Antiarrhythmic Drugs

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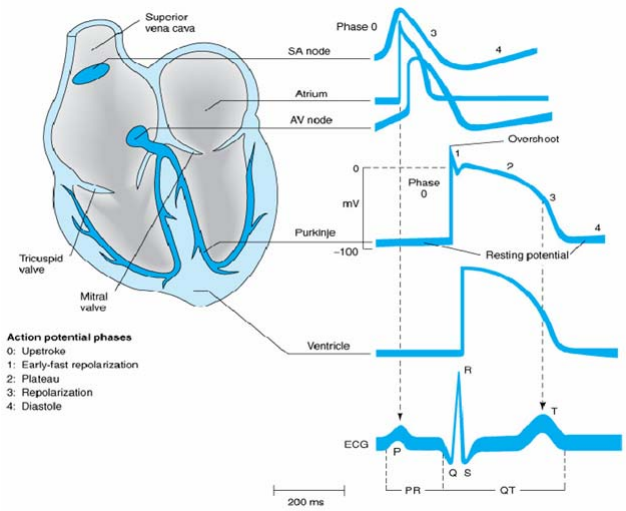
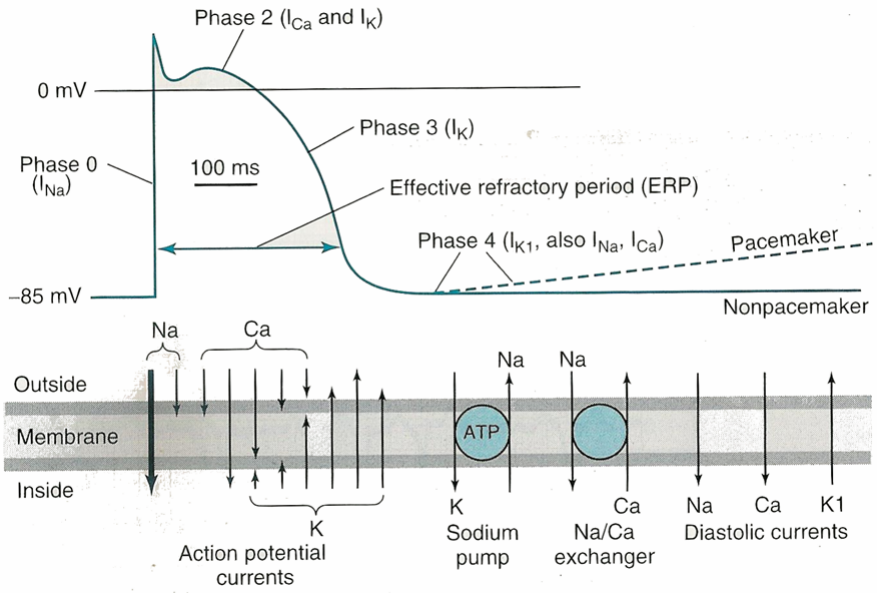
• **Class 1 (Na^+ channel blockers)**	*1a* 1. Disopiramide (Norpace) 2. Quinidine (Quinicardine) 3. Procainamide (*Pronestyl*) *1b* 1. Aprindin (*Fiboran*) 2. Phenitoin (Epanutin) 3. Lidocaine (Aritmal) 4. Mexiletine (Mexitil) 5. Tocainide (*Tonocard*) *1c* 1. Encainide (no preparation) 2. Flecainide (*Tambocor*) 3. Moricizine (*Ethmozine*) 4. Lorcainide (*Remivox*) 5. Propafenone (Rytmonorm)
• **Class 2 (β-blockers)**	1. Acebutolol (Prent) 2. Esmolol (Brevibloc) 3. Metoprolol (Beloc) 4. Pindolol (Apo-Pindol) 5. Propranolol (Dideral) 6. Sotalol (Darob)

• **Class 3 (K^+ channel blockers)**	1. Amiodarone (Cordarone) 2. Bretilium (*Bretylol*) 3. Dofetilide (*Tikosyn*) 4. Ibutilide (*Corvert*) 5. Sotalol (Darob)
• **Class 4 (Ca^{2+} channel blockers)**	1. Bepridil (*Vascor*) 2. Diltiazem (Diltizem) 3. Verapamil (Isoptin)
• **Other antiarrhythmic drugs**	1. Adenosine (*Adenocard*) 2. Digoxin (Digoxin) 3. Calcium (Calcium Sandoz) 4. Magnesium sulphate (generic) 5. Potasium chloride (generic)



• **Figure 14–1** Schematic representation of the heart and normal cardiac electrical activity (intracellular recordings from areas indicated and ECG). Sinoatrial node, atrioventricular node, and Purkinje cells display pacemaker activity (phase 4 depolarization). The ECG is the body surface manifestation of the depolarization and repolarization waves of the heart. The P wave is generated by atrial depolarization, the QRS by ventricular muscle depolarization, and the T wave by ventricular repolarization. Thus, the PR interval is a measure of conduction time from atrium to ventricle, and the QRS duration indicates the time required for all of the ventricular cells to be activated (ie, the intraventricular conduction time). The QT interval reflects the duration of the ventricular action potential.



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First choice antiarrhythmic drugs

Class		Atrial flutter or fibrilation	SVT	VEB	VT	VF
1	Quinidine			+	+	
	Lidocaine			+	+	+
2	Esmolol	+	+		+	
	Metoprolol	+			+	
	Propranolol	+			+	
3	Amiodaron			+	+	
4	Diltiazem	+	+			
	Verapamil	+	+			
Others	Adenosine		+			

SVT, supraventricular tachycardia; VEB, ventricular ectopic beat;
VT, ventricular tachycardia; VF, ventricular fibrillation

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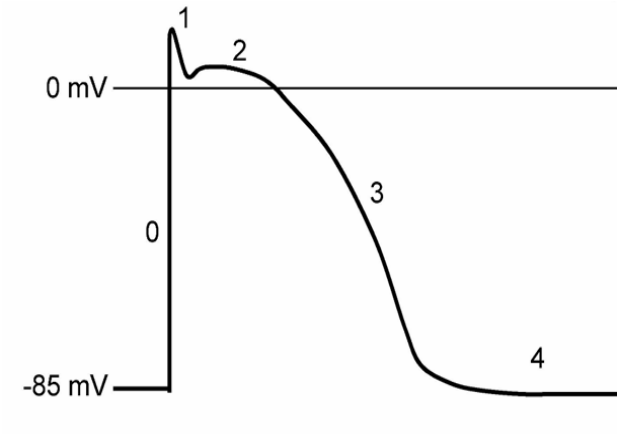
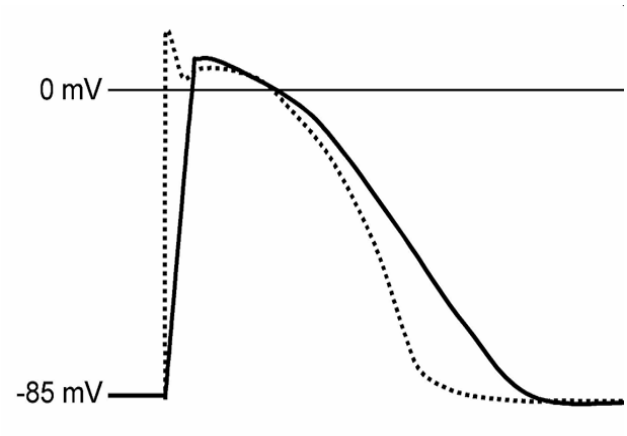
Sodium Channel-Blocking Drugs (Class 1)

No drug



Class 1a effect



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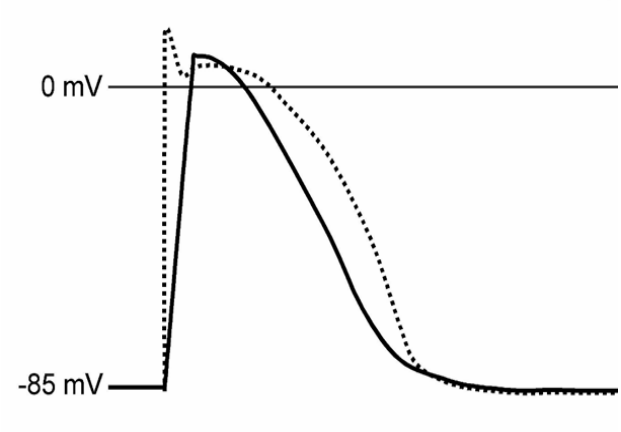
Class 1b effect



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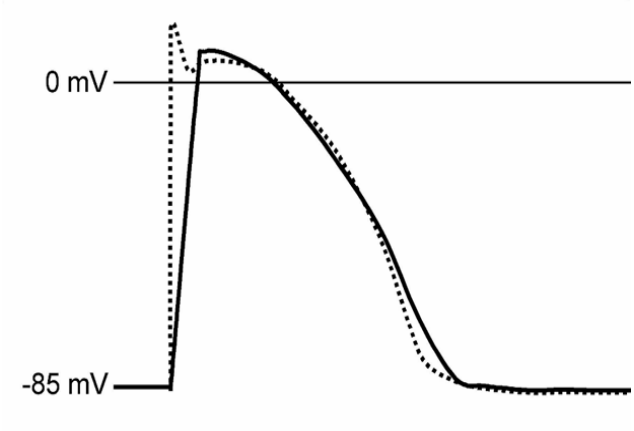
Class 1c effect



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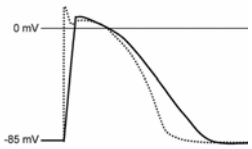
1a: Quinidine I



Cardiac Effects

- Quinidine has actions similar to those of procainamide: it slows the upstroke of the action potential and conduction, and prolongs the QRS duration of the ECG, by blockade of sodium channels.
- The drug also prolongs the action potential duration by nonspecific blockade of potassium channels.
- It has more pronounced cardiac antimuscarinic effects than procainamide.
- Its toxic cardiac effects include excessive QT interval prolongation and induction of torsade de pointes arrhythmia.
- Toxic concentrations of quinidine also produce excessive sodium channel blockade with slowed conduction throughout the heart.

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1a: Quinidine II

Extracardiac Effects

- Gastrointestinal side effects of diarrhea, nausea, and vomiting are observed in one third to one half of patients.
- A syndrome of headache, dizziness, and tinnitus **(cinchonism)** is observed at toxic drug concentrations.
- Idiosyncratic or immunologic reactions, including thrombocytopenia, hepatitis, angioneurotic edema, and fever, are observed rarely.

1a: Quinidine III

Pharmacokinetics

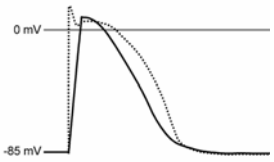
- Quinidine is absorbed readily following oral administration, bound to albumin and α1-acid glycoprotein, and eliminated primarily by hepatic metabolism.
- The elimination half-life is 6–8 hours. Quinidine is usually administered in a slow release formulation, eg, that of the gluconate salt.

1a: Quinidine IV

Therapeutic Use

- Quinidine is used only occasionally to maintain normal sinus rhythm in patients with atrial flutter/fibrillation. Because of its cardiac and extracardiac side effects, its use is now largely restricted to patients with arrhythmic but otherwise normal hearts.
- In randomized, controlled clinical trials, quinidine-treated patients are twice as likely to remain in normal sinus rhythm compared with controls, but the risk of death is increased two-to threefold.
- Quinidine is used rarely in patients with ventricular tachycardia. Quinidine is the optical isomer of quinine and is sometimes used intravenously for the treatment of acute, severe malaria.

1b: Lidocaine I



Cardiac Effects

- Lidocaine blocks activated and inactivated sodium channels with rapid kinetics; the inactivated state block ensures greater effects on cells with long action potentials such as Purkinje and ventricular cells, compared with atrial cells.
- The rapid kinetics at normal resting potentials result in recovery from block between action potentials and no effect on conduction.
- The increased inactivation and slower unbinding kinetics result in the selective depression of conduction in depolarized cells.

1b: Lidocaine II

Toxicity

- **CARDIAC**
- Lidocaine is one of the least cardiotoxic of the currently used sodium channel blockers.
- Proarrhythmic effects, including sinoatrial node arrest, worsening of impaired conduction, and ventricular arrhythmias, are uncommon with lidocaine use.
- In large doses, especially in patients with preexisting heart failure, lidocaine may cause hypotension—partly by depressing myocardial contractility.

1b: Lidocaine III

Toxicity

- **EXTRACARDIAC**
- Lidocaine's most common adverse effects—like those of other local anesthetics—are neurologic: paresthesias, tremor, nausea of central origin, lightheadedness, hearing disturbances, slurred speech, and convulsions.
- These occur most commonly in elderly or otherwise vulnerable patients or when a bolus of the drug is given too rapidly. The effects are dose-related and usually short-lived; seizures respond to intravenous diazepam.
- In general, if plasma levels above 9 mcg/mL are avoided, lidocaine is well tolerated.

1b: Lidocaine IV

- **Pharmacokinetics & Dosage**
- Because of its extensive first-pass hepatic metabolism lidocaine must be given parenterally.
- Lidocaine has a half-life of 1–2 hours. In adults, a loading dose of 150–200 mg administered over about 15 minutes (as a single infusion or as a series of slow boluses) should be followed by a maintenance infusion of 2–4 mg/min to achieve a therapeutic plasma level of 2–6 mcg/mL. Determination of lidocaine plasma levels is of great value in adjusting the infusion rate.
- Occasional patients with myocardial infarction or other acute illness require (and tolerate) higher concentrations. This may be due to increased plasma α1-acid glycoprotein, an acute phase reactant protein that binds lidocaine, making less free drug available to exert its pharmacologic effects.

1b: Lidocaine V

Therapeutic Use

- Lidocaine is the agent of choice for termination of ventricular tachycardia and prevention of ventricular fibrillation after cardioversion in the setting of acute ischemia.
- However, routine *prophylactic* use of lidocaine in this setting may actually increase total mortality, possibly by increasing the incidence of asystole, and is not the standard of care. Most physicians administer IV lidocaine only to patients with arrhythmias.

1c: Propafenone I

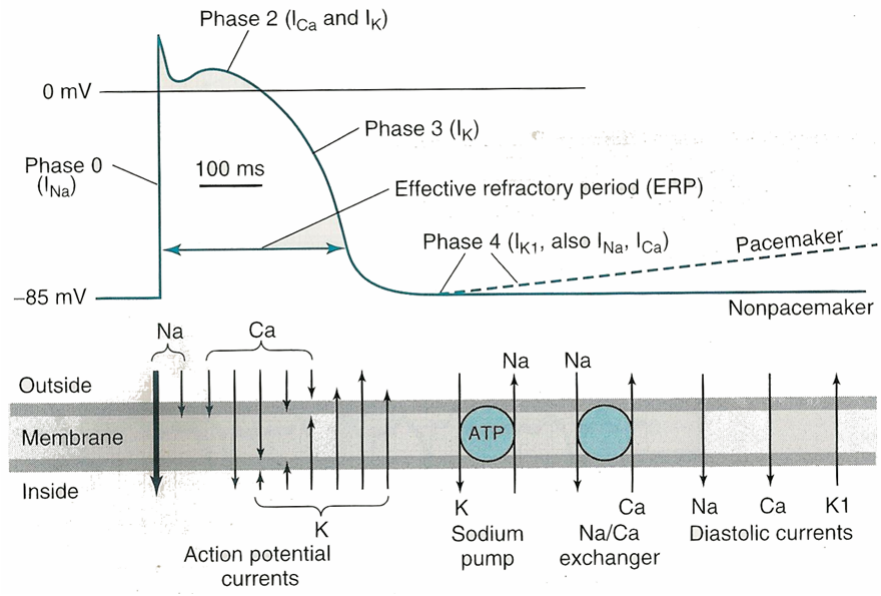
- Propafenone has some structural similarities to propranolol and possesses weak β-blocking activity.
- Its spectrum of action is very similar to that of quinidine. Its sodium channel blocking kinetics are similar to that of flecainide.

1c: Propafenone II

- Propafenone is metabolized in the liver, with an average half-life of 5–7 hours. The usual daily dosage of propafenone is 450–900 mg in three doses.
- The drug is used primarily for supraventricular arrhythmias. The most common adverse effects are a metallic taste and constipation; arrhythmia exacerbation can occur.

2: β-blockers II

- **Propranolol** and similar drugs have antiarrhythmic properties by virtue of their β-receptor–blocking action and direct membrane effects.
- Some of these drugs have selectivity for cardiac β1 receptors, some have intrinsic sympathomimetic activity, some have marked direct membrane effects, and some prolong the cardiac action potential.



2: β-blockers II

- The relative contributions of the β -blocking and direct membrane effects to the antiarrhythmic effects of these drugs are not fully known.
- Although β blockers are fairly well tolerated, their efficacy for suppression of ventricular ectopic depolarizations is lower than that of sodium channel blockers.
- However, there is good evidence that these agents can prevent recurrent infarction and sudden death in patients recovering from acute myocardial infarction.

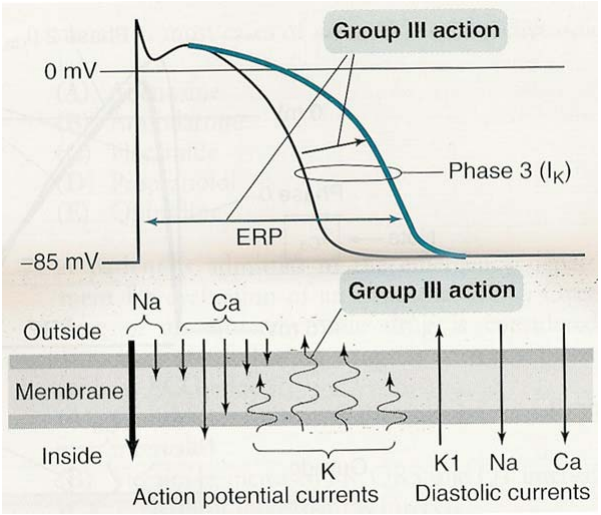
2: β-blockers II

- **Esmolol** is a short-acting β blocker used primarily as an antiarrhythmic drug for intraoperative and other acute arrhythmias.
- **Sotalol** is a nonselective β -blocking drug that prolongs the action potential (class 3 action).

Drugs That Prolong Effective Refractory Period by Prolonging Action Potential (Class 3)

- These drugs prolong action potentials, usually by blocking potassium channels in cardiac muscle or by enhancing inward current, eg, through sodium channels.
- Action potential prolongation by most of these drugs often exhibits the undesirable property of "reverse use-dependence": action potential prolongation is least marked at fast rates (where it is desirable) and most marked at slow rates, where it can contribute to the risk of torsade de pointes.

Drugs That Prolong Effective Refractory Period by Prolonging Action Potential (Class 3)



3: Amiodarone I

- Amiodarone is approved for oral and intravenous use to treat serious ventricular arrhythmias.
- However, the drug is also highly effective for the treatment of supraventricular arrhythmias such as atrial fibrillation.
- Amiodarone has a broad spectrum of cardiac actions, unusual pharmacokinetics, and important extracardiac adverse effects.

3: Amiodarone II

Cardiac Effects

- Amiodarone markedly prolongs the action potential duration (and the QT interval on the ECG) by blockade of IKr (rapid delayed rectifier potassium current). During chronic administration, IKs (slow delayed rectifier potassium current) is also blocked. The action potential duration is prolonged uniformly over a wide range of heart rates; that is, the drug does not have reverse use-dependent action.
- In spite of its present classification as a class 3 agent, amiodarone also significantly blocks inactivated sodium channels. Its action potential prolonging action reinforces this effect.

3: Amiodarone III

Cardiac Effects (continued)

- Amiodarone also has weak adrenergic and calcium channel blocking actions. Consequences of these actions include slowing of the heart rate and atrioventricular node conduction. The broad spectrum of actions may account for its relatively high efficacy and low incidence of torsade de pointes despite significant QT interval prolongation.

Extracardiac Effects

- Amiodarone causes peripheral vasodilation. This action is prominent following intravenous administration and may be related to the action of the vehicle.

3: Amiodarone IV

Toxicity

- **CARDIAC**
- Amiodarone may produce symptomatic bradycardia and heart block in patients with preexisting sinus or atrioventricular node disease.
- **EXTRACARDIAC**
- Amiodarone accumulates in many tissues, including the heart (10–50 times greater than plasma), lung, liver, and skin, and is concentrated in tears. Dose-related pulmonary toxicity is the most important adverse effect. Even on a low dose of 200 mg/d, fatal pulmonary fibrosis may be observed in 1% of patients. Abnormal liver function tests and hepatitis may develop during amiodarone treatment. The skin deposits result in a photodermatitis and a gray-blue skin discoloration in sun-exposed areas, eg, the malar regions. After a few weeks of treatment, asymptomatic corneal microdeposits are present in virtually all patients treated with amiodarone. Halos develop in the peripheral visual fields of some patients. Drug discontinuation is usually not required. Rarely, an optic neuritis may progress to blindness.
- Amiodarone blocks the peripheral conversion of thyroxine (T4) to triiodothyronine (T3). It is also a potential source of large amounts of inorganic iodine. Amiodarone may result in hypothyroidism or hyperthyroidism. Thyroid function should be evaluated prior to initiation of treatment and monitored periodically. Because effects have been described in virtually every organ system, amiodarone treatment should be reevaluated whenever new symptoms develop in a patient, including arrhythmia aggravation.

3: Amiodarone V

Pharmacokinetics

- Amiodarone is variably absorbed with a bioavailability of 35–65%. It undergoes hepatic metabolism, and the major metabolite, desethylamiodarone, is bioactive. The elimination half-life is complex, with a rapid component of 3–10 days (50% of the drug) and a slower component of several weeks. Following discontinuation of the drug, effects are maintained for 1–3 months. Measurable tissue levels may be observed up to 1 year after discontinuation. A total loading dose of 10 g is usually achieved with 0.8–1.2 g daily doses. The maintenance dose is 200–400 mg daily. Pharmacologic effects may be achieved rapidly by intravenous loading. QT-prolonging effect is modest with this route of administration, whereas bradycardia and atrioventricular block may be significant.
- Amiodarone has many important drug interactions and all medications should be reviewed during drug initiation or dose adjustments. Amiodarone is a substrate for the liver cytochrome metabolizing enzyme CYP3A4 and its levels are increased by drugs that inhibit this enzyme, eg, the histamine H2 blocker cimetidine. Drugs that induce CYP3A4, eg, rifampin, decrease amiodarone concentration when coadministered. Amiodarone inhibits the other liver cytochrome metabolizing enzymes and may result in high levels of drugs that are substrates for these enzymes, eg, digoxin and warfarin.

3: Amiodarone VI

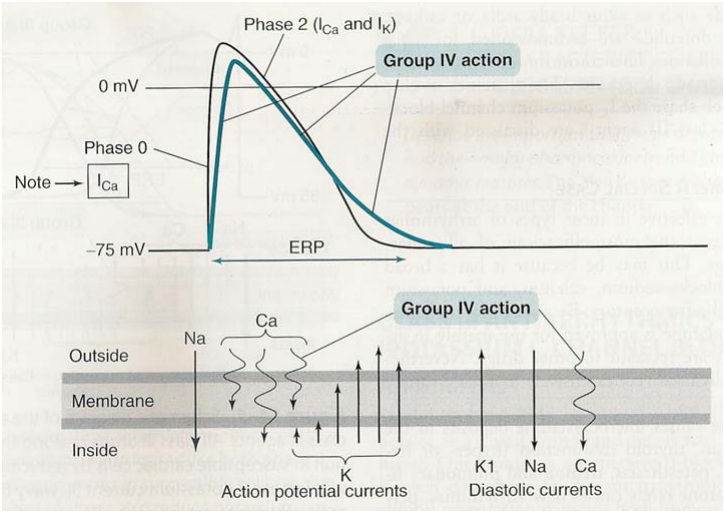
Therapeutic Use

- Low doses (100–200 mg/d) of amiodarone are effective in maintaining normal sinus rhythm in patients with atrial fibrillation. The drug is effective in the prevention of recurrent ventricular tachycardia. Its use is not associated with an increase in mortality in patients with coronary artery disease or heart failure. In many centers, the implanted cardioverter-defibrillator (ICD) has succeeded drug therapy as the primary treatment modality for ventricular tachycardia, but amiodarone may be used for ventricular tachycardia as adjuvant therapy to decrease the frequency of uncomfortable ICD discharges. The drug increases the pacing and defibrillation threshold and these devices require retesting after a maintenance dose has been achieved.

Calcium Channel–Blocking Drugs (Class 4)

- These drugs, of which verapamil is the prototype, were first introduced as antianginal agents and are discussed in greater detail in that lecture.
- Verapamil and diltiazem also have antiarrhythmic effects.

Calcium Channel–Blocking Drugs (Class 4)



4: Verapamil I

Cardiac Effects

- Verapamil blocks both activated and inactivated L-type calcium channels. Thus, its effect is more marked in tissues that fire frequently, those that are less completely polarized at rest, and those in which activation depends exclusively on the calcium current, such as the sinoatrial and atrioventricular nodes.
- Atrioventricular nodal conduction time and effective refractory period are invariably prolonged by therapeutic concentrations. Verapamil usually slows the sinoatrial node by its direct action, but its hypotensive action may occasionally result in a small reflex increase of sinoatrial nodal rate.

4: Verapamil II

Cardiac Effects (continued)

- Verapamil can suppress both early and delayed afterdepolarizations and may antagonize slow responses arising in severely depolarized tissue.

Extracardiac Effects

- Verapamil causes peripheral vasodilation, which may be beneficial in hypertension and peripheral vasospastic disorders. Its effects upon smooth muscle produce a number of extracardiac effects.

4: Verapamil III

Toxicity

- **CARDIAC**
- Verapamil's cardiotoxic effects are dose-related and usually avoidable. A common error has been to administer intravenous verapamil to a patient with ventricular tachycardia misdiagnosed as supraventricular tachycardia. In this setting, hypotension and ventricular fibrillation can occur. Verapamil's negative inotropic effects may limit its clinical usefulness in diseased hearts. Verapamil can induce atrioventricular block when used in large doses or in patients with atrioventricular nodal disease. This block can be treated with atropine and β-receptor stimulants. In patients with sinus node disease, verapamil can precipitate sinus arrest.
- **EXTRACARDIAC**
- Adverse effects include constipation, lassitude, nervousness, and peripheral edema.

4: Verapamil IV

Pharmacokinetics & Dosage

- The half-life of verapamil is approximately 7 hours. It is extensively metabolized by the liver; after oral administration, its bioavailability is only about 20%. Therefore, verapamil must be administered with caution in patients with hepatic dysfunction.
- In adult patients without heart failure or sinoatrial or atrioventricular nodal disease, parenteral verapamil can be used to terminate supraventricular tachycardia, although adenosine is the agent of first choice. Verapamil dosage is an initial bolus of 5 mg administered over 2–5 minutes, followed a few minutes later by a second 5 mg bolus if needed. Thereafter, doses of 5–10 mg can be administered every 4–6 hours, or a constant infusion of 0.4 mcg/kg/min may be used.
- Effective oral dosages are higher than intravenous dosage because of first-pass metabolism and range from 120 to 640 mg daily, divided into three or four doses.

4: Verapamil V

Therapeutic Use

- Supraventricular tachycardia is the major arrhythmia indication for verapamil. Adenosine or verapamil are preferred over older treatments (propranolol, digoxin, edrophonium, vasoconstrictor agents, and cardioversion) for termination.
- Verapamil can also reduce the ventricular rate in atrial fibrillation and flutter. It only rarely converts atrial flutter and fibrillation to sinus rhythm. Verapamil is occasionally useful in ventricular arrhythmias. However, the use of intravenous verapamil in a patient with sustained ventricular tachycardia can cause hemodynamic collapse.

First choice antiarrhythmic drugs

Class		Atrial flutter or fibrilation	SVT	VEB	VT	VF
1	Quinidine			+	+	
	Lidocaine			+	+	+
2	Esmolol	+	+		+	
	Metoprolol	+			+	
	Propranolol	+			+	
3	Amiodaron			+	+	
4	Diltiazem	+	+			
	Verapamil	+	+			
Others	Adenosine		+			

SVT, supraventricular tachycardia; VEB, ventricular ectopic beat;
VT, ventricular tachycardia; VF, ventricular fibrillation

Class	Drug	Effect on arrhythmias		Indications
		Supraventricular	Ventricular	
1a	Disopyramide	+	+++	AF, VT
	Quinidine	+	+++	AF, VT, VF
	Procainamide	+	+++	AF, VT, VF
1b	Phenitoin	0*	+	Digital arrhythmias
	Lidocaine	0*	+++	VT, VF, digital arrhythmias
	Mexiletine	0	+++	VT, VF
	Tokainide	0	+++	VT, VF
1c	Flecainide	+	++++	AF, SVT
	Propafenone	+	+++	AF, SVT
1	Morisizine	0	+++	VT, VF
2	Esmolol	+	+	AF, SVT
	Metoprolol	+	+	AF, SVT, VT, VF
	Propranolol	+	+	AF, SVT, VT, VF
3	Amiodaron	+++	+++	AF, VT, VF
	Bretilium	0	+	VT, VF
	Sotalol	+++	+++	AF, VT, VF
4	Diltiazem	++	0	AF, SVT
	Verapamil	+++	0	AF, SVT
Others	Adenosine	++++	0	SVT
	Digoxin	+	0	AF, SVT

* Useful at digital related supraventricular arrhythmia.

Class	Drug	Half Life	Application	Loading dose	Maintenance dose
1a	Disopyramide	6-8 h	Oral	–	300-600 mg/day
	Quinidine	6 h	Oral, IV	–	400-1800 mg/day
	Procainamide	3-4 h	Oral, IM, IV	IV, till arrhythmia supression 20-50 mg/min, max 17 mg/kg	Oral 2-4 g/day; IM 50 mg/kg/day; IV with infusion pump 1-4mg/min
1b	Phenitoin	24 h	IV	–	250-500 mg
	Lidocaine	1-2 h	IV	1-1.5 mg/kg	2-3 mg/kg/day
	Mexiletine	12 h	Oral	–	400-600 mg/day
	Tocainide	12 h	Oral	–	1200-1800 mg/day
1c	Flecainide	20 h	Oral	–	100-300 mg/day
	Propafenone	5-7 h	Oral, IV	2 mg/kg	450-900 mg/day
1	Moricizine	2-6 h	Oral	–	600-900 mg/day
2	Esmolol	10 min	IV	30 mg	3-12 mg/min
	Metoprolol	3-4 h	Oral, IV	5-10 mg	100-200 mg/day
	Propranolol	8 h	Oral, IV	1-3 mg	80-240 mg/day
3	Amiodarone	Weeks	Oral, IV	IV , 5 mg/kg in 30 min	Oral 100-600 mg/day; IV 10-15 mg/kg/day
	Bretilium	4 h	IV	150 mg	1-4 mg/min
	Sotalol	8 h	Oral	–	80-320 mg/day
4	Diltiazem	3.7 h	Oral, IV	Slow IV , 0.25 mg/kg	Oral 120-480 mg; IV 5-15 mg/h
	Verapamil	7 h	Oral, IV	2.5-10 mg	120-480 mg/day
Others	Adenosine	<10 sec	IV	6 mg	12 mg*
	Digoxin	40 h	Oral, IV	0.5-0.75 mg	0.125-0.25 mg

*If there is no change to sinus rhythm with initial 6 mg dose, give 12 mg after 1-2 min; this can be repeated once again for last time.

Thank you...

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