Anti arrhythmic Drugs

Definition

- An arrhythmia is any abnormality in the rate, regularity, or site of origin or a disturbance in conduction that disrupts the normal sequence of activation in the atria or ventricles.
- Arrhythmias can be due to a variety of reasons, such as electrolyte abnormalities, structural abnormalities, metabolic derangements, genetic mutations, and drug toxicity.
- Arrhythmias have varying degrees of severity and significance based on site of origin, symptoms, frequency, and duration. The aggressiveness of therapies is based on these factors.

Cardiac Electrophysiology

Normal Cellular Electrophysiology:

- The majority of myocardial cells share the same basic cellular electrophysiologic properties that allow contraction when a transmembrane action potential develops. Fully polarized cells have a resting membrane potential of -90 mV. This resting membrane potential exists because of the electrical gradient created by differences in extracellular and intracellular ion concentrations.
- Specifically, sodium and potassium concentrations are controlled primarily by the sodium–potassium pump. This pump tries to maintain intracellular sodium concentrations at 5 to 15 mEq/L and intracellular potassium concentrations at 135 to 140 mEq/L. In comparison, the extracellular sodium concentration is normally 135 to 142 mEq/L and extracellular potassium 3 to 5 mEq/L.

  Electrical stimulation of a myocardial cell results in depolarization. Depolarization is initiated by a slow inward leak of sodium. When the transmembrane potential reaches approximately -60 mV, the fast sodium channel opens, actively transporting sodium across the cell membrane and resulting in rapid cellular depolarization to approximately +20 mV. This is represented by phase 0 of the action potential and the QRS complex on a surface electrocardiogram (ECG).

  After the rapid membrane depolarization, the sodium channel closes and a complex exchange of sodium, calcium, and potassium occurs during the plateau phases 1 and 2 of the action potential.
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The dominant feature during the plateau phases of the action potential is movement of calcium ions into the intracellular space via L-type calcium channels. This feature differentiates myocardial cells from nerve tissue and starts the excitation–contraction cascade of the cell by initiating the release of intracellular calcium stores from the sarcoplasmic reticulum. Phase 3 of the action potential is dominated by repolarization of the cell membrane by outward movement of potassium ions. The rate of fall of phase 3 and its depth determine membrane responsiveness to stimulation.

Tissues may depolarize only after reaching a particular level of repolarization called the “threshold potential,” at least -50 to -55 mV for normal Purkinje fibers. This level of repolarization therefore determines the absolute refractory period (ARP). The ARP varies in length depending primarily on the action potential duration (APD). Phase 4 is the resting membrane potential that results from a combination of ionic currents, primarily the slow inward sodium current.

Anatomy of the electrical system of the heart. The impulse is generated by the sinoatrial (SA) node and is conducted through the atria to the atrioventricular node, which directs the current to the bundle of His, into the bundle branches, and finally to the Purkinje fibres. PA, pulmonary artery; SVC, superior vena cava.
Normal Cardiac Conduction

The electrical system of the heart consists of intrinsic pacemakers and conduction tissues. It is convenient to conceptualize the progression of normal cardiac rhythm in anatomic terms. The figure correlates the standard ECG with the normal electrical pathway.

The rate of electrical firing of the heart depends on the most rapid pacemaker. Spontaneous electrical firing or automaticity can occur anywhere in the heart under certain conditions. Normally, the sinoatrial (SA) node, located where the superior vena cava meets the right atrium, has the most rapid intrinsic rate (60 to 100 bpm). Therefore, any electrical activity not initiated by the SA node is considered an arrhythmia. Consequently, most arrhythmias are labeled by the anatomic location and rate.

The normal electrocardiogram. The P wave is atrial depolarization. The P-R interval (0.12 to 0.20 seconds) is formed from the firing of the SA node (SN) and conduction through the AV node (AVN), bundle of His (HB), bundle branches (BB), and Purkinje fibres (P). The QRS complex (0.05 to 0.10 seconds) is ventricular depolarization. The ST segment is the refractory period. The T wave is ventricular repolarization. The Q-T interval is 0.35 to 0.44 seconds in duration.

SA node firing initiates atrial contraction. The electrical impulse is conducted through the atria via the inter nodal tracts to the atroventricular (AV) node near the coronary sinus, between the two atria. The AV node has pacemaker
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properties but normally coordinates atrial and ventricular contraction. The AV node normally limits excessively rapid atrial rates from activating the ventricles.

The conduction system in the ventricles is more elaborate than that in the atria because the muscle mass is larger. Rapid and effective excitation is critical because the ventricles contribute the most to cardiac output. Fibers leaving the AV node are called the bundle of His. They separate into the bundle branches, which traverse the septum between the ventricles. Conduction between the AV node and the bundle of His is measured by the P-R interval (Fig. 22.2). The final conducting components of the ventricles are the Purkinje fibers, which emanate from the bundle branches to stimulate the ventricular cardiac muscle to contract. The QRS complex measures depolarization of the ventricles. The Q-T interval reflects both ventricular depolarization and repolarization

Antiarrhythmic Drugs:
Anti arrhythmic agents work by blocking the sodium channel, the potassium channel, the calcium channel and or the adrenergic receptors. Sodium channel blockade reduces the rate of rise of phase 0 of the monophasic action potential (V max) slowing conduction. Potassium channel blockers lengthen refractoriness.

Classification:
The widest employed classification of anti arrhythmic agents is the Vaughan-Williams classification.
In the Vaughan-Williams classification;

1. Class I agents are sodium channel blockers,
   A. Intermediate channel binding and recovery
   B. Rapid channel binding and recovery
   C. Slow channel binding and recovery
2. Class II are beta blockers,
3. Class III are potassium channel blockers and
4. Class IV are calcium channel blockers.

Class I: Sodium channel blockers
They block Na channels, just as local anaesthetics’ do, by binding to the sites of alpha subunit. Because it inhibits action potential in many excitable cells, it has been referred as Membrane stabilising agents.
Their characteristic is to reduce maximum rate of depolarisation during phase 0.
**Anti arrhythmic drugs**

**Subclass IA:** Drugs are Quinidine, procainamide, Disopyramide which are moderately decrease \( dv/dt \) of phase 0.

**Quinidine:**

**Brand Name:** Quinidine sulphate, Quininga, Natcardine

**MOA:** Quinidine blocks myocardial Na channels in open state, reduces automaticity and maximal rate of phase 0 depolarization.

**Drug interactions:**
- Abarelix, amiloride, amiodarone, amprenavir, anisindione, anticoagulants, aripiprazole, arsenic, ciprofloxacin, delavirdine, dicumarol, digoxin, duloxetine, enoxacin, fosamprenavir, gatifloxacin, itraconazole, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, pimozone, pipercuronium, quinolones, ritonavir, rocuronium,

**Adverse drug reaction:**
- Diarrhoea, GI intolerance, hepatic necrosis, thrombocytopenia, anaemia, hypersensitivity, heart block, torsades de pointes, fever, lupus-like syndrome.

**Dose:**
- **Adults** - Test dose 50 to 200mg p.o, then monitor vital signs before beginning vital therapy: 200 to 400mg p.o sulphate or equivalent base
- **Children** – test dose of 2mg/kg, then 30mg/kg/day p.o or 900mg/m2/day p.o in 5 divided doses

**Procainamide**

**Brand Name:** pronestyl, promine, procanbid.

**MOA:** It blocks sodium channels by slowing of phase 0 and impulse conduction prolongation of QRS and QT interval.

**Drug interactions:** Anticholinergic such as atropine and tricyclic anti depressants
- Antihypertensive, neuromuscular blocking agents such as pancuronium bromide, succinyl chloride, tubocurarine chloride and Cimetidine

**Adverse drug reactions:** Lupus-like syndrome, hypersensitivity, torsades de pointes, blood dyscrasias, hepatitis, myopathy IV: hypotension, heart block

**Dose:** for abolition of arrhythmia 0.5-1 g oral or I.M followed by 0.25-0.5g every 2 hours; or 500mg IV loading dose followed by 2mg/kg/hour

**Maintainance Dose:** 0.5g every 4-6 hours.
**Disopyramide:**

**Brand Name:** Norpace, Regubeat

**MOA:** Disopyramide phosphate decreases the rate of diastolic depolarization (phase 4) in cells with augmented automaticity, decreases the upstroke velocity (phase 0) and increases the action potential duration of normal cardiac cells, decreases the disparity in refractoriness between infarcted and adjacent normally perfused myocardium, and has no effect on alpha- or beta-adrenergic receptors.

**Drug interactions:** Rifampicin, Warfarin, and erythromycin and oral Antidiabetic agents

**Adverse drug reactions:** Anticholinergic effects, hypotension, heart failure, torsades de pointes, heart block, GI intolerance.

**Dose:**

For short-acting oral dosage form (capsules):
- Adults—100 to 150 mg taken every six to eight hours.
- Children—Dose is based on body weight and age and must be determined by your doctor. The dose is usually 6 to 30 mg per kilogram (kg) (2.73 to 13.64 mg per pound) of body weight per day. This dose is evenly divided and taken every six hours.

For long-acting oral dosage forms (extended-release capsules or tablets):
- Adults—200 or 400 mg every twelve hours.
- Children—Use is not recommended.

**Subclass I B:** Drugs are lidocaine, Mexiletine, Tocainide which make little decrease in dv/dt 0 phase.

**Lidocaine:**

**Brand Name:** Xylocard, Gesicard.

**MOA:** Membrane-stabilizing antiarrhythmic agent a Combines with fast sodium channels in their inactive state and inhibits recovery after repolarization in a time- and voltage-dependent manner Exhibits rapid rates of attachment to and dissociation from transmembrane sodium channels’

**Drug interactions:** Phenytoin, Propranolol, Succinylcholine and Cimetidine.
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**ADR:** CNS effects such as drowsiness, dizziness, disorientation, confusion, light headedness, tremulousness, psychosis, nervousness, apprehension, agitation, euphoria, tinnitus, visual disturbances, paresthesia, difficulty swallowing, dyspnoea, slurred speech, sensations of heat, cold, or numbness, nausea, vomiting.

**Contraindications**
- Adams-Stokes syndrome; severe degrees of SA, AV, or intraventricular heart block (unless a functioning pacemaker is present). Some manufacturers state that lidocaine is contraindicated in patients with Wolff-Parkinson-White syndrome
- Known hypersensitivity to amide-type local anaesthetics

**Dose:**

**Paediatrics**
Initially, 0.5–1 mg/kg as a rapid IV injection (i.e., bolus); dose may be repeated according to patient response, up to a maximum total dose of 3–5 mg/kg. Maintenance infusion of 10–50 mcg/kg per minute.

**Adults:**
Initial doses ranging from 0.5–0.75 mg/kg and up to 1–1.5 mg/kg (about 50–100 mg) administered as rapid IV injection may be used. If desired response is not achieved, 25–50 mg may be administered 5 minutes after completion of the first injection, or 0.5–0.75 mg/kg as rapid IV injection may be repeated at 5- to 10-minute intervals as necessary, up to a total of 3 doses (or up to 3 mg/kg).

**Mexiletine**

**Brand Name:** Mexitil

**MOA:** Mexiletine, like lidocaine, inhibits the inward sodium current, thus reducing the rate of rise of the action potential, Phase 0. Mexiletine decreased the effective refractory period (ERP) in Purkinje fibres. The decrease in ERP was of lesser magnitude than the decrease in action potential duration (APD), with a resulting increase in the ERP/APD ratio.

**Drug interactions:** with theophylline, caffeine, digoxin, Phenobarbital, metoclopramide.

**ADR:** GI upset, fatigue, nervousness, dizziness, tremor, sleep disturbances, seizures, visual disturbances, psychosis, hepatitis, blood dyscrasias.
Anti arrhythmic drugs

Contraindications

- Second- or third-degree AV block (unless a cardiac pacemaker is in place).
- Cardiogenic shock.

Dose:

**Oral:** Maximum 400 mg every 8 hours (1.2 g daily). If given twice daily, maximum 450 mg every 12 hours.

Tocainide

**Brand Name:** Tonocard,

**MOA:** Produces its helpful effects by slowing nerve impulses in the heart and making the heart tissue less sensitive.

**Drug interactions:**

- Cimetidine, Lidocaine, Rifampin, Rifapentine.

**ADR:** GI upset, paresthesias, CNS side effects similar to lidocaine, nightmares, psychotic reactions, blood dyscrasias, hepatitis, interstitial pneumonitis

**Dose:** For oral dosage form (tablets):

  - For irregular heartbeat:
    - Adults—At first, 400 milligrams (mg) every eight hours. Then, your doctor may increase your dose up to 600 mg three times a day.
    - Children—Use and dose must be determined by your doctor.

**Subclass Ic:** Drugs are Propafenone and flecainide which have marked decreased in \( \frac{dv}{dt} \) \( 0 \) phase

Propafenone

**Brand Name:** Rythmol.

**MOA:** Propafenone HCl manifests itself in a reduction of upstroke velocity (Phase 0) of the monophasic action potential. In Purkinje fibres\(^1\), and to a lesser extent myocardial fibres, Propafenone HCl reduces the fast inward current carried by sodium ions. Diastolic excitability threshold is increased and effective refractory period prolonged. Propafenone reduces spontaneous automaticity and depresses triggered activity.
**Anti arrhythmic drugs**

**Drug interactions:** Quinidine, Digitalis, Warfarin, Cimetidine, Desipramine, Cyclosporin, Rifampin, Theophylline.

**ADR:** Bradycardia, heart block, sustained ventricular tachycardia, heart failure, GI upset, dizziness, blurred vision, metallic taste, dry mouth, bronchospasm, hepatitis

**Contraindications:**
Propafenone HCl is contraindicated in the presence of uncontrolled congestive heart failure, cardiogenic shock, sinoatrial, atrioventricular and intraventricular disorders of impulse generation and/or conduction (e.g., sick sinus node syndrome, atrioventricular block) in the absence of an artificial pacemaker, bradycardia, marked hypotension, bronchospastic disorders, manifest electrolyte imbalance, and known hypersensitivity to the drug.

**Dose:**

**Paediatric Patients**

**Supraventricular Arrhythmias**

Oral (conventional [immediate-release] tablets)

Maximum daily dosage 600 mg/m²

**Adults**

**Paroxysmal Atrial Fibrillation/Flutter and Paroxysmal Supraventricular Tachyarrhythmias**

Oral (conventional [immediate-release] tablets)

Initially, 150 mg every 8 hours.

Increase dosage after 3–4 days to 225 mg 3 times daily (every 8 hours) if necessary.

If desired therapeutic response is not attained after an additional 3–4 days, increase dosage to 300 mg 3 times daily (every 8 hours).

**Flecainide**

**Brand Name:** Tambocor

**MOA:** Flecainide belongs to the group of medicines known as antiarrhythmic. It works directly on the heart tissue and will slow the nerve impulses in the heart. This helps keep the heart rhythm normal.
Anti arrhythmic drugs

Drug interactions:

Darifenacin, fosamprenavir, ritonavir, tipranavir, Sparfloxacain, Thioridazine, Tipranavir, Ziprasidone

ADR: Bradycardia, heart block, sustained ventricular tachycardia, heart failure, GI upset, dizziness, blurred vision, neutropenia

Contraindications:
Flecainide is contraindicated in patients with pre-existing second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock (bifascicular block), unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur. Flecainide is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

Dose;

For oral dosage form (tablets):
- For paroxysmal Supraventricular tachycardia (PSVT) and paroxysmal atrial fibrillation/flutter (PAF):
  - Adults—At first, 50 milligrams (mg) every 12 hours. Your doctor may increase your dose as needed.
  - Children—Use and dose must be determined by your doctor. Dose is based on body size and must be determined by your child's doctor. The starting dose is 100 milligrams (mg) per square meter (m[2]) per day for infants 6 months and older and 50 mg/m(2) per day in infants younger than 6 months. Doses are divided into two or three equal doses per day.
- For sustained ventricular tachycardia (sustained VT):
  - Adults—At first, 100 milligrams (mg) every 12 hours. Your doctor may increase your dose as needed. However, the dose is usually not more than 400 mg per day.
  - Children—Use and dose must be determined by your doctor. Dose is based on body size and must be determined by your child's doctor. The starting dose is 100 milligrams (mg) per square meter (m[2]) per day for infants 6 months and older and 50 mg/m(2) per day in infants younger than 6 months. Doses are divided into two or three equal doses per day.

Class II: Beta blockers

Primary action of this class of drugs is to suppress adrenergically mediated ectopic activity. Drugs included under this category are Propranolol, Esmolol, Acebutolol and sotalol (which is also used as potassium channel blocker).
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**Propranolol**

**Brand Name:** Inderal, Inderal LA, InnoPran XL.

**MOA:** Propranolol is a beta blocker. It works by decreasing the action of pace maker cells and slowing down impulses in heart. This helps to control irregular heart beat.

**ADR:** Bradycardia, nausea, vomiting, diarrhoea, epigastric distress, abdominal cramping, constipation, flatulence.

**Contraindications**
- Sinus bradycardia.
- Heart block greater than first degree.
- Cardiogenic shock.
- CHF (unless secondary to a tachyarrhythmia treatable with Propranolol).
- Reynaud’s syndrome.
- Malignant hypertension.

**Dose:** For irregular heartbeats:
- For oral dosage form (solution):
  - Adults—10 to 30 milligrams (mg) three or four times a day, given before meals and at bedtime.
  - Children—Dose is based on body weight and must be determined by your doctor.
- For oral dosage form (tablets):
  - Adults—10 to 30 milligrams (mg) three or four times a day, given before meals and at bedtime.
  - Children—Use and dose must be determined by your doctor.

**Esmolol**

**Brand Name:** Miniblock

**MOA:**
Esmolol hydrochloride is a beta1-selective (cardioselective) adrenergic receptor blocking agent with a very short duration of action (elimination half-life is approximately 9 minutes) and no significant intrinsic Sympathomimetic or membrane stabilizing activity at therapeutic dosages.

**ADR:** Hypotension, heart block, heart failure, bronchospasm, pain at injection site

**Drug Interactions:** clonidine, verapamil
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Contraindications:
Esmolol hydrochloride is contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock or overt heart failure

DOSE: An initial loading dose of 0.5 milligrams/kg (500 micrograms/kg) infused over a minute duration followed by a maintenance infusion of 0.05 milligrams/kg/min (50 micrograms/kg/min) for the next 4 minutes is recommended.

After the 4 minutes of initial maintenance infusion (total treatment duration being 5 minutes), depending upon the desired ventricular response, the maintenance infusion may be continued at 0.05 mg/kg/min or increased step-wise (e.g. 0.1 mg/kg/min, 0.15 mg/kg/min to a maximum of 0.2 mg/kg/min) with each step being maintained for 4 or more minutes.

Acebutolol

Brand Name: Sectral

MOA: A short-acting β₁-selective adrenergic blocking agent

Drug Interactions: calcium channel blockers, Reserpine, Sulphinpyrazone, Warfarin, Tolbutamide.

ADR: Fatigue, dizziness, headache, dyspnoea, constipation, diarrhoea, dyspepsia, nausea, flatulence, insomnia, increased micturition, chest pain, edema, depression, abnormal dreams, rash, arthralgia, myalgia, cough, rhinitis, abnormal vision

Contraindications:

- Patients with heart block >first degree, severe bradycardia, cardiogenic shock, or overt cardiac failure

Dose:

Ventricular Arrhythmias: Oral

Initially, 200 mg twice daily. Increase gradually until optimum effect is achieved. Usual maintenance dosage is 600–1200 mg daily
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Sotalol

**Brand Name:** Betapace, Sorine

**MOA:** Sotalol have both beta-adrenoreceptor blocking (Vaughan Williams Class II) and cardiac action potential duration prolongation (Vaughan Williams Class III) antiarrhythmic properties. Sotalol hydrochloride tablets are a racemic mixture of d- and l-Sotalol. Both isomers have similar Class III antiarrhythmic effects, while the I-isomer is responsible for virtually all of the beta-blocking activity. The beta-blocking effect of Sotalol is non-cardioselective,

**ADR:** Heart block, hypotension, bronchospasm, bradycardia, torsades de pointes

**Drug interactions:** ciprofloxacin, enoxacin, gatifloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, quinolones, sparfloxacin

**Contraindications**
Sotalol hydrochloride tablets are contraindicated in patients with bronchial asthma, sinus bradycardia, second and third degree AV block, unless a functioning pacemaker is present, congenital or acquired long QT syndromes, cardiogenic shock, uncontrolled congestive heart failure and previous evidence of hypersensitivity to Sotalol hydrochloride tablets.

**Dose:**

**Adults-Life-threatening Ventricular Arrhythmias:**

**Oral**
Initially, 80 mg twice daily.\(^1\) If necessary, dosage may be increased gradually after appropriate evaluation to 240–320 mg daily given in divided doses; allow 3 days between dosing increments.\(^1\)

Usual maintenance dosage: 160–320 mg daily in divided doses.\(^1\)

May increase to 480–640 mg daily in divided doses, but risk of potentially serious toxicity increases with such doses

**Initiation and Dosage Titration:**
Initially, 80 mg twice daily in adults with normal renal function (Cl\(_{cr}\) > 60 mL/minute) and a near normal QT interval (≤450 msec). If arrhythmia is well controlled (e.g., no recurrences of atrial fibrillation or flutter) during first 3 days of inpatient monitoring and QT interval is <500 msec, may discharge patient on current treatment with an adequate supply to allow uninterrupted therapy until the outpatient prescription is filled.
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Class III: Potassium channel blockers

The characterisation of this class is prolongation of repolarization; AP is widened and DRP is increased. Potassium channel blocking properties used in managing ventricular arrhythmias and atrial fibrillation.
Drugs involved are Amiodarone, Bretylium, Ibutilide and Dofetilide.

Amiodarone

Brand Name: Cordarone, Pacerone.

MOA: Amiodarone has a wide spectrum of electrophysiologic effects. Although classified as a class III agent, it displays use dependent sodium channel blockade, non-competitive alpha and beta adrenoreceptor blockade and calcium channel blockade. Some of its electrophysiologic effect is by reducing the conversion of T4 to T3 and increasing rT3. Amiodarone is also a vasodilator and was initially developed as an anti anginal agent. Amiodarone is used in managing atrial fibrillation

ADR: Ataxia, tremor, dizziness, pulmonary fibrosis, bradycardia, heart block, sustained ventricular tachycardia, GI upset, hepatitis, hypo– or hyperthyroidism, peripheral neuropathy, photosensitivity, blue-gray skin discoloration, corneal micro deposits.

Drug Interactions: Methotrexate, moxifloxacin, norfloxacin, ofloxacin, Quinidine, quinolones, rifabutin, Rifampin, Rifapentine, ritonavir, simvastatin,, sparflloxacin, tacrolimus, tipranavir, verapamil, warfarin.
It can increase digoxin and Warfarin levels by reducing their renal clearance.

Contraindications:
- Cardiogenic shock.
- Severe sinus node dysfunction resulting in marked sinus bradycardia (unless a functioning pacemaker is present).
- Second- or third-degree AV block (unless a functioning pacemaker is present).
- Bradycardia that has caused syncope (unless a functioning pacemaker is present).
- Known hypersensitivity to amiodarone or any ingredient in the formulation, including iodine

Dose: Orally 400-600mg/day for few weeks, followed by 100-200 mg OD for maintainance therapy.100-300mg slow I.V Inj over 30-60 min.
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**Bretylium**

**Brand Name:** Bretylol

**MOA:** Bretylium (also bretylium tosylate) is an antiarrhythmic agent. It blocks the release of noradrenaline from nerve terminals. In effect, it decreases output from the peripheral sympathetic nervous system. It also acts by blocking K⁺ channels and is considered a class III antiarrhythmic.

**ADR:** Transient initial hypertension; nausea, vomiting, local tissue necrosis after IM Inj (limit vol and vary site), bradycardia and renal impairment, dyspnoea, chest pain, flushing, increase in premature ventricular contractions, nasal congestion, syncope.

**Contraindications:** Hypersensitivity, pheochromocytoma, severe aortic stenosis, severe pulmonary hypertension. Not to be used when there is digitalis-induced arrhythmias.

**Dose:**

Intravenous

**Life-threatening ventricular arrhythmias**

**Adult:** Initially, 5 mg/kg as an undiluted solution via rapid IV inj. If condition persists, may increase to 10 mg/kg and repeat as necessary. To continue suppression, dilute 500 mg of bretylium tosilate with at least 50 ml of 5% dextrose inj, USP or 0.9% sodium chloride Inj, USP and administer the diluted solution at a constant infusion rate of 1-2 mg bretylium tosilate/minute.

**Renal impairment:** May need to increase dosing interval. Parenteral

**Other ventricular arrhythmias**

**Adult:** Dose can be given via IM or IV admin. IM admin: Use undiluted bretylium tosilate inj. Initially, 5-10 mg/kg. If arrhythmia persists, subsequent doses may be given at 1-2 hr intervals, thereafter maintain the same dosage every 6-8 hr. IV admin: Use diluted solution; dilute 500 mg of bretylium tosilate with at least 50 ml of 5% dextrose Inj, USP or 0.9% sodium chloride Inj, USP. Initially, 5-10 mg/kg given as IV infusion over at least 8 minutes. If arrhythmia persists, subsequent doses may be given at 1-2 hr intervals, thereafter maintain the same dosage every 6 hr or a constant infusion of 1-2 mg/minute may be given.

**Renal impairment:** May need to increase dosing interval.
Ibutilide:

**Brand Name:** Corvert

**MOA:** Short acting intravenous potassium channel blocker used only for the acute termination of atrial fibrillation or flutter. It can cause sustained ventricular arrhythmias and patients who receive this agent should be monitored electrocardiographically, with resuscitative equipment readily available, for 8 hours.

**ADR:** AV block, torsades de pointes

**Drug Interactions:** Interactions with procainamide and Quinidine have greater risk of arrhythmias

**Contraindications**
- History of polymorphic VT (e.g., torsades de pointes).
- Known hypersensitivity to Ibutilide or any ingredient in the formulation

**Dose:**

**Adults**

**Supraventricular Tachyarrhythmia’s, Atrial Flutter and/or Fibrillation**

IV

Adults weighing ≥60 kg: Initially, 1 mg. Alternatively, 2 mg has been used.

Adults weighing <60 kg: Initially, 0.01 mg/kg (10 mcg/kg).

If arrhythmia does not terminate within 10 minutes after completion of initial infusion, repeat initial dose.

**Atrial Flutter and/or Fibrillation following Coronary Bypass Graft or Valvular Surgery**

IV

Adults weighing ≥60 kg: 1 or 2 infusions of 0.5 mg each (given 10 minutes apart) have been used.

Adults weighing <60 kg: 1 or 2 infusions of 0.005 mg/kg (5 mcg/kg) each (given 10 minutes apart) have been used.
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**Dofetilide**

**Brand Name:** Tikosyn

**MOA:** Blockade of the cardiac ion channel carrying the rapid component of the delayed rectifier potassium currents.

**ADR:** AV block, torsades de pointes, Headache; dizziness; insomnia; migraine

**Drug Interactions:** Cimetidine, inhibitors of renal cationic exchange (eg, megestrol, phenothiazines), ketoconazole, trimethoprim (alone or in combination with sulfamethoxazole), verapamil Contraindicated.

**Dose:** The dose of TIKOSYN must be individualized according to calculated creatinine clearance and QTc. (QT interval should be used if the heart rate is < 60 beats per minute. There are no data on use of TIKOSYN when the heart rate is < 50 beats per minute.) The usual recommended dose of TIKOSYN is 500 mcg BID.

**Class IV: Calcium channel blockers**

Only the nondihydropyridine calcium channel blockers, verapamil and diltiazem, exert antiarrhythmic utility. Similar to β-blockers, these agents exert their antiarrhythmic efficacy by slowing AV nodal conduction and reducing ventricular rates during certain Supraventricular tachyarrhythmia. These agents inhibit channel-mediated entry of calcium into the cell. Effects are most evident in the SA node, AV node, and cardiac and peripheral vascular smooth muscles because these tissues depend on calcium flux for action potential generation.

**Verapramil**

**Brand Name:** Calan, Covera-HS, Isoptin SR, Tarka, Verelan, Calaptin.

**MOA:** Verapamil hydrochloride is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist) that exerts its pharmacologic effects by modulating the influx of ionic calcium across the cell membrane of the arterial smooth muscle as well as in conductile and contractile myocardial cells.

**ADR:** Heart block, heart failure, hypotension, asystole, dizziness, headache, edema, constipation

**Drug Interactions:** Beta-blockers, Aspirin, Digitalis.
Contra indications:
Verapamil tablets are contraindicated in:

- Severe left ventricular dysfunction.
- Hypotension (systolic pressure less than 90 mm Hg) or cardiogenic shock
- Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker)
- Second-or third-degree AV block (except in patients with a functioning artificial ventricular pacemaker)

Dose:

Usual Adult Verapamil Dose for Arrhythmias:

Initial dose (oral): The dosage in digitalized patients with chronic atrial fibrillation ranges from 240-320 mg/day in divided (t.i.d. or q.i.d.) doses. The dosage for prophylaxis of PSVT (non-digitalized patients) ranges from 240-480 mg/day in divided (t.i.d or q.i.d.) doses. In general, maximum effects for any given dosage will be apparent during the first 48 hours of therapy.

Usual Adult Verapamil dose for Supraventricular Tachycardia:

Initial dose (IV): 5-10 mg (0.075-0.15 mg/kg) given as an IV bolus over at least 2 minutes. Repeat dose: 10 mg (0.15 mg/kg) 30 minutes after the first dose if the initial response is not adequate.
An optimal interval for subsequent IV doses has not been determined, and should be individualized for each patient.

Diltiazem

Brand Name: Dilzem, Cardizem, Cardizem CD, Cardizem LA, Cartia XT, Dilacor XR, Dilt-CD, Dilt-XR.

MOA: Diltiazem inhibits the influx of extracellular calcium across both the myocardial and vascular smooth muscle cell membranes. Resulting in dilation of the coronary and systemic arteries; improved oxygen delivery to the myocardial tissue; and decreased total peripheral resistance, systemic blood pressure, and after load.

- It is a negative dromotrope & creates refractoriness in the AV node. Its effects on calcium channels in SA and AV nodes, and peripheral vasculature are equipotent

ADR: Heart block, hypotension, asystole, heart failure
Anti arrhythmic drugs

Drug Interactions:

• May prolong the sedative effects of midazolam.

• May enhance the effects of ASA and prolong bleeding time.

• Additive effects with antihypertensive, alpha-blockers, & diuretics.

• Should not be used in combination with IV beta-blockers. The negative inotropic, chronotropic, & hypotensive effects can induce heart failure.

• Calcium salts can antagonize the hypotensive effects, but do not seem to have an effect on AV conduction.

• Incompatible with simultaneous furosemide injection

Contraindications:

• 2nd or 3rd degree AV block (in the absence of a functioning pacemaker)

• Sick Sinus Syndrome (in the absence of a functioning pacemaker)

• Cardiogenic shock

• Hypersensitivity

Dose:

➤ Adults:

DOSE: IV: 10 mg slow over 2 minutes. Repeat every 10-15 minutes PRN rate control. MAX 40 mg.

➤ Paediatrics:

• Rarely required, doses are the same as adult.
• (Medical Control Order) 0.25 mg/kg IV over 2 minutes (Usual dose about 20 mg). May repeat in 15 minutes @ 0.35 mg/kg.
Anti arrhythmic drugs

Newly approved FDA Drug:

Brand Name: Nexterone

Active Ingredient: Amiodarone HCl Premixed in Dextrose.

Company: Baxter

Pharmacological Class: Class III Antiarrhythmic Drug.

Indication: Premixed Injection is indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation (VF) and hemodynamically unstable ventricular tachycardia (VT) in patients refractory to other therapy. NEXTERONE also can be used to treat patients with VT/VF for whom oral amiodarone is indicated, but who are unable to take oral medication.

Dosage Forms and Strengths:

Injection, 1.5 mg/ml (150 mg/100 ml) Premixed in Dextrose

Injection, 1.8 mg/ml (360 mg/200 ml) Premixed in Dextrose
REFERENCES:


5. Introduction to Antiarrhythmic Agents, Munther K. Homoud, MD Tufts-New England Medical Center, Spring 2008.


