, megaloblastic anemia and fetopathy.

Other class-Ib drugs are Tocainide and Mexiletine. Tocainide is no longer used because it has caused fatal marrow suppression and pulmonary fibrosis.

3. Mexiletine

It has lidocaine like antiarrhythmic actions and is effective orally because of less presystemic elimination. It is an adjunct in the treatment of life endangering VT and fibrillation and can be given along with quinidine, sotalol or amiodarone to counteract APD (QT) prolongation by these agents. Unlike quinidine, it does not significantly alter BP and cardiac hemodynamics and no antimuscarinic action is there. Mexiletine can be used in patients with implanted cardioverter

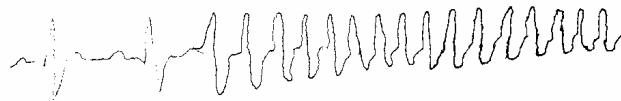
defibrillator (ICD) in situ. Its usual dose is 300 mg given three times a day. It is reported to rectify the molecular defect in a rare form of QT prolongation syndrome in which a defect in Na⁺ channel inactivation is the underlying cause. Mexiletine reduces QT dispersion and QT interval in this syndrome. Mexiletine is also found useful in painful diabetic neuropathy and traumatic neuropathies in a dose of 450-750 mg/day. Adverse effects of mexiletine include tremor, nausea, blurring of vision and lethargy.

4. Moricizine

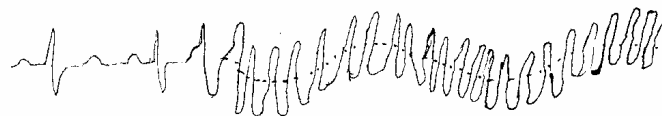
It has class Ib and Ic effects. It is a phenothiazine, which blocks Na⁺ channels and does not prolong APD. It is effective in suppression of VT but overall mortality may increase. It forms active longer acting metabolites. Usual dose is 200-300 mg three times a day. Its use is decreasing.

III. Class Ic Drugs

Class Ic agents are powerful blockers of fast Na⁺ channels and thus *reduce upstroke of AP in normal and diseased myocardium*. There is delayed inactivation of slow Na⁺ channels during down slope of AP and this result in prolongation of APD. In addition, there is inhibition of delayed rectifier K⁺ current (less K⁺ efflux) so the APD is prolonged in His bundle Purkinje fiber system. These changes create heterogeneity of impulse conduction, nonuniform slowing and unidirectional block predisposing to development of reentry (proarrhythmic potential). Arrhythmias are more likely to occur in structural heart disease, sympathetic overactivity and at faster heart rates. Monomorphic VT is most likely to occur in this way (Fig-10)



A = Monomorphic ventricular tachycardia (VT) caused by flecainide. Slow conduction with unidirectional block favours reentry and VT. Note the widening and similar shapes of QRS complexes.



B = Polymorphic ventricular tachycardia caused by Class-Ia and class III drugs (sotalol). Note the undulating tortuous mean axis of QRS complexes. The left two configurations are normal ECG complexes.

Fig 10: Proarrhythmic activity of antiarrhythmic drugs.

1. Flecainide

Flecainide blocks Na⁺ and K⁺ channels in normal and ischaemic myocardium. The recovery of blocked Na⁺ channels is slower. It is devoid of autonomic actions.

Uses: Flecainide is useful in terminating PSVT and treating atrial fibrillation and atrial flutter occurring in normal heart. It also suppresses VPBs. It is useful in PSVT with WPW syndrome and maintaining NSR after cardioversion of Atrial fibrillation.

Limitations: Despite effectiveness, flecainide has several drawbacks, which limit its usefulness.

- i. In Cardiac Arrhythmia Suppression Trial (CAST) it caused serious ventricular arrhythmias and sudden death.
- ii. It is a direct myocardial depressant.
- iii. It is contraindicated in sick sinus syndrome, bundle branch block and should be avoided in acute MI. In atrial fibrillation it may cause paradoxical tachycardia if a rate-reducing drug (digoxin) is not given simultaneously.

2. Propafenone

Propafenone blocks fast Na⁺ channels, has mild β -blocking action (1/10 of propranolol) and class-IV action (Ca⁺⁺ channel block). QT interval does not change significantly but QRS and PR intervals are prolonged. It is effective orally and is metabolized by CYP 2D6 (in some persons with deficiency of CYP 2D6 it is slowly metabolized). Its usual dose is 150-300 mg three times a day.

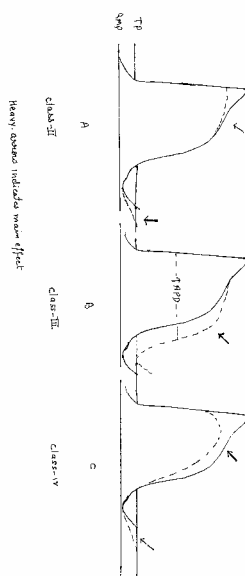
Uses: It is indicated in serious life threatening ventricular tachyarrhythmias, for suppression of supraventricular tachycardia in WPW syndrome, in recurrent atrial fibrillation and flutter when reentry is the main mechanism. It has been reported to be effective in suppression of paroxysms of atrial fibrillation when taken by patient 'on demand' in a dose of 600 mg immediately and 300 mg every 8 hours.

Adverse effects: It causes metallic taste, constipation and worsens CHF. Serious ventricular arrhythmias, sudden death and increased mortality were reported in Cardiac Arrest Study-Hamberg (CASH). It is contraindicated in sick sinus syndrome and bundle branch blocks.

IV. Class-II Antiarrhythmic Drugs

Beta-adrenergic receptor blockers have important electrophysiological effects (fig-11 A). The slope of phase-4 of action potential becomes less steep (β_1 blockade). Some reduction in intracellular Ca⁺⁺ leads to reduce phase-2 of AP. There is reduction in SA nodal automaticity, slowing of conduction and prolongation of ERP in AV node. They counteract catecholamine induced afterdepolarizations(arrhythmias) by reducing c'AMP and Ca⁺⁺ accumulation.

β -blockers are most effective in those arrhythmias where catecholamine excess plays a role such as early after MI, CHF, pheochromocytoma, anxiety, anaesthesia & postoperative period, exercise and mitral valve prolapse. Excess of c'AMP is considered to be responsible for causing ischaemia induced ventricular fibrillation. β -blockers are also effective prophylactically in suppressing supraventricular tachycardias because they suppress automaticity of ectopic foci and slow AV nodal conduction thereby reducing ventricular response in atrial fibrillation. β -Blockers reduce cardiac contractility and blood pressure.



- (A) Class-II drugs slow diastolic depolarization during phase-4 in pacemaker cells (SA and AV node) and inhibit pacemaker current I_f . They also reduce Ca^{++} movement by reducing production of cAMP
- (B) Class-III drugs prolong APD by inhibiting K^+ efflux during phase-3. There is inhibition of rapid component of delayed rectifier K^+ current (I_{Kr})
- (C) Class-4 drugs reduce height of AP during phase-2 and also suppress phase-4 in pacemaker cells by inhibiting Ca^{++} entry through L-type Ca^{++} channels

Fig 11: Effects of Class-II, III and IV drugs on cardiac action potentials

It has been found recently that β -blockers are very effective in ventricular arrhythmias also. Metoprolol is as effective as other agent in the treatment of sustained VT. When arrhythmias arise after MI, β -blockers are more effective than other agents. *The most notable effect is that they also reduce all cause mortality and arrhythmia induced sudden death, such benefit is not observed with class-I drugs.*

Uses: At present these are considered to be better antiarrhythmics because they improve survival, have broader spectrum of antiarrhythmic action, are safer compared to other antiarrhythmics. In addition they act synergistically with many other antiarrhythmics reducing their arrhythmogenic potential. β_1 blocking property is important. A β -blocker with membrane stabilizing property (propranolol) is desirable but not a prerequisite. ISA (intrinsic sympathomimetic activity) is undesirable. Sotalol has class-II and class-III properties. Esmolol is an ultrashort acting β -blocker administered intravenously. Propranolol, metoprolol and esmolol are frequently used in cardiac arrhythmias Such as

- i. Sinus tachycardia causing palpitations and nervousness in anxiety neurosis (propranolol 20 mg-80 mg 3-4 times a day, orally)
- ii. Exercise induced paroxysmal atrial tachycardia (Oral as above; i.v. 1 mg slow, max 5 mg)

- iv. Tachyarrhythmias in mitral valve prolapse
- v. Recurrent VT (metoprolol)
- vi. Along with amiodarone to reduce amiodarone induced VT.
- vii. To prevent tachycardia in hereditary prolonged QT syndrome
- viii. Along with α -blockers in preventing tachyarrhythmias in pheochromocytoma
- ix. To reduce ventricular rate in atrial fibrillation (may be used with digoxin)
- x. Frequent APBs causing palpitations
- xi. Digitalis induced supraventricular tachycardia (propranolol orally or IV as above)

Adverse effects: Worsening of CHF, bronchospasm, cardiac conduction blocks, bradycardia, peripheral vasospasm, insomnia and hypotension can occur.

Special role of esmolol: It is an ultrashort acting cardioselective β -blocker with half-life of 9-10 minutes because of rapid hydrolysis by red cell esterase. Because of short $t_{1/2}$, it can be used when other β -blockers are contraindicated (effect dissipates in half an hour). Its usual dose is 0.5 mg/kg given initially, then 0.05-0.2 mg/kg/min infusion.

Uses:

- i. Termination of PSVT, atrial fibrillation or flutter in patients with COPD and poor left ventricular function (EF <40%).
- ii. Emergency control of ventricular rate in patients during anesthesia and cardiac surgery. It also rapidly lowers raised BP during cardiac surgery.

V. Class-III antiarrhythmic drugs

Class-III antiarrhythmic agents prolong duration of action potential and may have other effects also. Amiodarone, sotalol and bretylium are mixed acting class-III drugs. Sotalol is a β -blocker, bretylium is an adrenergic neurone blocker while amiodarone has multiple cardiac & systemic effects. Dofetilide and Ibutilide are pure class-III drugs because they have cardiac electrophysiological actions mainly. The characteristic class-III antiarrhythmic action is shown in Fig-11 B and is discussed with amiodarone.

1. Amiodarone

It is a potent and broad-spectrum antiarrhythmic drug and has cardiac and extracardiac actions.

Cardiac actions: Amiodarone prolongs APD of atrial and ventricular tissues by blocking delayed rectifier K^+ current (K^+ channel block prevents K^+ efflux so down slope of AP, phase-3 is delayed). In addition, it also blocks Na^+ channels that inactivate late during phase-3; this also prolongs APD. The recovery of Na^+ channels from block is rapid. It blocks Ca^{++} channels and thus alters phase-4 of AP. Amiodarone is a potent inhibitor of abnormal automaticity and slows conduction by prolonging ERP in all tissues. ERP is prolonged by i. blocking Na^+ & K^+ channels and ii. inhibition of cell-cell coupling of impulses. Other effects are also there. It disturbs lipid membrane of myocytes and has weak antiadrenergic (α -& β -blocking) and coronary dilatory action. ECG effects are prolongation of PR, QT (QTc) intervals & QRS duration (Fig-12).

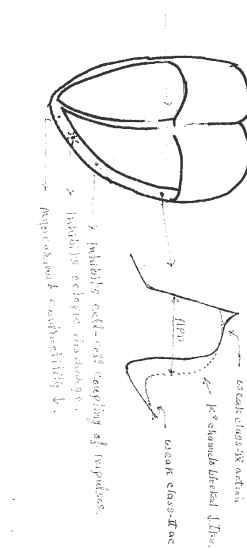


Fig 12: Multiple electrophysiological effects of amiodarone

Amiodarone prolongs APD by reducing K^+ efflux ($\downarrow I_{K_r}$) and blocking Na^+ channels which inactivate late during phase-3. Ectopic impulse generation is also blocked. Since less Ca^{++} entry occurs during phase-4, it is less likely to cause TDP, unlike sotalol.

Extracardiac actions: Peripheral vasodilation on IV administration may be due to drug per se and also due to solvent-alcohol. Several systemic adverse effects occur on prolonged use.

Pharmacokinetics: Amiodarone is effective orally but bioavailability is 30%-60% only. It is highly lipophilic agent (lipid:plasma ratio 3000:1) so is concentrated(accumulated) in body tissues such as heart(cardiac concentration 20 times plasma), lungs, liver, tears and skin. Protein binding is 90% or more. It has very long terminal $t_{1/2}$ of 30-110 days (other drug with such long $t_{1/2}$ is clofazimine), and the elimination is slow. Because of long half-life steady state concentration is achieved after several months without a loading dose. Thus, a loading dose is needed for rapid antiarrhythmic effects. It is eliminated by liver (nonrenal mechanism) as desethyl amiodarone which is as active as amiodarone. Usually dose adjustments are not needed in renal, hepatic or cardiac diseases.

Doses: Oral loading dose is 800-1600 mg/day for 2 weeks, then 400-800 mg/day for 3 weeks and finally maintained on 100-300 mg/day. Intravenous loading dose is given in 24 hours as 150 mg in 10 minutes slowly (hypotension), 360 mg in next 6 hours and 540 mg in remaining duration of 24 hours, followed by oral maintenance dose.

Drug interactions: Amiodarone is potent inhibitor of CYP 3A4, Cyp 2C9, and p-glycoprotein so interacts with a number of drugs .It increases blood levels and toxicity of class-I antiarrhythmics, digoxin and warfarin requiring dose reductions of these drugs. QT prolongation may occur with concurrent use of tricyclic antidepressants, thiazides and phenothiazines. Rifampicin (enzyme induction) may reduce effects of amiodarone.

Uses:

1. It is commonly used nowadays for suppression of chronic atrial fibrillation & to maintain NSR after cardioversion.
2. To prevent recurrent ventricular extrasystoles and VT alone or as an adjunct to Implanted cardioverter defibrillator (ICD). It raises pacing threshold.
3. It is also effective in suppression of PSVT and atrial fibrillation in WPW syndrome.
4. *It reduces mortality by 30% on long-term use.*

Adverse effects: Amiodarone causes cardiac and extracardiac ADRs. Hypotension may be due to direct myocardial depression, vasodilation and solvent injection. Bradycardia and QT prolongation may occur but TDP is less common. Long-term use causes following toxicities. Pulmonary fibrosis, corneal micro deposits & halos in visual fields, optic neuritis, hepatic dysfunction, peripheral neuropathy, proximal muscle weakness, photodermatitis, slate blue discoloration of skin, testicular failure and *thyroid malfunction*, because it contains about 75 mg iodine per tablet. Amiodarone and its metabolites are potent inhibitors of iodothyronine deiodination, des-ethyl amiodarone reduces action of T_3 (its binding on nuclear receptors) and induce thyroiditis. These changes lead to a rise in T_4 & rT_3 and a fall in T_3 . Amiodarone is a common cause of drug induced hypothyroidism and may also cause thyrotoxicosis in iodine deficient areas.

2. Sotalol

It is a nonselective β -blocker without intrinsic sympathomimetic activity. Its L-isomer has Class-II antiarrhythmic action while D- and L- isomers have class-III antiarrhythmic action, block K^+ channels and inhibit delayed rectifier K^+ current. It prolongs APD (& QT interval) in atrial and ventricular tissues. Automaticity is reduced and AV nodal conduction is slowed. Additionally it slows conduction in accessory pathways bi-directionally. AV nodal refractoriness is increased by K^+ -channel blocking and β -blocking actions. Unlike amiodarone, sotalol causes EADs and triggered activity in a dose dependent manner and therefore it predisposes to TDP especially in hypokalemia.

Pharmacokinetics: It is completely absorbed orally but undergoes extensive first pass effect. It is not bound to plasma proteins and has a half-life of 8-12 hours. It is mostly excreted unchanged through kidneys. Usual dose is 80-320 mg/day

Uses: It is an effective alternative to quinidine for the treatment of recurrent or sustained VT and can be given in structural heart disease (where flecainide cannot be given). It is also used to maintain NSR in atrial flutter/fibrillation. It can be given in children also. It is useful in tachyarrhythmia in WPW syndrome also.

Adverse effects: Bradycardia, depression of cardiac contractility, CHF, dose-dependent TDP, fatigue and bronchospasm. TDP is due to more dispersion of impulses during repolarization and enhanced Ca^{++} entry during longer AP. Sotalol should be avoided in heart blocks, in congenital long QT interval syndrome, asthmatics and severe LV dysfunction.

3. Bretylium

Bretylium tosylate is concentrated in adrenergic neurons and acts as an adrenergic neurone blocker so reduces noradrenaline release. It has direct antiarrhythmic effect also i.e., prolongs ERP and APD as a result of K⁺-channel blocking action. It is found to be effective in resistant ventricular fibrillation when lidocaine and DC cardioversion fail. It is given in a dose of 5-10mg/kg, 8 hourly, intravenously. It is rarely used now days because of advent of newer drugs and devices.

4. Magnesium ions

Magnesium ions depress heart and brain function. i.v. Magnesium sulphate or chloride (1-2 gm or 10-20 ml of 20% solution given in 20 minutes, repeated once if needed and then 1 gm/hour infusion) is used in prevention of recurrence and treatment of TDP. It is also effective in digitalis induced tachyarrhythmia and resistant ventricular fibrillation. Its exact mechanism of action is not known but may involve reduced inward movement of Ca⁺⁺. QT interval is not affected.

5. Dofetilide

It is a potent and a pure K⁺ channel blocker and prolongs APD and QT interval. There is no effect on Na⁺ movements. About 90% of the orally given dose is bioavailable and about 80% of the drug is excreted unchanged. Its half-life is 7-10 hours. Its usual dose is 0.25-0.5 mg 12 hourly and need to be reduced in renal impairment. It is indicated in maintaining NSR in atrial fibrillation and atrial flutter (more effective). Overall mortality is unaltered by dofetilide. It can be given in the presence of poor cardiac function. Dofetilide reduces fibrillation threshold in patients with ICD. A major problem is TDP (1%-3%) particularly when bradycardia is there. A number of drugs interact with it. Enzyme inhibitors (ketoconazole, ritonavir, erythromycin) raise its plasma levels. Hypokalemia (diuretics) causes further QT prolongation and increases likelihood of TDP.

6. Ibutilide

Ibutilide blocks not only K⁺ channels but also *activates* Na⁺ channels. There is no cardiac depressant action. It exhibits phenomena of 'reverse use dependence'. It is not used orally because of extensive presystemic elimination. Its half-life is 6 hours and is eliminated by nonrenal pathway (liver). It is used for rapid conversion of atrial fibrillation & flutter (more effective) to NSR as such and during cardiac surgery and is as effective as amiodarone. It is also used as a precardioversion drug for atrial fibrillation to facilitate reversion of fibrillation by DC shock. Its usual dose is 1.0 mg i.v. in 10 minutes, a second dose is repeated after 10 mins. Its adverse effects include polymorphic (TDP in 4%-6%) and also monomorphic VT. Other class-III drugs are azimilide and dronedarone (amiodarone like but has only cardiac actions).

Mechanism of Torsades de pointes –TDP (Polymorphic Ventricular tachycardia) (Fig-10)

Prolongation of phase-3 of action potential & QT or heart-rate corrected QT (QTc) interval may occur due to a number of causes such as-

1. **Drugs:** Class-Ia, Class-III antiarrhythmics, tricyclic antidepressants, phenothiazines, halofantrine, fluoroquinolones (gatifloxacin, sparfloxacin and moxifloxacin), terfenadine & cisapride (banned drugs), astemizole,. Drugs which inhibit CYP3A4 enzyme (erythromycin) can increase arrhythmogenic potential of above drugs.

2. Congenital QT prolongation syndromes (Several syndromes)

3. Electrolyte disturbance: Hypokalemia (diuretics), hypomagnesemia, hypocalcemia).

In all these conditions delayed rectifier K⁺ current (efflux) is blocked thus APD is prolonged i.e., repolarization is delayed. During this time there is inhomogeneous recovery in different fibers (uneven dispersion) and entry of Ca⁺⁺ triggers EADs, which gets conducted in different pathways because of heterogeneity of refractoriness of different fibers. This results in characteristic polymorphic (many shapes) ventricular tachycardia resembling 'Russian ballet'. The arrhythmia looks like twisting on its mean axis so is called as TDP (Fig-10).

NB: There are other drugs which induce a variety of cardiac arrhythmias by different mechanisms. Some of such drugs are amphetamine, excess of β_2 agonists, fenfluramine, bupivacaine, pimozone and cocaine.

VI. Class-IV Antiarrhythmic drugs

This group includes calcium channel blockers, verapamil, diltiazem and bepridil (blocks Na⁺ channels also). The dihydropyridines (nifedipine, amlodipine and others) are devoid of significant antiarrhythmic action). The characteristic effects of class-IV on AP are shown in Fig 9 C.

1. Verapamil

Verapamil blocks L-type voltage operated Ca⁺⁺ channels in activated and inactivated state. Since Ca⁺⁺ is the main ion participating in generation of AP in slow automatic tissues of SA and AV nodes, verapamil has predominant depressant effects on these pacemakers. It slows automaticity and increases refractoriness. It also blocks reentry in AV node. Verapamil also suppresses EADs and DADs, which are Ca⁺⁺ dependent. These effects cause bradycardia, prolongation of PR interval and reduction in number of anterograde impulses from atria to ventricles, thus slowing ventricular rate in atrial fibrillation/flutter. It has negative inotropic and peripheral vasodilatory effects also. It is absorbed orally but presystemic elimination results in low bio-availability (20% only). It is metabolized by CYP1A2 isoenzyme and has a half-life of 7-8 hours only requiring frequent dosing. A longer acting formulation may be used twice a day.

Uses: Verapamil is an effective agent to terminate PSVT in a dose of 5 mg i.v. given over two minutes. The same dose may be repeated after 5-10 minutes. Hypotension, bradycardia and sinus arrest may occur sometimes during IV administration. Oral maintenance dose is 120-240 mg in three divided doses. Sometimes an infusion is given at a rate of 0.4 μ g/kg/minute. Now a days adenosine is considered to be the first drug of choice in PSVT. Verapamil can also be used as a rate reducing agent in atrial fibrillation and atrial flutter and can be used along with digoxin, keeping in mind that digoxin levels are raised by verapamil. Verapamil is not effective in ventricular arrhythmias (may cause severe hypotension and collapse so it is contraindicated) except in a rare form called as fascicular tachycardia. It is also contraindicated in wide complex PSVT and atrial tachycardia in WPW syndrome because it shortens ERP of accessory pathway so ventricular rate paradoxically increases markedly.

2. Diltiazem

It shares many of the actions of verapamil and can be used in same disorders. Initial dose is 0.25 mg/kg given i.v. in 2 minutes then 0.35 mg/kg after 15 minutes. In atrial fibrillation, ventricular rate can be controlled by an infusion 5-10 mg/hour to a total dose of 15 mg/kg in 24 hours.

3. Bepridil

Bepridil blocks Na^{++} channels and may prolong APD predisposing to TDP. It is used in some countries as an antianginal drug.

Miscellaneous Agents

1. Adenosine

Adenosine is a natural nucleoside and has salutary effects in supraventricular arrhythmias.

Mechanism of action: Adenosine acts on purinergic P_1 receptors, which are linked to G-protein coupled receptors. The A_1 and A_3 subtypes of purinergic receptors couple with G_i . Activation of these adenosine (purinergic) receptors inhibits adenylate cyclase and *open acetylcholine sensitive potassium K^+ channels (IK_1) in atria, SA and AV nodes*. Indirectly there is inhibition of Ca^{++} channels. This allows efflux of K^+ and reduction in the APD. The automaticity of SA node is slowed due to hyperpolarization of membranes. AV nodal refractoriness is increased and conduction slowed. There is inhibition of DADs caused by sympathetic stimulation (Fig 13). Some inhibition of Ca^{++} entry also occurs. Rapid IV administration causes hypotension and bradycardia.

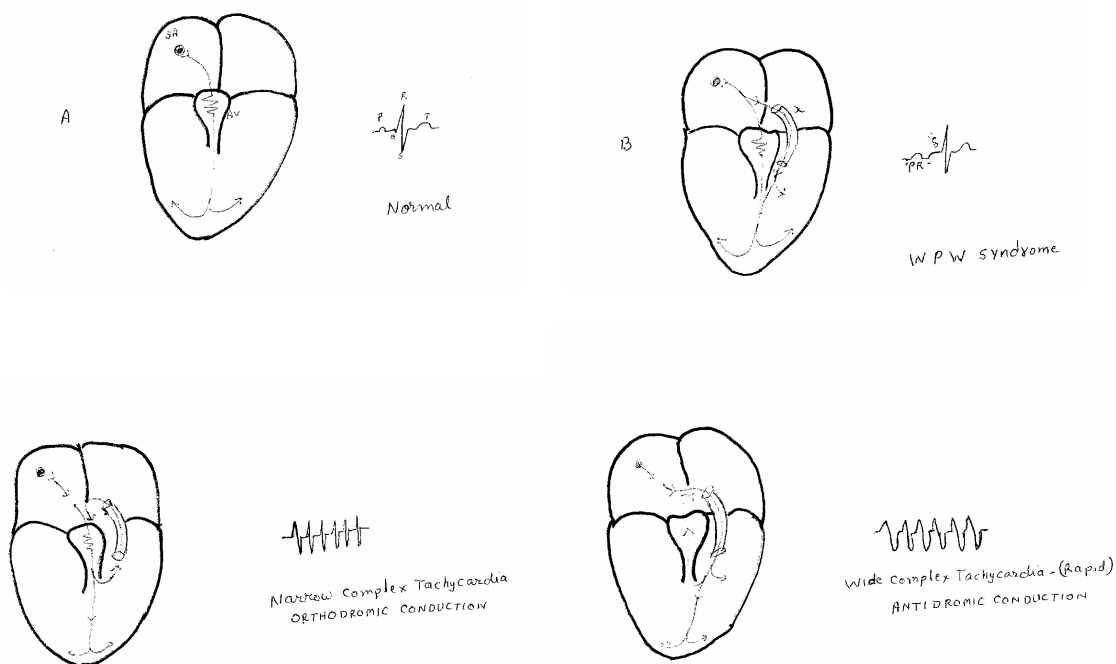


Fig 13: Multiple electrophysiological effects of adenosine on heart

Black line = Normal atrial AP.

Adenosine depresses pacemaker automaticity and reduces APD in atrial tissues. The RMP' denotes more negative resting membrane potential due to membrane hyperpolarization. Atrial myocytes become less excitable.

Pharmacokinetics: Adenosine is given as i.v. bolus and has a short half-life of <10 minutes. It is transported inside RBCs and vascular endothelial cells by a carrier mediated uptake where it is inactivated by deamination to 5'AMP and inosine.

Uses: It is used as a therapeutic and diagnostic agent in cardiology.

1. At present it is the drug of choice to terminate paroxysmal atrial tachycardia. Usual dose is 6 mg IV stat, repeated if needed once or twice after 2-4 minutes. The **Advantages over verapamil are:**
 - Onset is quicker than verapamil.
 - Effects are short lived so even if adverse effects (asystole, severe bradycardia) occur, they last for short duration only (few seconds).
 - Efficacy is high-90%-95% effectiveness.
 - There is no peripheral vasodilation so can be used even in moderate hypotension. (Caution).
 - It is safer for the therapy of PSVT in WPW syndrome.
 - It is preferred in newborn and children.
2. Rarely, adenosine is useful in VT due to sympathetic overactivity induced DADs.
3. It is useful to produce controlled hypotension during cardiac surgery.
4. Another utility of adenosine is in differential diagnosis of wide complex PSVT. If it reverts, the cause is PSVT with aberrant conduction and if no change, the cause is VT, which can be managed accordingly.
5. Adenosine *reveals latent preexcitation* in suspected case of WPW syndrome. In this situation it shortens PR interval or widens QRS duration.
6. Diagnosis of coronary artery disease-Adenosine stress testing is done in those patients with IHD who cannot perform exercise. i.v. infusion of adenosine causes increased coronary flow in nonischemic zones (coronary steal) and produces abnormal wall motion in ischemic areas. Thallium scanning can image this abnormality.

Adverse effects and interactions:

1. Dipyridamole potentiates adenosine action by inhibiting uptake of adenosine into cells.
2. Adenosine sensitivity is more in cardiac transplant.
3. Theophylline and caffeine block adenosine receptors so reduce therapeutic effects of adenosine.
4. Nifedipine inhibits its transport into cells so potentiates its actions.
5. Diazepam is an inhibitor of deaminase enzyme so reduces inactivation of adenosine.

The adverse effects are flushing, transient asystole, AV nodal blocks, hypotension, numbness, paresthesia, dyspnea and chest pain on rapid injection, bronchospasm, and breathlessness. Rarely it may worsen atrial fibrillation. It may act on carotid artery baroreceptors and increase reflex sympathetic activity.

ATP: When injected i.v., it is converted into adenosine. Usual dose is 10-20 mg.

2. Digoxin as an antiarrhythmic drug

It is useful as a rate reducing agent in chronic atrial fibrillation and flutter. It may convert flutter into fibrillation, which is easier to treat. It is less effective than adenosine in PSVT. It has narrow therapeutic margin so is less often used as an antiarrhythmic agent.

Table-2: paradoxical tachycardia with quinidine: role of digoxin

	Atrial rate	Ventricular rate or HR	AV effect
Untreated	360	120	Only 1 in 3 impulses pass to ventricles
Quinidine	180	180	Quinidine induced facilitated Conduction (Antivagal effect)
Prior-Digoxin	<180	100	Digoxin ↓conduction and ↑ Refractoriness by vagal action

3. Potassium chloride

Potassium ion is important in maintaining normal RMP. It reduces automaticity and slows conduction and has a protective effect against drug-induced arrhythmias even when serum K is normal. Hypokalemia predisposes to EADs and DADs, increases digoxin & lidocaine toxicities and propensity to TDP. Potassium chloride, 20-40 mEq, is usually infused at a rate of 20 mEq per hour well diluted in 5% dextrose under ECG control. Oral potassium (15 ml of 10% solution given three times a day) corrects mild hypokalemia due to diuretics.

Drug Treatment of Common Arrhythmias

General: Electrolyte imbalance must be corrected. Identification of reversible and treatable cause and drug-induced arrhythmias is important. A close monitoring is required.

Atrial fibrillation: In this condition there are irregular and weak atrial contractions at very high rate of 300-600 /minute. This results in irregular pulse rate and low cardiac output. Treatment depends on duration and cardiovascular status. The objectives are

- Rate control by drugs.
- Restoration to NSR.
- Prevention of thromboembolic complications.

If it is acute in onset and patient is haemodynamically unstable (low BP, heart failure or shock) then choice is DC cardioversion (100-360 joules). In some cases it may become more effective after i.v. ibutilide 1 mg in 10 min and repeated after 10 minutes. In haemodynamically stable patients AV nodal blocking agents are needed to control heart rate. Digoxin 0.25 mg to 0.5 mg i.v. repeated till 1.0-mg is administered in 24 hours may be suitable. If BP is normal or high or IHD then i.v. metoprolol 5 mg, repeated two times at 5-10 minute interval is effective. Alternatively, esmolol 0.5 mg/kg i.v. then an infusion is given at a rate of 0.05-0.2 mg/kg/minute. If β -blockers are contraindicated then i.v. diltiazem (20 mg stat, repeat after 15 minutes then 5-15 mg/hour) or verapamil (5-10 mg IV in 3 minutes then repeated after 30 minutes) are used. If rate control is inadequate then trans-esophageal echocardiography is done

to find atrial thrombus. If present, anticoagulation (heparin followed by warfarin or acenocoumarol) is done for 3-4 weeks before cardioversion. Maintenance is done with oral verapamil, digoxin or diltiazem. Addition of small dose of propranolol with digoxin further reduces ventricular rate. In chronic cases if cardioversion is indicated then pharmacological agents may be used. i.v. ibutilide may be used after adequate anticoagulation with warfarin (PT/INR 2-2.5). Amiodarone i.v. or orally, 300-400 mg BD for 2 weeks and then maintenance dose of 200 mg/day is very effective but slower acting (adjust warfarin dose). Procainamide 20 mg/min, total 1 gm may be successful. Propafenone, flecainide and dofetilide may be also used. Propafenone is also recommended for self-administration by patient in paroxysmal atrial fibrillation in a dose of 600 mg initially then 300 mg after 8 hours. In recurrent cases radiofrequency AV nodal ablation with permanent pacemaker is used.

Paroxysmal Supraventricular Tachycardia-PSVT (Paroxysmal Atrial Tachycardia)

In this condition there are sudden episodes of tachycardia associated with fast atrial contractions at a rate of 180-220/min. PSVT is commonly seen in structural heart disease, chronic lung disease or may be due to digitalis overdose. There are two common forms of it, A-V nodal reentrant and AV reentrant tachycardia. In the first type there is *reentry within the node* and in second case reentry involves atria also.

Non-drug measures: Commonly used non-drug measures are; Valsalva's maneuver (forced expiration against closed glottis), straining over stools, gagging and carotid massage (first on right side for 10-20 seconds then on left side and never on both side simultaneously).

Drug treatment: Adenosine is the first choice. It is given as 6 mg bolus into a large vein and if needed it can be repeated. Heart rate and BP should be carefully watched. DC-defibrillator should be available.

Alternatively verapamil-5mg i.v. in 2 minutes and repeated after 10 minutes, if needed.

Diltiazem 20 mg i.v. in 2-5 minutes a second dose of 0.35 mg/kg after 15 minutes then 5-15 mg/hour.

Esmolol i.v. 0.5 mg/kg in 1 minute, then 50 µg/kg/minute for 4 minutes

Occasionally, propafenone is needed. Synchronized DC cardioversion (100-200 joules) is rarely required. Edrophonium, a short acting reversible cholinesterase inhibitor, was used earlier. Rapid digitalization is also helpful.

Maintenance of NSR: Oral verapamil(80-120 mg three times a day), diltiazem (60-90 mg three times a day) or propranolol (40-80 mg 3-4 times a day) are required. Alternative drugs for maintenance therapy are amiodarone, propafenone, sotalol or azilimide.

A permanent cure can be achieved by radiofrequency catheter ablation of abnormal pathway.

Precautions: One must avoid verapamil, diltiazem and digoxin in wide complex tachycardia in WPW syndrome. Here class-Ia or III drugs are useful because the refractoriness of accessory pathway is increased and thus reentry is abolished.

Atrial Flutter

In this disorder, the atria contract at a rate of 240-340/minute and there is some degree of A-V nodal block (usually 2:1) so that ventricular rate is half of it. It is an unstable arrhythmia and may change into atrial fibrillation. ECG shows saw-tooth appearance of P waves. It is less common than atrial fibrillation and is usually associated with structural heart disease. A macroreentry circuit moving in counter clock direction around inferior vena cava has been identified. Atrial flutter is difficult to treat with drugs.

New onset atrial flutter is treated by DC cardioversion or by overdrive pacing if patient is haemodynamically unstable. In stable cases pharmacological reversion can be attempted by i.v. ibutilide, procainamide, quinidine (always digitalize first) or amiodarone. Amiodarone is useful for oral maintenance also. In chronic cases ventricular rate control can be achieved by digoxin, amiodarone or sotalol. Definitive curative treatment is by radiofrequency flutter ablation. Anticoagulation as in atrial fibrillation is also needed.

Ventricular Premature Beats (VPBs)

Treat the underlying cause (acute MI or stop digoxin) of ventricular extrasystoles. If frequency is >3/mnt at heart rate of 100/minute, are in couplets, after MI, showing *R on T* phenomena require drug treatment. Propranolol- if due to stress, lidocaine- if due to myocardial ischaemia (MI) or phenytoin- if due to digoxin; are some of the drugs used. Amiodarone and procainamide are very effective for maintenance therapy.

Ventricular Tachycardia

It is a serious arrhythmia requiring urgent attention because it is associated with high mortality.

In monomorphic VT if patient is haemodynamically unstable: DC cardioversion(100-360 joules) is the choice. This is followed by maintenance therapy with drugs.

In haemodynamically stable patient: One of the following drugs can be helpful. Lidocaine, 100 mg i.v. stat, 50 mg i.v. 8 hourly, 3 doses then 1-4 mg/minute for 1-2 days. It is most common and effective therapy in acute MI. Parenteral disopyramide, flecainide, sotalol, procainamide or amiodarone can also be used. Amiodarone is slower acting even through i.v. route but the same can be given orally for maintenance also.

Procainamide, quinidine or sotalol are used for maintenance therapy. Implanted cardioverter defibrillator (ICD) is increasingly being used as a long-term device to prevent ventricular fibrillation. Nonsustained VT in IHD may require long-term oral propranolol or metoprolol. These reduce mortality also.

Polymorphic VT (TDP): It is a special type but uncommon form of ventricular tachycardia (Fig-8) and thus requires different therapy. i.v. magnesium sulphate (1-2 gm) may terminate it. Intravenous isoprenaline may be helpful. In congenital Long QT syndrome, i.v. metoprolol is found to be effective. Serum potassium must be normalized. Oral spironolactone (K⁺ retention) is advocated for long-term use. In resistant cases temporary cardiac overdrive pacing may be helpful.

Suggested readings

1. Dimarco JP, Gersh BJ, Opie LH: Antiarrhythmic Drugs and strategies (chapter-8). In Opie LH and Gersh BJ editors-drugs for the heart, 6th ed, New Delhi, Elsevier, 2005, pp 218-274.
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3. Sharma HL & Sharma KK. Drug therapy of cardiac arrhythmias (chapter 23) In Principles of Pharmacology, 1st Ed, Hyderabad, Paras Publishers,2007, pp297-313.
4. Tripathy KD. Antiarrhythmic drugs (chapter 36),In essentials of medical pharmacology, 5th Ed, New Delhi, Jaypee,2003, pp 472-485.