Antiarrhythmics

Cardiac arrhythmias are a frequent problem in clinical practice occurring in up to 50% of anesthetized patients. Arrhythmias may require treatment because rhythms that are too rapid, too slow, or asynchronous can reduce COP. Some arrhythmias can precipitate more serious or even lethal rhythm disturbances; e.g. early PVCs can precipitate VF. In such patients, antiarrhythmics may be lifesaving. On the other hand, the hazards of antiarrhythmics have led to reevaluation of their risks and benefits and treatment of asymptomatic or minimally symptomatic arrhythmias should be avoided for this.

Mechanisms of Action

Arrhythmias are caused by abnormal pacemaker activity or abnormal impulse propagation.

Arrhythmic drugs decrease the automaticity of ectopic pacemakers more than that of the SAN. They also reduce conduction and excitability and increase the refractory period to a greater extent in depolarized tissue than in normally polarized tissue.

Classification

The most widely used scheme for the classification of antiarrhythmic drug actions recognizes four classes:

1-Class 1 action is sodium channel blockade. Subclasses of this action reflect effects on the action potential duration (APD). Drugs with class 1A action prolong the APD; drugs with class 1B action have no significant effects on the APD; and drugs with class 1C action have minimal effects on the APD.

2. Class 2 action is sympatholytic.

3. Class 3 action is manifest by prolongation of the APD by blocking K channels.

4. Class 4 action is blockade of the cardiac calcium current.

Class 1 antiarrhythmic drugs

Sodium Channel Blockers

Class 1 drugs have the common property of inhibiting the fast inward depolarizing current carried by sodium ion.
**Class 1A**

**Quinidine**

It slows conduction and prolongs QRS duration by blocking activated Na channels. It also prolongs the APD as a result of K channel blockade.

Quinidine is orally administered. It is 80% bound to albumin and $\alpha_1$-acid glycoprotein. It is eliminated by hepatic metabolism. The elimination half-life is 6-8 hours.

Quinidine is used for the maintenance of normal sinus rhythm in patients with atrial flutter or fibrillation. It is also used occasionally to treat patients with ventricular tachycardia. Because of its cardiac and extracardiac side effects, its use has decreased considerably.

Its major cardiac side effects are excessive QT interval prolongation and induction of torsade de pointes arrhythmia, and syncope. Other side effects are diarrhea, nausea and vomiting. A syndrome of headache, dizziness and tinnitus (cinchonism) is observed with toxic concentration.

**Procainamide**

It prolongs conduction and increases the ERP in atrial and His-Purkinje portions of the conduction system, which may prolong PR interval and QRS complex.

Administered IV, procainamide is an effective emergency treatment for ventricular arrhythmias, especially after lidocaine failure, but recently amiodarone has become more popular. Procainamide is also used to suppress atrial premature beats to prevent the occurrence of AF and flutter.

Its dose is 100 mg, or 1.5 mg/kg given at 5-minute intervals or a total dose of 1 gm or 15 mg/kg is given. ABP and ECG should be monitored during loading and administration stopped if significant hypotension occurs or if QRS complex is prolonged.

Procainamide has both hepatic and renal routes of elimination. The primary metabolite N-acetylprocainamide has antiarrhythmics effects as well as toxic side effects and is excreted almost entirely by the kidney.

Procainamide may cause GI disturbances, CNS symptoms, rash, agranulocytosis, pleuritis, or pericarditis similar to that with lupus erythematosus.
**Class 1B**

**Lidocaine**

Lidocaine depresses the slope of phase 4 diastolic depolarization in Purkinje fibers and increases the VF threshold. Conduction velocity is not affected by lidocaine in normal tissue, but is significantly decreased in ischemic tissue. In atrial tissue, it has no effect on APD, while in Purkinje fibers, APD is markedly decreased. Because lidocaine decreases APD, its antiarrhythmic effect has been attributed to improved conduction in ectopic foci, which would decrease the likelihood of reentry.

Distribution and elimination half-lives of lidocaine are short, about 60 seconds and 100 minutes respectively. Hepatic e extraction is about 60 to 70%. Hepatic metabolism produces monoethylglycine-xylidide and glycine-xylidide, both of which possess antiarrhythmics effects.

Metabolic products are eliminated by the kidney, and accumulation of the monoethyl metabolite is related to the toxicity of IV lidocaine.

An initial bolus dose of 1-1.5 mg/kg should be followed immediately by a continuous infusion of 20 to 50μg/kg/min in order to compensate for rapid redistribution half-life of lidocaine.

Therapeutic levels of lidocaine range from 1.5 to 5μg/ml, signs of toxicity appear above 9μg/ml.

The major toxic effect of lidocaine is associated with the CNS and is manifested by drowsiness and disorientation which progress to agitation, and terminate in seizures. Benzodiazepines are superior to barbiturates for stopping local anesthetic-induced seizure activity.

**Mexiletine and Tocainide**

Both have electrophysiological properties similar to those of lidocaine (decreases in APD and ERP but little effect on conduction).

The antiarrhythmics effects decrease the frequency of acute and chronic ventricular ectopy but not supraventricular arrhythmias. Mexiletine may be more effective than lidocaine when used IV to suppress PVCs and VT in acute MI. Mexiletine may be used in children.

Mexiletine is eliminated by hepatic metabolism with less than 10 % renally excreted unchanged in the urine.

**Diphenylhydantoin**

Diphenylhydantoin (DPH) or phenytoin is unique among class 1A
drugs in that it has central sympatholytic effect.

DPH shortens APD. It can abolish the delayed afterpotentials associated with digitalis intoxication.

DPH exerts its antiarrhythmic effect by increasing ERP/APD ratio and by decreasing automaticity.

The drug is useful to treat the atrial and ventricular arrhythmias produced by cardiac glycoside toxicity and in some patients with arrhythmias secondary to prolonged QT syndrome. It is less effective for other supraventricular arrhythmias and chronic ventricular ectopy.

The drug is also useful for children.

Doses of 50 to 100 mg (0.5 to 1.5 mg/kg) are given at 5-minute intervals up to a total dose of 1gm (15 mg/kg); the usual therapeutic plasma concentration is 8 to 10 μg/ml. The drug undergoes primary hepatic metabolism, with urinary excretion of unchanged DPH accounting for only 5% of the total dose.

Administered IV it depresses contractile function.

Infusion rates above 50 mg/min produce cardiovascular collapse, VF, and death. Other side effects include visual disturbances (nystagmus and blurring), nausea, and cerebellar ataxia.

**Class IC**

**Flecainide**

Flecainide increases intracardiac APD. The sodium channel depressant effects are slow onset and offset and use dependent. It can also inhibit the slow calcium channel.

This drug is indicated for life-threatening ventricular arrhythmias, supraventricular arrhythmias, and atrial fibrillation. It is also effective in patients with the WPW syndrome. It is probably the most effective antiarrhythmics at eliminating premature depolarizations.

It is administered orally with plasma half-life of 20 hours. It is 85% excreted renally. Effective plasma concentrations range from 0.2 to 1 μg/ml. Doses range from 100 to 200 mg twice a day.

Adverse effects are usually minor at therapeutic doses, but the QT interval has been prolonged with induction of polymorphic VT.

**Propafenone**

This drug blocks the fast sodium current in a use-dependent manner. It also blocks β-receptors and is a weak K channel blocker. This drug generally slows conduction and prolongs refractoriness of most cardiac conduction system tissue. It is indicated for life-threatening ventricular arrhythmias, various supraventricular arrhythmias, and atrial fibrillation.

Propafenone is well absorbed orally with an elimination half-life of 6 to 8 hours. Therapeutic serum levels are from 0.2-1.5 μg/ml.

Propafenone worsens bronchospastic lung disease and may cause
dizziness and some GIT complaints.

Moricizine
It is a potent Na channel blocker with mild potassium blocking effects. It prolongs AV node, and QRS duration. The drug is indicated for life-threatening ventricular arrhythmias.

Class II Antiarrhythmic Drugs
β-Adrenergic receptor Antagonists
β-Adrenergic receptor blockers are very effective antiarrhythmics in patients during the perioperative period or who are critically ill because many arrhythmias in these patients are adrenergically mediated.

Propranolol
Propranolol was the major β-receptor blocking drug to be used clinically. It is very potent, but is nonselective for β1/2 receptor subtypes. Because it interferes with the bronchodilating actions of epinephrine and the sympathetic stimulating effects of hypoglycemia, it is less useful in patients with diabetes or bronchospasm. These difficulties stimulated the search for β-receptor-blocking drugs with receptor subtype specificity, as metoprolol, esmolol, and atenolol.

The electrophysiologic effects are increased automaticity, increased APD, primarily in ventricular muscle and increased ERP in the AV node.

Blockade decreases the rate of spontaneous depolarization in the SAN. Automaticity in the AVN and more distal portions

In the conduction system is also depressed. β-blockade consistently reverses the fibrillation threshold-lowering effect of catecholamines. Propranolol decreases intramyocardial impulse conduction in acutely ischemic myocardium but does not do so in normal myocardium.

Pharmacokinetics show that absorption after oral administration is 100% but bioavailability is impaired by first-pass hepatic metabolism. The degree of hepatic extraction is highly variable.

Propranolol is 90% to 95% protein bound in plasma, which further confounds the use of plasma concentration as a guide for therapy. The elimination half-life of oral propranolol is 3 to 4 hours.

Major toxic side effects of propranolol relate to β-blockade per se. Cardiac toxicity includes CHF (uncommon without other causes of ventricular dysfunction) and depressed AV conduction. Sudden discontinuation of β-blockade therapy may precipitate a withdrawal syndrome of excessive β-adrenergic activity, as a result of upregulation of β-receptors. Increased airway resistance results from β2-receptor blockade. The hypoglycemic action of insulin is accentuated by propranolol. Side effects perhaps not related to β-receptor blockade
include CNS disturbances such as insomnia, hallucinations, depression, and dizziness, and minor allergic manifestations such as rash, fever, and purpura.

The IV dose for acute control of arrhythmias is 0.5 to 1 mg titrated to therapeutic effect up to a total of 0.1 to 0.15 mg/kg. An effective level of β-blockade may be obtained with a continuous infusion approximating 3 mg/hr in adult, postoperative patients previously receiving chronic treatment; however, with the availability of esmolol, the need for a propranolol infusion is no longer necessary.

**Metoprolol**

It is a relatively selective β-receptor antagonist. Metoprolol is rapidly absorbed after oral administration. Plasma half-life after oral administration is approximately 3 hours. Metoprolol is 90% metabolized, with hydroxylation and O-demethylation.

Metoprolol is useful for treating supraventricular and ventricular arrhythmias that are adrenergically driven. The primary advantage of metoprolol is its relative lack of most of bronchoconstrictive effects. Acute IV dosage is 1 mg titrated up to 0.1 to 0.2 mg/kg.

**Esmolol**

Esmolol is a cardioselective β₁-receptor antagonist with an extremely brief duration of action.

Electrophysiologic effects of esmolol are those of β-adrenergic receptor antagonism.

Esmolol is rapidly metabolized in blood by hydrolysis of its methyl ester linkage. Its half-life in whole blood is 27.1 min. Esmolol is not affected by plasma cholinesterase; the esterase responsible is located in erythrocytes and is not inhibited by cholinesterase inhibitors but it is deactivated by sodium fluoride.

Clinically, in asthmatic patients, esmolol (300μg/kg/min) only slightly increases airway resistance. In a comparison with propranolol for the treatment of PSVT, esmolol has the advantage of a much faster termination of b-blockade. It is a very useful agent in controlling sinus tachycardia in the perioperative period.

Dosing begins at 25 mg/kg/min and is titrated to effect up 250 mg/kg/min. Doses higher than this may cause significant hypotension due to reduced CO in patients. Esmolol is especially effective in treating
acute onset atrial fibrillation or flutter perioperatively and results in both acute control of the ventricular response and conversion of the arrhythmia back to sinus rhythm.

**Class III: Agents That Block Potassium channels and Prolong Repolarization**

**Amiodarone**

Amiodarone has a wide spectrum of effectiveness including supraventricular, ventricular and preexcitation arrhythmias. It may also be effective against VT and VF refractory to other treatment. Amiodarone has been approved by the AHA as the first-line antiarrhythmic in cardiopulmonary resuscitation. Amiodarone may be effective prophylactically in preventing AF postoperatively.

Amiodarone prolongs repolarization and refractoriness in the SAN, in atrial and ventricular myocardium, in the AVN, and in the His-Purkinje system.

There are substantial differences in the electrophysiologic effects of acute and chronic amiodarone administration.

Acutely, the drug slightly increases ERP of the His-Purkinje system and ventricular myocardium. Although AV nodal ERP increases with acute IV amiodarone therapy, the increase is greater following chronic use. In other cardiac tissue, there is little or no change in ERP following intravenous administration; however, after-chronic oral use, ERP is increased globally.

Amiodarone increases VF threshold. Mostly refractory VT is suppressed by acute IV use of amiodarone. This effect has been attributed to a selectively increased activity in diseased tissue, is has been seen with lidocaine. Amiodarone also has an α and β antagonistic effect.

IV amiodarone decreases BP, LVEDP, and SVR and increases CO, but it does not affect HR.

Pharmacokinetics of amiodarone are notable for the low bioavailability, very long elimination half-life, relatively low clearance, and large volume of distribution.
Adverse reactions to amiodarone are numerous in the form of photosensitivity of the skin, abnormal pigmentation (slate gray) and an erythematous, pruritic rash. Corneal microdeposits occur with chronic amiodarone therapy.

Pulmonary side effects are more severe. They include exertional dyspnea and cough. Chest X-ray may show fibrosing alveolitis.

Thyroid abnormalities are associated with amiodarone. Amiodarone therapy increases both T₄ and reverse T₃, but only slightly decreases T₃.

Anesthetic complications have infrequently been reported in the form of bradycardia and hypotension.

**Bretylium**

It is a quaternary ammonium compound that produces a biphasic cardiac response after acute intravenous administration. Initially, norepinephrine is displaced from adrenergic nerve endings, and there are increases in BP, SVR, and cardiac automaticity. After 20 to 30 minutes, this response wanes and the adrenergic-blocking effects of bretylium predominate. These latter effects depend on uptake of bretylium by adrenergic neurons; however, inhibition of its adrenergic blocking effects does not impair the antiarrhythmic effect.

The direct electrophysiologic effect of bretylium is prolongation of the ventricular ERP. Bretylium delays conduction of premature impulses from normal myocardium to the border of ischemic zones. Bretylium increases VF threshold and may convert VF to sinus rhythm.

Clinical indications for bretylium include refractory VT or VF. For VF, bretylium is administered as a 5 to 10 mg/kg IV bolus, which can be repeated to a total dose of 30 mg/kg if VF persists. Administration for recurrent VT is similar to that for VF. Continuous infusion of 2 mg/min may be used to maintain plasma levels. The effect of bretylium in VT and VF may take 20 to 30 minutes to manifest.

Adverse reactions include nausea and vomiting. During chronic therapy, postural hypotension may develop.

**Sotalol**

Sotalol is classified as a class III agent, but also has class II β-blocking properties. Sotalol prolongs refractoriness in both atrial and ventricular tissues due to blockade of the delayed rectifier potassium current. The β-blocking effects result in decreased HR and increased
refractory periods at both the atrial and ventricular levels. It is indicated for life-threatening ventricular arrhythmias and atrial fibrillation. Sotalol can be administered orally or intravenously.

It undergoes renal excretion with an elimination half-life of 12 hours. The usual starting oral dose is 80 to 160 mg every 12 hours. Peak plasma concentration is seen within 4 hours.

Sotalol is used to treat both supraventricular and ventricular tachyarrhythmias. Sotalol was found to be superior to class I agents in preventing the recurrence of ventricular arrhythmias. Sotalol is also effective in the prevention of paroxysmal supraventricular tachyarrhythmias.

Sotalol administration has some side effects as increased risk of torsade de pointes and QT interval prolongation.

**Ibutilide**

Ibutilide converts atrial flutter and atrial fibrillation to sinus rhythm. Ibutilide prolongs the cardiac refractory period at both the atrial and ventricular levels by activating a slow inward sodium current.

It is administered intravenously and undergoes hepatic metabolism. Its elimination half-life ranges from 2 to 6 hours. The usual dose is 1 mg administered over 10 minutes. This may be followed by a second dose of 0.5 to 1 mg.

Torsade de pointes may occur with ibutilide administration.

**Dofetilide**

This drug blocks the rapid component of the delayed rectifier potassium current of repolarization without slowing conduction. Similar to ibutilide, dofetilide has a profound effect on prolonging the QT interval. Atrial tissue is more affected by dofetilide than ventricular tissue. Thus, dofetilide is indicated for acute conversion and chronic suppression of AF.

Dofetilide is only available orally. About 50% of the drug is excreted in the urine with an elimination half-life of 8 to 12 hours. Several drugs increase dofetilide serum concentrations including verapamil, cimetidine and ketoconazole.
Dosing is from 0.125 mg to 0.5 mg twice a day and should be performed during EGG monitoring and measuring of the QT interval. QT prolongation with polymorphic VT may also occur.

Electrolyte abnormalities and acquired prolong QT interval should be corrected prior to ibutilide and dofetilide therapy.

**Class IV: Calcium Channel Antagonists**

Verapamil and diltiazem are the primary antiarrhythmics.

**Verapamil and diltiazem**

Verapamil and diltiazem are used in the treatment of supraventricular arrhythmias, AF, and atrial flutter. They are especially effective at preventing or terminating PSVT by blocking impulse transmission through the AV node by prolonging AV nodal conduction and refractoriness. They are also useful in the treatment of AF and atrial flutter by slowing AV nodal conduction and decreasing the ventricular response.

In the perioperative period, verapamil is a useful antiarrhythmic agent. However, verapamil should be used cautiously intraoperatively because, in conjunction with inhalation anesthetics, significant cardiac depression may occur.

Verapamil and diltiazem cause prolongation of discharge rate and recovery time in the SA, AV conduction time and AV node ERP.

The pharmacokinetics of IV and orally administered verapamil differ. The hepatic extraction of orally administered verapamil is extensive. After intravenous administration of verapamil, plasma clearance approximates splanchnic blood flow rate, and the apparent volume of distribution is large. Elimination half-life of verapamil is approximately 5 hours. Excretion of verapamil is renal (65 to 70 %). Verapamil and metabolites are highly protein bound (90%).

Verapamil dosage for acute intravenous is 0.07 to 0.15 mg/kg over 1 minute, with the same dose repeated after 30 minutes if the initial response is inadequate (10 mg maximum). Since the cardiovascular depressant effects of the inhalation anesthetics involve inhibition of calcium-related intracellular processes, the interaction of verapamil and these anesthetics is synergistic. AV block can occur, and may be refractory.
Diltiazem in doses of 0.25 to 0.3 mg/kg administered intravenously followed by a titratable intravenous infusion of 10 to 20 mg/hr has been shown to be rapid acting and efficacious in controlling ventricular response rate in new-onset AF and atrial flutter. Diltiazem may also have a role in treating ventricular arrhythmias.

Another adverse effect of verapamil is the potentiation of neuromuscular blockade.

**Other antiarrhythmics:**

**Digoxin**

Cardiac glycosides affect the heart both directly and indirectly. The direct effect is to inhibit the membrane-bound sodium-potassium ATPase enzyme that supplies energy for the system that pumps sodium out of and transports potassium into contracting and conducting cells. By reducing the exchange of extracellular sodium with intracellular calcium, digoxin raises the store of intracellular calcium, which facilitates muscular contraction. The indirect effect is to enhance vagal activity.

The clinically important consequences are on:

- The contracting cells: increased contractility and excitability.
- SA and AV nodes and conducting tissue: decreased generation and propagation.

Digoxin is not strictly an antiarrhythmic agent but rather it modulates the response to arrhythmias. The main uses are in atrial fibrillation and atrial flutter.

Digoxin is eliminated 85% unchanged by the kidney and the remainder is metabolized by the liver. The $t_{1/2}$ is 36h.

Its adverse effects are in the form of ectopic arrhythmias (ventricular ectopic beats, ventricular tachyarrhythmias, and paroxysmal supraventricular tachycardia) and heart block, gastrointestinal side effects, disturbances of color vision, photophobia, and blurring, gynecomastia, and mental side effects such as confusion.

Acute digoxin poisoning causes initial nausea and vomiting and hyperkalemia because inhibition of the Na-K ATPase pump prevents intracellular accumulation of potassium. There may be exaggerated sinus arrhythmia, bradycardia and ectopic rhythms with or without heart blocks.
**Adenosine**

It slows AV conduction and dilates coronary and peripheral arteries. It is rapidly metabolized by circulating adenosine deaminase and is also taken up by cells; hence its residence in plasma is brief ($t_{1/2} < 2s$) and it must be given rapidly IV.

Administered as a bolus injection, adenosine is effective in terminating PSVT, including episodes in patients with WPW syndrome. The initial dose in adults is 6 mg over 2s with continuous ECG monitoring, with doubling increments every 1-2min. The average total dose is 125µg/kg. Adenosine is an alternative to verapamil for supraventricular tachycardia and possibly safer because adenosine is short acting and not negatively inotropic.

Adverse effects from adenosine are not serious because of its brief action; but it may cause very distressing dyspnea, facial flushing, chest pain and transient arrhythmias, e.g. bradycardia. Adenosine should not be given to asthmatics or to patients with second- or third-degree AV block or sick sinus syndrome.

**Magnesium**

Hypomagnesemia is associated with a variety of cardiovascular disturbances, including arrhythmias. Functionally, magnesium is required for the membrane-bound Na-K ATPase, which is the principal enzyme that maintains normal intracellular potassium concentration.

Arrhythmias induced by magnesium deficiency may be refractory to treatment with antiarrhythmic drugs and either electrical cardioversion or defibrillation. For this reason, adjunctive treatment of refractory arrhythmias with magnesium has been advocated even when magnesium deficiency has not been documented.