Chapter 39 | Antiarrhythmic Drugs

These are drugs used to prevent or treat irregularities of cardiac rhythm.

Nearly 3 out of 4 patients of acute myocardial infarction (MI) and about half of those given a general anaesthetic exhibit at least some irregularity of cardiac rhythm. Arrhythmias are the most important cause of sudden cardiac death. However, only few arrhythmias need to be treated with antiarrhythmic drugs.

Abnormal automaticity or impaired conduction or both underlie cardiac arrhythmias. The generation and propagation of cardiac impulse and properties of excitability and refractoriness are described on p. 521–23. Ischaemia, electrolyte and pH imbalance, mechanical injury, stretching (due to heart failure), neurogenic and pharmacological influences, including antiarrhythmic drugs themselves, can cause arrhythmias by altering electrophysiological properties of cardiac fibres.

Important mechanisms of cardiac arrhythmias are:

A. Enhanced/ectopic pacemaker activity The slope of phase-4 depolarization may be increased pathologically in the automatic fibres or such activity may appear in ordinary fibres. Ectopic impulse may also result from current of injury. Myocardial cells damaged by ischaemia become partially depolarized: a current may flow between these and normally polarized fibres (injury current) and initiate an impulse.

B. After-depolarizations These are secondary depolarizations accompanying a normal or premature action potential (AP), Fig. 39.1.

Early after-depolarization (EAD) Repolarization during phase-3 is interrupted and membrane potential oscillates. If the amplitude of oscillations is sufficiently large, neighbouring tissue is activated and one or more extra impulses are

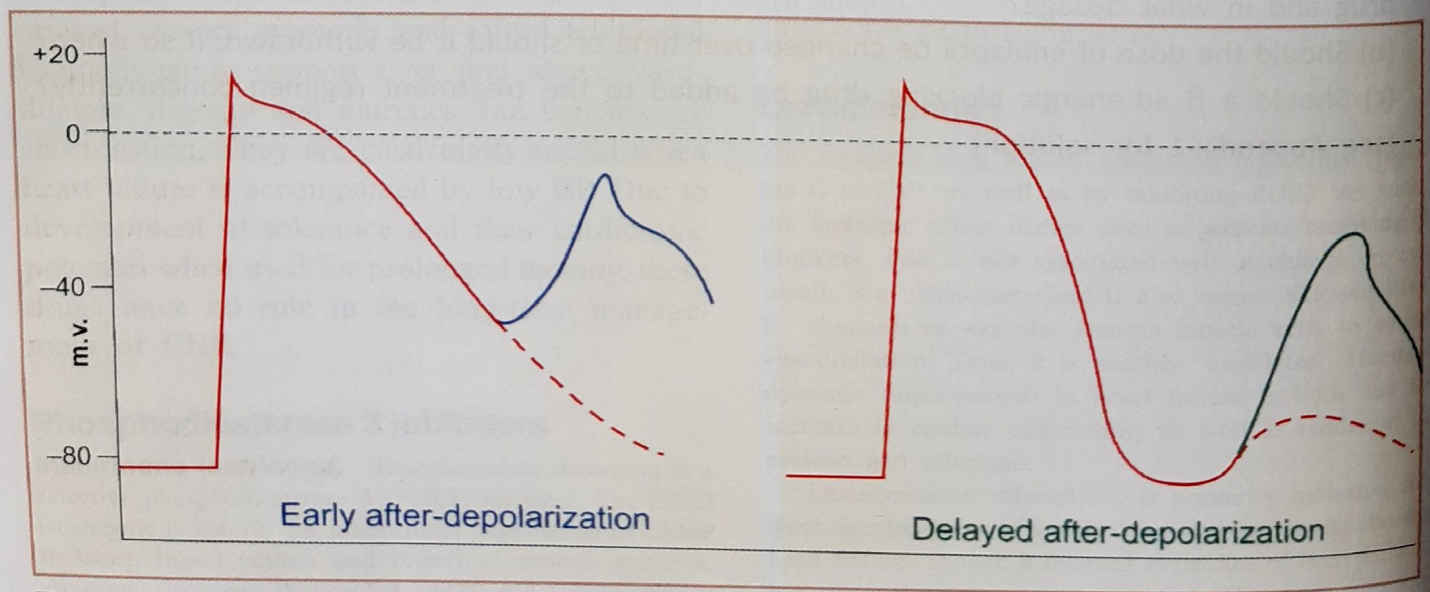


Fig. 39.1: Action potential in a nonautomatic ventricular fibre (in red) followed by early or delayed after-depolarizations.

propagated. EADs are frequently associated with long Q-T interval due to slow repolarization and markedly prolonged APs with slow heart rate. They result from depression of delayed rectifier K^+ current.

Delayed after-depolarization (DAD) After attaining resting membrane potential (RMP) a secondary deflection occurs during phase 4, which may reach threshold potential and initiate a single premature AP. This is more common with fast heart rate, and generally results from Ca^{2+} overload (e.g. in digitalis toxicity, ischaemia-reperfusion).

Because an AP is needed to trigger after-depolarizations, arrhythmias based on these have been called *triggered arrhythmias.*

C. Reentry Due primarily to abnormality of conduction, an impulse may recirculate in the heart and cause repetitive activation without the need for any new impulse to be generated. These are called *reentrant arrhythmias.*

(i) *Circus movement reentry* It occurs in an anatomically defined circuit. A premature impulse, temporarily blocked in one direction by refractory tissue, makes a one-way transit around an obstacle (natural orifices in the heart, A-V nodal region) or through an abnormal tract, finds the original spot in an advanced state of recovery and reexcites it, setting up recurrent activation of adjacent myocardium (Fig. 39.2). This type of reentry is often responsible for PSVT, atrial flutter and atrioventricular reciprocal rhythm in WPW.

Reentry occurring in an anatomically fixed circuit can be permanently cured by radiofrequency catheter ablation of the defined pathway.

(ii) *Functional reentry* In this type of reentry there is no fixed 'obstacle' or 'pathway'. Rather, a functional obstacle (core of the circuit) and unidirectional conduction pathway is created by a premature impulse which travels through electrophysiologically inhomogeneous myocardium. On encountering refractory tissue in one direction, the wavefront travels through partially recovered fibres—gets markedly slowed and can set up small reentry circuits which may constantly shift location. Functional reentry may be responsible for ventricular extrasystoles, polymorphic ventricular tachycardia, atrial/ventricular fibrillation.

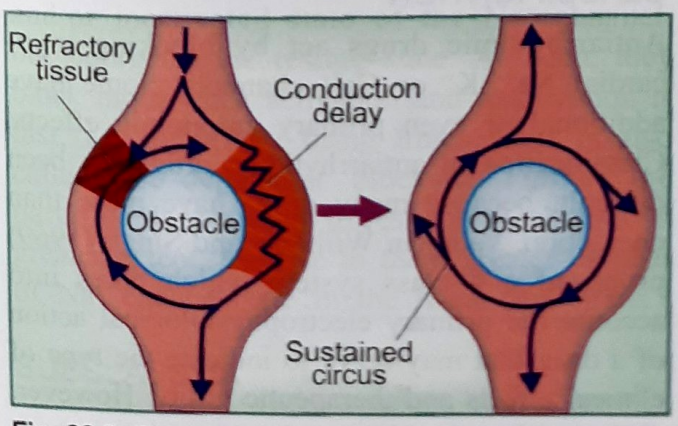


Fig. 39.2: Diagrammatic depiction of circus movement reentry in atrium

For reentry to occur, the path length of the circuit should be greater than the wave length (ERP × conduction velocity) of the impulse. Slow conduction in the reentrant circuit may be caused by:

(a) Partial depolarization of the membrane decreases the slope of phase 0 depolarization, i.e. depressed fast channel response.

(b) Cells changing over from fast channel to slow channel depolarization which conducts extremely slowly. When a fibre is depolarized to a RMP of about –60 mv, the Na^+ (fast) channels are inactivated, but the fibre can still develop Ca^{2+} (slow) channel response.

Reentry can be abolished both by marked slowing of conduction (converting unidirectional block to bidirectional block) as well as by acceleration of impulse (retrograde impulse reaches so early as to meet refractory tissue).

(iii) *Fractionation of impulse* When atrial ERP is brief and inhomogeneous (under vagal overactivity), an impulse generated early in diastole gets conducted irregularly over the atrium, i.e. it moves rapidly through fibres with short ERP (which have completely recovered) slowly through fibres with longer ERP (partially recovered) and not at all through those still refractory. Thus, asynchronous activation of atrial fibres occurs resulting in atrial fibrillation (AF). This arrhythmia must be initiated by a premature depolarization, but is self sustaining, because passage of an irregular impulse leaves a more irregular refractory trace and perpetuates the inhomogeneity of ERPs.

The important types of cardiac arrhythmias are:

1. *Extrasystoles (ES)* are premature ectopic beats due to abnormal automaticity or after-depolarization arising from an ectopic focus in the atrium (AES), A-V node (nodal ES) or ventricle (VES). The QRS complex in VES is broader and abnormal in shape.
2. *Paroxysmal supraventricular tachycardia (PSVT)* is sudden onset episodes of atrial tachycardia (rate 150–200/min) with 1:1 atrioventricular conduction: mostly due to circus movement type of reentry occurring within or around the A-V node or using an accessory pathway between atria and ventricle (Wolff-Parkinson-White syndrome or WPW).
3. *Atrial flutter (AFl)* Atria beat at a rate of 200–350/min and there is a physiological 2:1 to 4:1 or higher A-V block (because A-V node cannot transmit impulses faster than 200/min). AFl is mostly due to a stable reentrant circuit in the right atrium, but some

cases may be due to rapid discharge of an atrial focus.

4. *Atrial fibrillation (AF)* Atrial fibres are activated asynchronously at a rate of 350–550/min (due to electrophysiological inhomogeneity of atrial fibres), associated with grossly irregular and often fast (100–160/min) ventricular response. Atria remain dilated and quiver like a bag of worms. It is the most common chronic arrhythmia.
5. *Ventricular tachycardia (VT)* is a run of 4 or more consecutive ventricular extrasystoles. It may be a sustained or nonsustained arrhythmia, and is due either to discharges from an ectopic focus or after-depolarizations or single site (monomorphic) or multiple site (polymorphic) reentry circuits.
6. *Torsades de pointes* (French: twisting of points) is a life-threatening form of polymorphic VT with rapid QRS complexes which appear as undulating wave around the baseline in the ECG. Hypokalaemia and hypomagnesemia predispose to torsades de pointes, which is generally associated with long Q-T interval.
7. *Ventricular fibrillation (VF)* is grossly irregular, rapid and fractionated activation of ventricles resulting in incoordinated contraction of its fibres with loss of pumping function. It is fatal unless reverted within 2–5 min. VF is the most common cause of sudden cardiac death.
8. *Atrio-ventricular (A-V) block* is due to depression of impulse conduction through the A-V node and bundle of His, mostly due to vagal influence or ischaemia.

   First degree A-V block: Slowed conduction resulting in prolonged P-R interval (>0.21 sec).

   Second degree A-V block: Some supraventricular complexes are not conducted: drop beats.

   Third degree A-V block: No supraventricular complexes are conducted; ventricle generates its own impulse; also called complete heart block.

Proarrhythmic potential of antiarrhythmic drugs

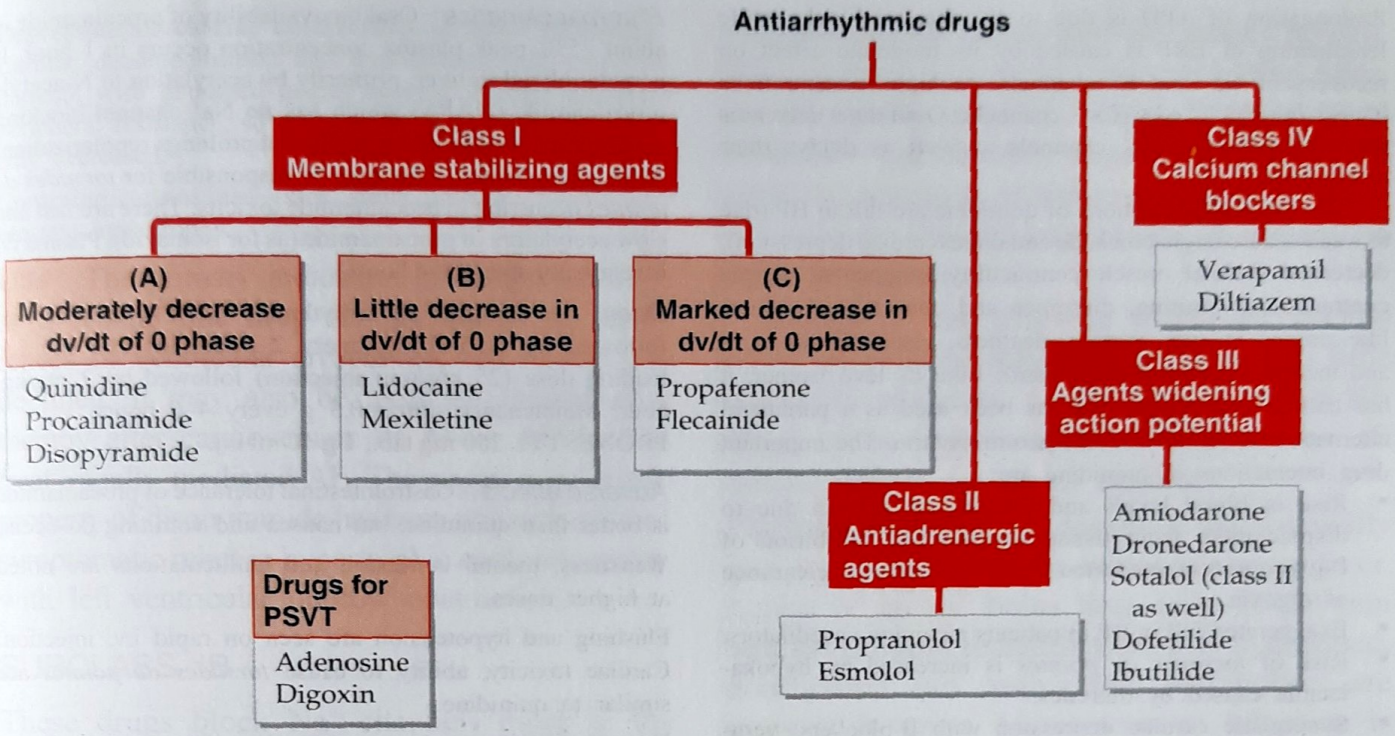
Most antiarrhythmics can themselves be the cause of serious arrhythmias, especially during long-term prophylactic use. Two multicentric trials 'Cardiac Arrhythmia Suppression Trial I and II' (CAST I, II, 1991, 1992) showed that post-MI patients randomized to receive encainide, flecainide, moricizine on a long-term basis had higher incidence of sudden death, though initially the same drugs had suppressed VES in these patients. It is possible that during transient episodes of ischaemia, the intraventricular conduction slowing action of these drugs gets markedly accentuated resulting in VT and VF. Similar increased mortality has been reported by the "Mortality in the survival with D-sotalol (SWORD) trial. It is therefore not prudent to try and suppress all extrasystoles/arrhythmias, especially those not causing symptoms, with chronic prophylactic antiarrhythmic therapy. Only the β blockers and amiodarone have been found to decrease cardiac mortality in the long term.

Drugs that prolong Q-T interval (have potential to precipitate Torsades de pointes)

1. *Antiarrhythmics*	:	Quinidine, procainamide, disopyramide, propafenone, amiodarone
2. *Antimalarials*	:	Quinine, mefloquine, artemisinin, halofantrine
3. *Antibacterials*	:	Sparfloxacin, moxifloxacin
4. *Antihistaminics*	:	Terfenadine, astemizole, ebastine
5. *Antidepressants*	:	Amitryptyline and other tricyclics
6. *Antipsychotics*	:	Thioridazine, pimozide, aripiprazole, ziprasidone
7. *Prokinetic*	:	Cisapride

CLASSIFICATION

Antiarrhythmic drugs act by blocking myocardial Na^+, K^+ or Ca^{2+} channels. Some have additional or even primary autonomic effects. Classification of antiarrhythmic drugs has been difficult, because many drugs have more than one action. Vaughan Williams and Singh (1969) proposed a 4 class system which takes into account the primary electrophysiological action of a drug that may serve to indicate the type of clinical effects and therapeutic utility. However, different drugs within a class have their own specific set of properties.



PSVT: Paroxysmal supraventricular tachycardia

A simplified clinical classification of antiarrhythmic drugs is given at the end of the chapter.

CLASS I

The primary action of drugs in this class is to limit the conductance of Na^+ (and K^+) across cell membrane—a local anaesthetic action. They also reduce rate of phase-4 depolarization in automatic cells.

The class I drugs bind easily to the activated and/or inactivated state of the Na^+ channel, but poorly to the resting state. As such, they block more when activation and inactivation is fast, i.e. in rapidly firing fibres. This is also called 'use dependent' blockade. Further, the partially depolarized fibres are blocked to a greater extent, because in them greater number of Na^+ channels are in the inactivated state.

SUBCLASS IA

The subclass IA containing the oldest antiarrhythmic drugs *quinidine* and *procainamide* are open state Na^+ channel blockers with little effect on resting channels. They also moderately delay channel recovery (channel recovery time $\tau_{recovery}$ 1–10s), suppress A-V conduction and prolong refractoriness. The Na^+ channel blockade is greater at higher frequency (premature depolarization is affected more). These actions serve to extinguish ectopic pacemakers that are often responsible for triggered arrhythmias and abolish reentry by converting unidirectional block into bidirectional block.

Quinidine

It is the dextro isomer of the antimalarial alkaloid quinine found in cinchona bark. In addition to Na^+ channel blockade, quinidine has cardiac antivagal action which augments prolongation of atrial ERP and minimizes RP disparity of atrial fibres. A-V node ERP is increased by direct action of quinidine, but decreased by its antivagal action; overall effect is inconsistent. Quinidine depresses myocardial contractility; failure may be precipitated in damaged hearts.

ECG: Quinidine increases P-R and Q-T intervals and tends to broaden QRS complex. Changes in the shape of T wave may be seen reflecting effect on repolarization.

Mechanism of action: Quinidine blocks myocardial Na^+ channels in the open state—reduces automaticity and rate of 0 phase depolarization in a frequency dependent manner.

Prolongation of APD is due to K^+ channel block, while lengthening of ERP is caused by its moderate effect on recovery of Na^+ and K^+ channels. At high concentrations it also inhibits L type Ca^{2+} channels. Quinidine decreases the availability of Na^+ channels as well as delays their reactivation.

The extracardiac actions of quinidine are fall in BP (due to weak α adrenergic blockade and direct cardiac depression), decreased skeletal muscle contractility, augmented uterine contractions, vomiting, diarrhoea and neurological effects like ringing in ears, vertigo, deafness, visual disturbances and mental changes (Cinchonism). Like its levo isomer, it has antimalarial action, and has been used as a parenteral alternative to quinine for falciparum malaria. The important drug interactions of quinidine are:

- Rise in blood levels and toxicity of digoxin due to displacement from tissue binding and inhibition of P-glycoprotein mediated renal and biliary clearance of digoxin.
- Exaggerated fall in BP in patients receiving vasodilators.
- Risk of *torsades de pointes* is increased by hypokalaemia caused by diuretics.
- Synergistic cardiac depression with β-blockers, verapamil, K^+ salts.
- Quinidine inhibits CYP2D6: prolongs t½ of propafenone and inhibits conversion of codeine to morphine.

Use: Though quinidine is effective in many atrial and ventricular arrhythmias, it is seldom used now, because of risk of adverse effects, including that of *torsades de pointes*, sudden cardiac arrest or VF; idiosyncratic angioedema, vascular collapse, thrombocytopenia, etc.

In a dose of 100–200 mg TDS quinidine may rarely be used to maintain sinus rhythm after termination of AF or AFI.

QUINIDINE SULPHATE 200 mg tab; NATCARDINE 100 mg tab.

Procainamide

It is orally active amide derivative of the local anaesthetic procaine, with cardiac electrophysiological actions almost identical to those of quinidine, *viz.* slowing of upstroke of AP and impulse conduction, prolongation of APD, ERP, QRS complex and Q-T interval. Significant differences between the two are:

- Procainamide is less effective in suppressing ectopic automaticity than quinidine.
- Procainamide is a weaker depressant of cardiac contractility and A-V conduction.
- Antivagal action is absent.
- Procainamide is not an α blocker: causes less fall in BP. At high doses, fall in BP is due to ganglionic blockade.

Pharmacokinetics Oral bioavailability of procainamide is about 75%, peak plasma concentration occurs in 1 hour. It is metabolized in liver, primarily by acetylation to N-acetylprocainamide (NAPA) which has no Na^+ channel blocking property but blocks K^+ channels and prolongs repolarization: APD is lengthened. This may be responsible for *torsades de pointes* occurring in procainamide toxicity. There are fast and slow acetylators of procainamide (as for isoniazid). Plasma t½ is relatively short (3–4 hours).

Dose: For abolition of arrhythmia—0.5–1 g oral or i.m. followed by 0.25–0.5 g every 2 hours; or 500 mg i.v. loading dose (25 mg/min injection) followed by 2 mg/kg/hour. Maintenance dose—0.5 g every 4–6 hours.
PRONESTYL 250 mg tab., 1 g/10 ml inj.

Adverse effects Gastrointestinal tolerance of procainamide is better than quinidine, but nausea and vomiting do occur.

Weakness, mental confusion and hallucinations are noted at higher doses.

Flushing and hypotension are seen on rapid i.v. injection. Cardiac toxicity, ability to cause *torsades de pointes* are similar to quinidine.

Hypersensitivity reactions are rashes, fever, angioedema. Agranulocytosis and aplastic anaemia is rare.

Long-term high dose procainamide therapy can cause systemic lupus erythematosus (SLE), especially in slow acetylators.

Use Procainamide (i.v.) is a second line drug to terminate monomorphic VT and some supraventricular arrhythmias. Many WPW reciprocal VTs respond and it has been used to prevent recurrences of VF. However, oral use of procainamide has been dropped due to poor efficacy and risk of proarrhythmia as well as lupus.

Disopyramide

It is a quinidine like Class IA drug that has prominent cardiac depressant and anticholinergic actions, but no α adrenergic blocking property. Disopyramide usually has no effect on sinus rate because of opposing direct depressant and antivagal actions. Prolongation of P-R interval and QRS broadening are less marked.

Pharmacokinetics Bioavailability of oral disopyramide is about 80%. It is partly metabolized in liver by dealkylation, nearly half is excreted unchanged in urine; plasma t½ is 6–8 hrs. The t½ is increased in patients of MI and in renal insufficiency.

Dose: 100–150 mg 6–8 hourly oral.

NORPACE 100, 150 mg cap, REGUBEAT 100 mg tab.

Adverse effects Disopyramide causes less g.i. effects. Anticholinergic side effects are prominent: dry mouth, constipation, urinary retention (especially in elderly males), and blurred vision; which limit its long term use. Risk of torsades de pointes is like other class IA drugs.

Depression of cardiac contractility is more prominent. Cardiac decompensation and hypotension may occur in patients with damaged hearts because it also increases peripheral resistance, so that cardiac output may be markedly decreased.

Contraindications are—sick sinus, cardiac failure and prostate hypertrophy.

Use The primary indication of disopyramide is as a second line drug for prevention of recurrences of ventricular arrhythmia, but its use has declined. It may also be used for maintenance therapy after cardioversion of AF or AFl and to treat vagally mediated AF. The negative inotropic property of disopyramide has been utilized to afford symptomatic relief in hypertrophic cardiomyopathy with left ventricular outflow obstruction.

SUBCLASS IB

These drugs block Na^+ channels more in the inactivated than in the open state, but do not delay channel recovery (channel recovery time < 1S). They do not depress A-V conduction or prolong (may even shorten) APD, ERP and Q-T.

Lidocaine (Lignocaine)

It is the most commonly used local anaesthetic (*see* Ch. 26). In addition, it is a popular antiarrhythmic in intensive care units.

The most prominent cardiac action of lidocaine is suppression of automaticity in ectopic foci. Enhanced phase-4 depolarization in partially depolarized or stretched PFs, and after-depolarizations are antagonized, but SA node automaticity is not depressed.

The rate of 0 phase depolarization and conduction velocity in A-V bundle or ventricles is not decreased. Lidocaine abbreviates (contrast quinidine which prolongs) APD in PF and ventricular muscle, but has practically no effect on APD and ERP of atrial fibres. Atrial reentry is not affected. However, it can suppress reentrant ventricular arrhythmias either by abolishing one-way block or by producing two way block.

Lidocaine is a blocker of inactivated Na^+ channels more than that of open state. As such, it is relatively selective for partially depolarized cells and those with longer APD (whose Na^+ channels remain inactivated for longer period). While normal ventricular and conducting fibres are minimally affected, depolarized/damaged fibres are significantly depressed. Brevity of atrial AP and lack of lidocaine effect on channel recovery might explain its inefficacy in atrial arrhythmias.

Lidocaine has minimal effect on normal ECG; QT interval may decrease. It causes little depression of cardiac contractility or arterial BP. There are no significant autonomic actions: all cardiac effects are direct actions.

Pharmacokinetics Lidocaine is inactive orally due to high first pass metabolism in liver. Action of an i.v. bolus lasts only 10–20 min because of rapid redistribution. It is hydrolysed, deethylated and conjugated; metabolites are excreted in urine. Metabolism of lidocaine is hepatic blood flow dependent.

The t½ of early distribution phase is 8 min while that of later elimination phase is nearly 2 hours. Its t½ is prolonged in CHF, because of decrease in volume of distribution and hepatic blood flow: rate of infusion should be reduced.

Dose and preparations Lidocaine is given only by i.v. route: 50–100 mg bolus followed by 20–40 mg every 10–20 min or 1–3 mg/min infusion.

XYLOCARD, GESICARD 20 mg/ml inj. (5, 50 ml vials). These preparations for cardiac use contain no preservative. The local anaesthetic preparations should not be used for this purpose.

Propranolol prolongs t½ of lidocaine by reducing hepatic blood flow. Cimetidine also increases plasma levels of lidocaine.

Adverse effects The main toxicity is dose related neurological effects:

Drowsiness, nausea, paresthesias, blurred vision, disorientation, nystagmus, twitchings and fits.

Lidocaine has practically no proarrhythmic potential and is the least cardiotoxic antiarrhythmic. Only excessive doses cause cardiac depression and hypotension.

Use Lidocaine is safe if given by slow i.v. injection; is used to suppress VT and prevent VF. It is ineffective in atrial arrhythmias. Because of rapidly developing and titratable action

it is a good drug in the emergency setting, e.g. arrhythmias following acute MI or during cardiac surgery. In acute MI, i.v. infusion of lidocaine can prevent VF, but a metaanalysis has shown that it fails to improve survival; may even increase short term mortality. Therefore, lidocaine is no longer administered prophylactically to all MI patients, but may be used in selected cases, and to treat ventricular arrhythmias when they occur.

Efficacy of lidocaine in chronic ventricular arrhythmia is poor, but it suppresses VT due to digitalis toxicity, for which it is used because it does not worsen A-V block.

Mexiletine

It is a local anaesthetic and an orally active antiarrhythmic; chemically and pharmacologically similar to lidocaine. Automaticity in PF is reduced both by decreasing phase-4 slope and by increasing threshold voltage. By reducing the rate of 0 phase depolarization in ischaemic PF it may convert one-way block to two-way block.

Mexiletine is almost completely absorbed orally, 90% metabolized in liver and excreted in urine; plasma t½ 9–12 hours.

Bradycardia, hypotension and accentuation of A-V block may attend i.v. injection of mexiletine.

Neurological side effects—tremor, nausea and vomiting are common; dizziness, confusion, blurred vision, ataxia can occur.

Dose: 100–250 mg i.v. over 10 min., 1 mg/min infusion. Oral: 150–200 mg TDS with meals.

MEXITIL 50, 150 mg caps, 250 mg/10 ml. inj.

Use Parenteral mexiletine may be used in post-infarction sinister ventricular arrhythmias as alternative to lidocaine. Survival is not improved in high risk patients. Oral use for long term suppression of VES/VT is of questionable merit; therefore, infrequently prescribed.

SUBCLASS IC

These are the most potent Na^+ channel blockers with more prominent action on open state and the longest recovery times (> 10S). They markedly delay conduction, prolong P-R interval, broaden QRS complex, but have variable effect on APD. Drugs of this subclass have high proarrhythmic potential when administered chronically; sudden deaths have occurred.

Propafenone By blocking Na^+ channels propafenone considerably depresses impulse transmission and has profound effect on His-Purkinje as well as accessory pathway conduction. Anterograde as well as retrograde conduction in the bypass tract of WPW syndrome is retarded. Propafenone prolongs APD and has β adrenergic blocking property—can precipitate CHF and bronchospasm. It is not suitable for patients with damaged hearts, and those with ischaemic heart disease.

Propafenone is absorbed orally and undergoes variable first pass metabolism; there being *extensive* or *poor* metabolizers because the major metabolic isoenzyme CYP2D6 is deficient in poor metabolizers. CYP2D6 inhibitors like fluoxetine increase its bioavailability and plasma concentration. Bioavailability and t½ differs considerably among individuals. Some metabolites are active. Side effects are nausea, vomiting, bitter taste, constipation and blurred vision. As mentioned above, it can worsen CHF, asthma and increase the risk of sudden death.

Propaphenone is used mainly for maintaining sinus rhythm in patients with peroxysmal or persistentAF. It has also been advocated for self-treatment of paroxysmal AF. It is useful for prophylaxis of PSVT involving A-V node or accessory pathway. It can occasionally increase ventricular rate in AFl by slowing atrial rate and allowing 1:1 A-V transmission, therefore, should be combined with an A-V node blocking drug. Propafenone has been used to treat VES and VT, but some reentrant VTs may be worsened.

Dose: 150 mg BD–300 mg TDS;
RHYTHMONORM, PRADIL 150 mg tab.

Flecainide It is the prototype class IC antiarrhythmic which markedly delays Na^+ channel recovery. In contrast to propafenone, flecainide has no consistent effect on APD and no β adrenergic blocking property. It suppresses VES, VT, WPW tachycardia and prevents recurrences of AF and PSVT. But in the CAST study it was found to increase mortality in patients recovering from MI; can itself provoke arrhythmias during chronic therapy. It is reserved for resistant cases of paroxysmal AF and for life-threatening sustained VT in patients not having associated CHF.

CLASS II

The primary action of class II drugs is to suppress adrenergically mediated ectopic activity.

Propranolol (*see* Ch. 10) It is the most commonly selected β blocker for treatment and prevention of cardiac arrhythmias. At high doses some quinidine like direct membrane stabilizing action is also evident. However, in the clinically used dose range—antiarrhythmic action is exerted primarily because of cardiac adrenergic blockade. In a normal resting individual propranolol has only mild depressant action on SA node automaticity, but marked decrease in the slope of phase-4 depolarization and automaticity occurs in SA node, PF and other ectopic foci when the same has been increased under adrenergic influence. The other most important action is to prolong the ERP of A-V node (an antiadrenergic action). This impedes A-V conduction so that no paradoxical tachycardia can occur when atrial rate is reduced in AF or AFl (as occurs with quinidine).

Slow channel responses and after-depolarizations that have been induced by catecholamines (CAs) are suppressed. Reentrant arrhythmias that involve A-V node (many PSVTs) or that are dependent on slow channel/depressed fast channel response may be abolished by its marked depressant action on these modalities.

The most prominent ECG change is prolongation of PR interval. Depression of cardiac contractility and BP are mild.

Administration For rapid action, propranolol may be injected i.v. 1 mg/min (max. 5 mg) under close monitoring. The usual oral antiarrhythmic dose is 40–80 mg 2–4 times a day.

Use Propranolol is very useful in treating inappropriate sinus tachycardia. Atrial and nodal ESs, especially those provoked by emotion or exercise are suppressed by propranolol, but these ESs need to be treated only when symptomatic and disturbing. Propranolol is less effective than adenosine and verapamil for termination of PSVT (success rate ~ 60%), but can be used to prevent recurrences.

Propranolol rarely abolishes AF or AFl, but is used to control ventricular rate in patients with these arrhythmias. It is highly effective in sympathetically mediated arrhythmias seen in pheochromocytoma and during anaesthesia with halothane. Digitalis induced and thyrotoxicosis associated tachyarrhythmias may be suppressed.

Propranolol is less effective than Class I and Class III drugs in suppressing VES and VT, but some nonsustained VTs may respond, and it may prevent recurrences of VT. Its antiischaemic action may also be protective. Prophylactic treatment with β blockers reduces mortality in post-MI patients. Propranolol or esmolol injected i.v. may terminate *torsades de pointes*. Along with a class IA or IC drug, it may be used for WPW reciprocal rhythms. Combination of β blocker with amiodarone has been found to afford additive protection against life-threatening arrhythmias in intensive care units.

Esmolol (*see* p. 163) This quick and short acting β_1 blocker administered i.v. is very useful for emergency control of ventricular rate in AF/AFl. It can terminate supraventricular tachycardia, and is mainly used for arrhythmias associated with anaesthesia where rapidly developing β adrenergic blockade is desired.
MINIBLOCK 100 mg/10 ml, 250 mg/10 ml inj.; 0.5 mg/kg in 1 min followed by 0.05–0.2 mg/kg/min i.v. infusion.

CLASS III

The characteristic action of this class is prolongation of repolarization (phase-3); AP is widened and ERP is increased. The tissue remains refractory even after full repolarization; reentrant arrhythmias are terminated.

Amiodarone

This unusual iodine containing highly lipophilic long-acting antiarrhythmic drug exerts multiple (Class I, II, III and IV) actions:

- Prolongs APD and Q-T interval attributable to block of myocardial delayed rectifier K^+ channels. This also appears to reduce nonuniformity of refractoriness among different fibres.
- Preferentially blocks inactivated Na^+ channels (like lidocaine) with relatively rapid rate of channel recovery: more effective in depressing conduction in cells that are partially depolarized or have longer APD.

- Partially inhibits myocardial Ca^{2+} channels.
- Has noncompetitive β adrenergic blocking property and alters thyroid function.

Thus, amiodarone is a multichannel blocker with some additional activities.

Conduction is slowed and ectopic automaticity is markedly depressed, but that of SA node is only slightly affected. Effect of oral doses on cardiac contractility and BP are minimal, but i.v. injection frequently causes myocardial depression and hypotension.

Despite prolongation of APD, the arrhythmia (*torsades de pointes*) provoking potential of amiodarone is low, probably because it does not exhibit 'reverse use-dependence' of APD prolongation and a uniform action on this modality, or because of its multiple antiarrhythmic mechanisms. The prolongation of APD by other class III drugs is more marked at slower rates of activation (encouraging EAD) than at higher rates (reverse use-dependence), while with amiodarone it is independent of rate of activation.

Pharmacokinetics Amiodarone is incompletely and slowly absorbed from the g.i.t. Oral bioavailability varies from 35–65%. On daily oral ingestion the action develops over several days, even weeks. However, on i.v. injection, action develops rapidly. It has a very large volume of distribution, accumulates in muscle and fat from which it is slowly released and then metabolized in liver primarily by CYP3A4; and excreted mainly into bile. One metabolite is active. The duration of action is exceptionally long; t½ 3–8 weeks.

Dose: Amiodarone is mainly used orally 400–600 mg/day for few weeks, followed by 100–200 mg OD for maintenance therapy. 100–300 mg (5 mg/kg) slow i.v. injection over 30–60 min.

CORDARONE, ALDARONE, EURYTHMIC 100, 200 mg tabs, 150 mg/3 ml inj.

Use Amiodarone is effective in a wide range of ventricular and supraventricular arrhythmias including PSVT, nodal and ventricular tachycardia, AF, AFl, etc. Resistant VT and recurrent VF are the most important indications. It is also used to maintain sinus rhythm in AF when other drugs have failed. Rapid termination of ventricular (VT and VF) and supraventricular arrhythmias can be obtained by i.v. injection. WPW tachyarrhythmia is terminated by suppression of both normal and aberrant pathways.

The long duration of action makes amiodarone suitable for chronic prophylactic therapy. Apart from propranolol, it is the only antiarrhythmic drug which in the long term has been found to reduce sudden cardiac death. Because of high and broad spectrum efficacy and relatively low proarrhythmic potential, amiodarone is a very commonly used antiarrhythmic, despite its organ toxicity.

Adverse effects These are dose-related and increase with duration of therapy. Fall in BP, bradycardia and myocardial depression occurs on i.v. injection and after drug cumulation.

Nausea, gastrointestinal upset may attend oral medication, especially during the loading phase.

Photosensitization and sun burn like skin pigmentation occurs in about 10% patients. Corneal microdeposits are common with long-term use, may cause headlight dazzle, but are reversible on discontinuation.

Pulmonary alveolitis and fibrosis is the most serious toxicity of prolonged use, but is infrequent if daily dose is kept below 200 mg.

Peripheral neuropathy generally manifests as weakness of shoulder and pelvic muscles. Liver damage is rare. Amiodarone interferes with thyroid function in many ways including inhibition of peripheral conversion of T_4 to T_3 and interaction with thyroid hormone receptor. It is a source of iodine as well. Goiter, hypothyroidism and rarely hyperthyroidism may develop on chronic use.

Interactions Amiodarone can increase digoxin and warfarin levels by reducing their renal clearance. Additive A-V block can occur in patients receiving β blockers or calcium channel blockers.

Inducers and inhibitors of CYP3A4 respectively decrease and increase amiodarone levels.

Amiodarone itself inhibits CYP3A4, CYP2C9 and P-glycoprotein, to interact with many drugs.

Dronedarone This is a recently introduced noniodinated congener of amiodarone, less toxic, but also less effective class III antiarrhythmic. Clinical utility of dronedarone is limited to supraventricular arrhythmias; primary indication being maintenance of sinus rhythm in

haemodynamically stable patients of paroxysmal/non-permanent AF, and to control ventricular rate during AF/AFl.

In clinical trials, recurrence time for AF was increased by 2–3 times in dronedarone recipients. Like amiodarone, dronedarone is a multichannel blocker, inhibits delayed rectifier and other types of cardiac K^+ channels, inward Na^+ channel and L-type Ca^{2+} channel. The noncompetitive β adrenergic blocking activity is more marked compared to amiodarone, but it does not interfere with thyroid function. It increases myocardial APD, ERP and slows A-V conduction.

Dronedarone is less lipophilic; its absorption is doubled when taken with meals. It is metabolized by CYP3A4 and CYP2D6; inhibitors of these isoenzymes (Ketoconazole, erythromycin, metoprolol, etc.) markedly increase its blood levels. The elimination t½ is 24 hours. Side effects are mainly gastrointestinal disturbances, bradycardia, weakness, cough and dermatological reactions. Though it prolongs Q-T interval, risk of *torsades de pointes* is very low. Hypothyroidism, pulmonary fibrosis and peripheral neuropathy does not occur. Dronedarone is contraindicated in moderate-to-severe CHF, 2nd/3rd degree A-V block and in permanent AF.

Dose: 400 mg BD oral; MULTAQ, DILSAVE 400 mg tab.

Note: On the basis of two clinical trials PALLAS and ATHENA, the US-FDA in Dec 2011 issued a safety alert that dronedarone should not be used in AF patients who cannot and will not be converted to sinus rhythm (permanent AF), because it doubles the rate of stroke, heart failure and cardiovascular death in such patients. If during dronedarone therapy the patient is found to have AF, he should either be cardioverted or dronedarone should be stopped. Another trial (ANDROMEDA) has demonstrated that dronedarone therapy to prevent recurrence of AF, increases mortality due to worsening of heart failure in patients with ejection fraction <35%. Thus, it is contraindicated in such patients. A recent meta-analysis has also noted unfavourable cardiovascular and mortality outcomes with dronedarone, especially in patients with cardiovascular risk factors.

Sotalol (*see* p. 162) It is a nonselective β blocker having prominent Class III action of prolonging repolarization by blocking cardiac inward rectifier K^+ channels. It is a racemic mixture; the d-isomer has pure class III property, while the l-isomer is a β blocker. Sotalol is not a Na^+ channel blocker—does not depress conduction in fast response tissue, but delays A-V conduction and prolongs its ERP. Sotalol is effective in polymorphic VT, some WPW arrhythmias and for maintaining sinus rhythm in AF/AFl. Due to prolongation of APD and Q-T, risk of dose-dependent *torsades de pointes* is the major limitation. It is contraindicated in patients with long Q-T interval.

SOTALAR 40 mg tab, SOTAGARD 40, 80 mg tabs.

Dofetilide This newer antiarrhythmic prolongs APD and ERP by selectively blocking rapid component of delayed rectifier K^+ current (I_{kr}) without affecting other channels or receptors; has no autonomic or peripheral actions. It is therefore labelled as *pure* class III antiarrhythmic.

Oral dofetilide can convert AF or AFl to sinus rhythm in ~30% cases, but is more effective in maintaining sinus rhythm in converted patients, which is its primary indication. It is noteworthy that chronic therapy with dofetilide in patients with high risk of sudden cardiac death/post MI cases has not increased mortality, despite provoking *torsades de pointes* in some recipients. Dofetilide is mainly excreted unchanged in urine and produces few side effects. It is contraindicated in the presence of hypokalaemia and bradycardia.

Ibutilide This is another new class III antiarrhythmic that blocks rapid inward rectifier K^+ current (I_{kr}) used i.v. for pharmacological conversion of AFl and AF to sinus rhythm. Efficacy is higher in recent onset cases and in AFl compared to AF. Patients who respond, generally convert within 20–30 min of the injection. Induction of *Torsades de pointes* is a risk.

CLASS IV

The primary action of this class of drugs is to inhibit Ca^{2+} mediated slow channel inward current.

Verapamil

Of the many Ca^{2+} channel blockers, verapamil has the most prominent cardiac electrophysiological action (Table 39.1). It blocks L type Ca^{2+} channels and delays their recovery. Its antiarrhythmic aspects are described here, while other aspects are covered in Ch. 40 and 41.

The basic action of verapamil is to depress Ca^{2+} mediated depolarization. This suppresses automaticity and reentry dependent on slow

Table 39.1: Electrophysiological actions of calcium channel blockers

		Verapamil	Diltiazem	Nifedipine
1.	SA node automaticity	↓	↓, –	—
2.	Ventricular automaticity	↓, –	—	—
3.	ERP : atrial	—	—	—
	: A-V nodal	↑↑	↑	↑↓
	: ventricular	—	—	—
	: bypass tract	↑↓	↑↓	—
4.	ECG : R-R interval	↑	↑↓	↓
	: P-R interval	↑	↑	—

↑ : increase; ↓ : decrease; — no change

channel response which is more likely in partially depolarized fibres. Phase-4 depolarization in SA node is reduced resulting in bradycardia. Reflex sympathetic stimulation due to vasodilatation partly counteracts the direct bradycardia producing action. Delayed after-depolarizations in PFs are dampened.

The most consistent action of verapamil is prolongation of A-V nodal ERP. As a result A-V conduction is markedly slowed (P-R interval increases) and reentry involving A-V node is terminated. Intraventricular conduction, however, is not affected. Verapamil has negative inotropic action due to interference with Ca^{2+} mediated excitation-contraction coupling in myocardium. This may precipitate failure in damaged hearts.

Uses and precautions

1. PSVT—Verapamil can terminate attacks of PSVT; 5 mg i.v. over 2–3 min is effective in ~ 80% cases. However, i.v. verapamil carries the risk of marked bradycardia, A-V block, cardiac arrest and hypotension. It should not be used if PSVT is accompanied with hypotension or CHF and in patients who have received β blockers. For preventing recurrences of PSVT, verapamil 60 to 120 mg TDS may be given orally.

2. To control ventricular rate in AF or AFl: Verapamil in a dose range of 40–120 mg TDS oral causes a dose dependent reduction in ventricular rate and is a first line drug for this purpose. In case of inadequate response, digoxin may be added to it. Verapamil can also be injected i.v. for emergency control of ventricular rate in AF and AFl.

Reentrant supraventricular and nodal arrhythmias are susceptible to verapamil, but it is contraindicated in broad QRS complex WPW tachycardia in which it may abbreviate the ERP of bypass tract. A class IA (procainamide) or IC (propafenone) drug which prolongs ERP of bypass tract and depresses conduction is to be combined with verapamil so as to concurrently depress A-V conduction.

Verapamil has poor efficacy in ventricular arrhythmias. In contrast to β blockers, verapamil prophylaxis does not reduce mortality in post-MI patients. In some patients of VT, i.v. injection of verapamil has precipitated VF: therefore contraindicated. It is also not recommended for digitalis toxicity, because additive A-V block may occur. It is contraindicated in partial heart block and sick sinus.

CALAPTIN 40, 80 mg tab; 120, 240 mg SR tab, 5 mg/2 ml inj.

Diltiazem The direct cardiac actions of diltiazem are similar to those of verapamil. However, bradycardia and depression of cardiac contractility are less marked. Diltiazem is an alternative to verapamil for termination as well as prophylaxis of PSVT.

For rapid control of ventricular rate in AF or AFl, i.v. diltiazem is preferred over verapamil, because it can be more easily titrated to the target heart rate, causes less hypotension or

myocardial depression and can be used even in the presence of mild-to-moderate CHF.
DILZEM 30, 60, 90 mg tabs, 25 mg/5 ml inj.

Drugs for PSVT

An attack of PSVT can be terminated by reflex vagal stimulation through Valsalva maneuver, splashing ice cold water on face, hyperflexion (head between knees), etc. Alternatively, or if it does not work, the drug of choice is adenosine (i.v.). Other alternatives are i.v. injection of verapamil/diltiazem/esmolol. To prevent recurrences, oral therapy with verapamil, diltiazem or propranolol alone or combined with digoxin may be prescribed.

Adenosine

Adenosine is an ultrashort acting endogenous purine signal molecule. Administered by rapid i.v. injection (over 1–3 sec) either as the free base (6–12 mg) or as ATP (10–20 mg), it terminates within 30 sec. more than 90% episodes of PSVT involving the A-V node. It activates ACh sensitive K^+ channels to accentuate inward rectifier K^+ current and causes membrane hyperpolarization through interaction with A1 type of adenosine GPCRs on SA node fibers (pacemaker depression → bradycardia), on A-V node fibres (prolongation of ERP → slowing of conduction) and in atrium (shortening of AP, reduced excitability). Adenosine indirectly reduces Ca^{2+} current in A-V node. Depression of the reentrant circuit through A-V node is responsible for termination of majority of PSVTs. Adrenergically induced DADs in ventricle are also suppressed. Coronary dilatation occurs transiently.

ADENOJECT, ADENOCOR 3 mg adenosine (base) per ml in 2 ml and 10 ml amp.

Adenosine has a very short t½ in blood (~10 sec) due to uptake into RBCs and endothelial cells where it is converted to 5-AMP and inosine. Almost complete elimination occurs in a single passage through coronary circulation. Injected ATP is rapidly converted to adenosine. Dipyridamole potentiates adenosine action by inhibiting uptake, while theophylline/caffeine antagonize its action by blocking A1 receptors. Higher doses may be required in heavy tea/coffee drinkers. Patients on carbamazepine are at greater risk of developing heart block. Advantages of adenosine for termination of PSVT are:

- Efficacy equivalent to or better than verapamil.
- Action lasts < 1 min; adverse effects (even cardiac arrest, if it occurs) are transient.
- No haemodynamic deterioration. It can be given to patients with hypotension, CHF or those receiving β blockers. Verapamil is contraindicated in these situations.
- Safe in wide QRS tachycardia (verapamil is unsafe).
- May be effective in patients not responding to verapamil.

However, adenosine produces transient dyspnoea, chest pain, fall in BP and flushing in 30–60% patients; ventricular standstill for few sec or VF occurs in some patients, but resolves quickly. Bronchospasm may be precipitated in asthmatics; verapamil is the drug of choice for such patients. Adenosine has to be rapidly injected in a large vein and has brief action. Therefore, it is not suitable for prophylaxis in recurrent cases.

Other uses of adenosine

(a) Diagnosis of tachycardias dependent on A-V node.
(b) To induce brief coronary vasodilatation during certain diagnostic/interventional procedures.
(c) To produce controlled hypotension during surgery.

Drugs for sinus tachycardia

Ivabradine

Inappropriate sinus tachycardia is a relatively uncommon disorder which may produce troublesome symptoms like palpation, dyspnoea, anxiety, dizziness, postural hypotension, and can precipitate angina. It is treated with drugs, only when symptomatic; and β blockers or verapamil are the first line drugs. *Ivabradine* is a pure bradycardic drug which lowers heart rate, but has no other significant cardiac action. It is primarily used as antianginal drug (*see* p. 600). Recently, it has been found clinically useful in symptomatic inappropriate sinus tachycardia as an alternative drug. Ivabradine lowers heart rate and relieves the symptoms, but should be used only when β blockers and verapamil are contraindicated or not tolerated.

Drugs for A-V Block

The definitive treatment of persistent heart block is pacing with an implanted cardiac pacemaker.

Drugs are of value only for acute/transient A-V block and as an interim measure.

Atropine: When A-V block is due to vagal overactivity, e.g. digitalis toxicity, some cases of MI; the block can be improved by atropine 0.6–1.2 mg i.m. Atropine abbreviates A-V node ERP and increases conduction velocity in bundle of His.

Sympathomimetics (Adr, isoprenaline): These drugs may overcome partial heart block by facilitating A-V conduction and shortening ERP of conducting tissues.

They may also be used in complete (3rd degree) heart block to maintain a sufficient idioventricular rate (by increasing automaticity of ventricular pacemakers) till external pacemaker can be implanted.

Choice and use of antiarrhythmic drugs

Mere detection of an arrhythmia does not necessitate treatment.

Asymptomatic arrhythmias and those which do not jeopardize haemodynamics, e.g. most AES and occasional VES, first degree A-V block, bundle branch block, etc. in an otherwise normal heart, do not require antiarrhythmic treatment; reassurance is enough. If a patient is particularly disturbed by AES, propranolol is the best option. Chronic prophylactic therapy with class I and class IV antiarrhythmics does not appear to afford survival benefit, except in few selected cases. The proarrhythmic potential of antiarrhythmic drugs and the increased risk of sudden cardiac death seems to offset any survival advantage that these drugs might afford over long-term. Only propranolol and to some extent amiodarone have been shown to reduce cardiovascular mortality in the long-term. On the other hand, vigorous therapy is indicated when:

- Arrhythmia is life-threatening, e.g. sustained VT, *torsades de pointes,* VF.
- Arrhythmia is causing hypotension, breathlessness, activity limitation or cardiac failure.
- Palpitation is marked, e.g. in PSVT, sustained VT, AF, *torsades de pointes.*
- When simple arrhythmia may lead to more serious ones, e.g. after MI (warning arrhythmias).

In the above situations antiarrhythmic drugs are mostly needed for short periods. Majority of antiarrhythmic drugs have narrow margin of safety. A simple clinical classification of antiarrhythmic drugs is presented in the box below.

The selection of an antiarrhythmic in a patient depends on:

(a) ECG diagnosis
(b) Possible mechanism underlying the arrhythmia
(c) Mechanism of action and range of antiarrhythmic activity of the drug
(d) Pharmacokinetic profile of the drug.
(e) Haemodynamic effects of the drug.

The aim is to improve cardiovascular function either by restoring sinus rhythm, or by controlling ventricular rate, or by conversion to a more desirable pattern of electrical and mechanical activity.

Despite extensive investigation, choice of an antiarrhythmic is still largely empirical. A practical guide to the choice and use of antiarrhythmic drugs is summarized in the box on next page.

Clinical classification of antiarrhythmic drugs

Supraventricular arrhythmias only	*Supraventricular and ventricular arrhythmias*		*Ventricular arrhythmias only*
Adenosine	Amiodarone	Procainamide	Lidocaine
Verapamil	β blockers	Disopyramide	Mexiletine
Diltiazem	Propranolol	Quinidine	
Dronedarone	Sotalol	Flecainide	
Digoxin	Esmolol	Propafenone	

Choice of antiarrhythmic drugs for cardiac arrhythmias

	Arrhythmia		*Clinical objective*	*Drug(s)*
1.	Atrial extrasystoles (Symptomatic)	:	Suppression, symptom relief	No drug if asymptomatic or non-disturbing Propranolol (only if disturbing)
2.	Paroxysmal supraventricular tachycardia (PSVT)	: :	Termination of PSVT Prevention of recurrence	i.v. adenosine / verapamil / diltiazem / esmolol Oral verapamil / diltiazem / propranolol / sotalol
3.	Atrial fibrillation (AF)	:	Reversal to SR (Rhythm control) (for paroxysmal / persistent AF)	Cardioversion i.v. amiodarone, catheter ablation
			Maintenance of SR	Sotalol / propafenone / amiodarone / dronedarone / dofetilide
		:	Ventricular rate control (for permanent AF / during recurrence of AF)	oral verapamil / diltiazem / propranolol ± digoxin
		:	Urgent vent. rate control	i.v. esmolol / verapamil / amiodarone
4.	Atrial flutter (AFl)	:	Reversal to SR	Cardioversion, radiofrequency ablation, Propafenone (after rate control with diltiazem / verapamil / propranolol)
		:	Ventricular rate control	Propranolol / verapamil / diltiazem ± digoxin or Amiodarone
5.	Wolff-Parkinson-White syndrome (WPW) tachycardia	: :	Termination Maintenance - narrow QRS - wide QRS	Radiofrequency ablation, cardioversion Propafenone / procainamide Propafenone + verapamil / propranolol or Amiodarone / sotalol
6.	Acute-MI arrhythmia			
	Bradycardia	:	Reversal to normal rate	Atropine (i.v.)—no effect—Pacing
	Vent. extrasystoles / tachycardia	:	Abolition to prevent serious arrhythmia	i.v. Lidocaine / procainamide / amiodarone Cardioversion (if haemodynamically unstable)
7.	Chronic vent. tachycardia			
	Nonsustained VT	:	Suppression	Propranolol / amiodarone (oral)
	Sustained VT	:	Abolition	i.v. Amiodarone ± propranolol or cardioversion or propafenone / lidocaine (i.v.)
		:	Maintenance therapy (prevention of VF / arrest)	Amiodarone / sotalol Implantable defibrillator
8.	Ventricular fibrillation (VF)	: :	Termination Recurrence prevention	Defibrillation ± amiodarone (i.v.) Amiodarone (oral) / propranolol

SR—Sinus rhythm

PROBLEM DIRECTED STUDY

39.1 A sales executive aged 55 years presented with palpitation felt off-and-on, both during activity as well as at rest for the last one month or so. He also complained of tiredness and anxiety. The pulse was irregular in volume and frequency with average rate 104/min, respiration 20/min, BP 130/84 mm Hg, apex beat was irregular, with an average rate 120/min. Heart sounds were irregular, but there was no murmur. The ECG showed atrial fibrillation (AF) with no sign of ischaemia. A diagnosis of persistent AF was made, and it was decided to electrically cardiovert him. He was put on warfarin sod. 5 mg twice daily for 2 days followed by 5 mg once daily and dose to be adjusted to an INR between 2–2.5. This was to be maintained for 1 month before attempting cardioversion.

(a) Why the patient has been put on warfarin therapy before attempting cardioversion?
(b) Can some drugs be given to control and regularize his heart rate in the mean time? If so, which drug(s)?
(c) If electrical cardioversion does not succeed, can some drugs be given to revert him to sinus rhythm (SR)?
(d) After cardioversion, can some drugs be given to maintain SR and prevent recurrence of AF?

(see Appendix-1 for solution)