Anti-arrhythmic drugs

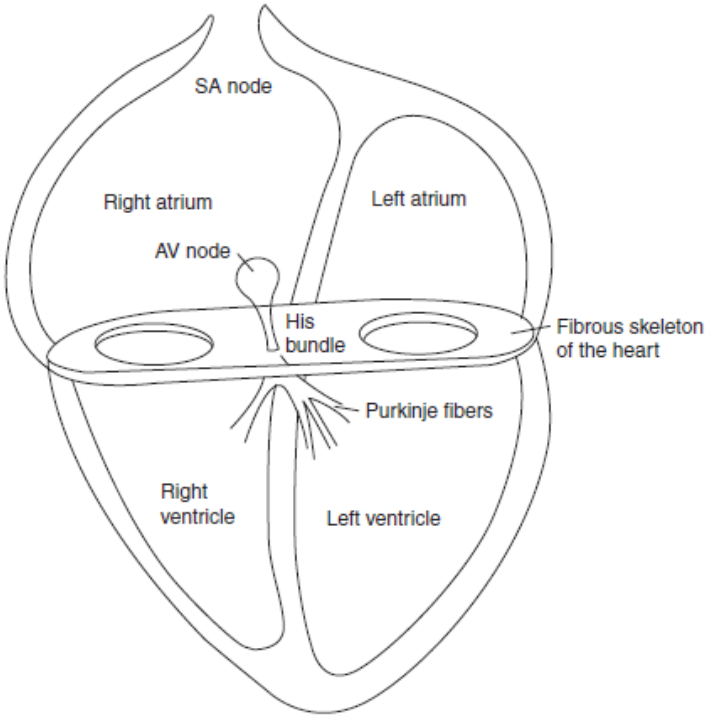
Arrhythmias

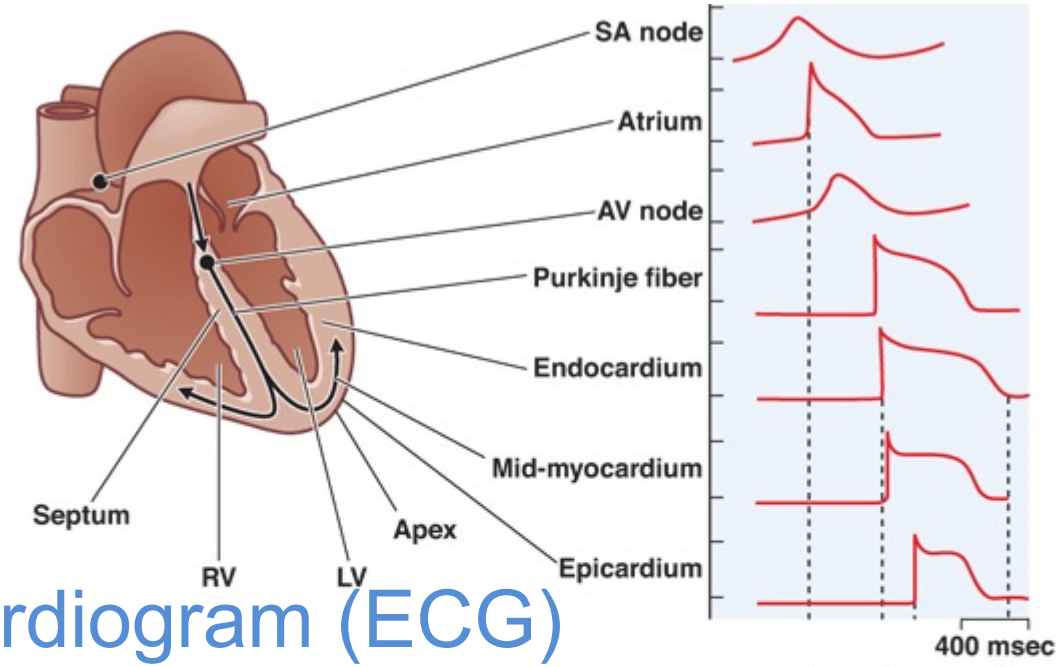
❑ Arrhythmias consist in occasional or persistent alterations in the regular sequence of depolarization and repolarization in the heart conduction system.

❑ Arrhythmias are usually classified according:
- to the site of origin (atrial, junctional or ventricular arrhythmias);
- to the heart rate (tachyarrhythmias or bradyarrhythmias).

❑ The most common test used to diagnose an arrhythmia is the electrocardiogram (ECG).

Electrical system of the heart

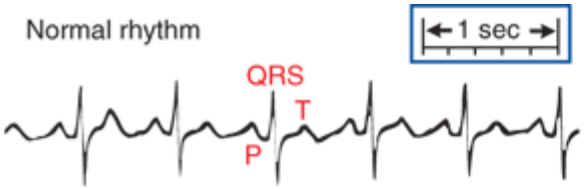




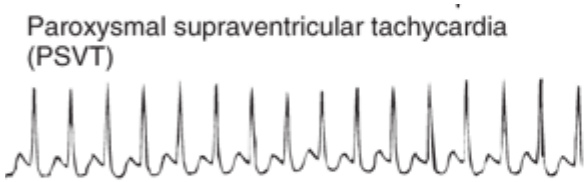
Electrocardiogram (ECG)

Source: L. L. Brunton, B. A. Chabner, B. C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12ed.
www.accesspharmacy.com

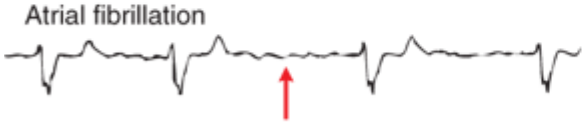
Types of Arrhythmias



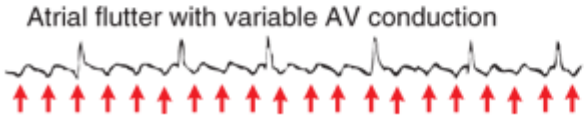
a) Paroxysmal supraventricular tachycardia (PSVT)

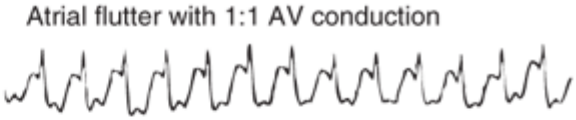


b) Atrial fibrillation

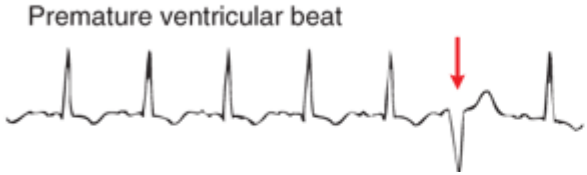


c) Atrial flutter

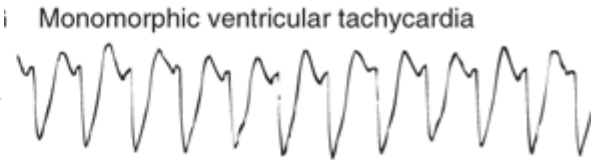




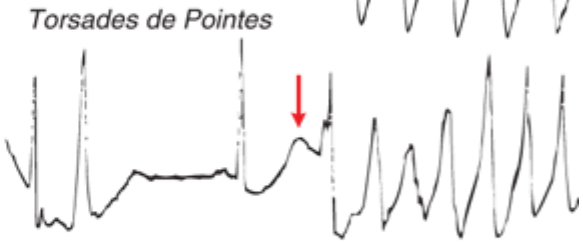
d) Extrasystoles



e) Monomorphic ventricular tachycardia



f) Torsades de Pointes



Arrhythmias

Certain factors can precipitate arrhythmias:

- ischemia,
- hypoxia,
- acidosis or alkalosis,
- electrolyte abnormalities,
- excessive catecholamine exposure,
- autonomic influences,
- drug toxicity (eg, digitalis or antiarrhythmic drugs),
- overstretching of cardiac fibers,
- presence of scarred or otherwise diseased tissue.

frontiers | Frontiers in Cardiovascular Medicine

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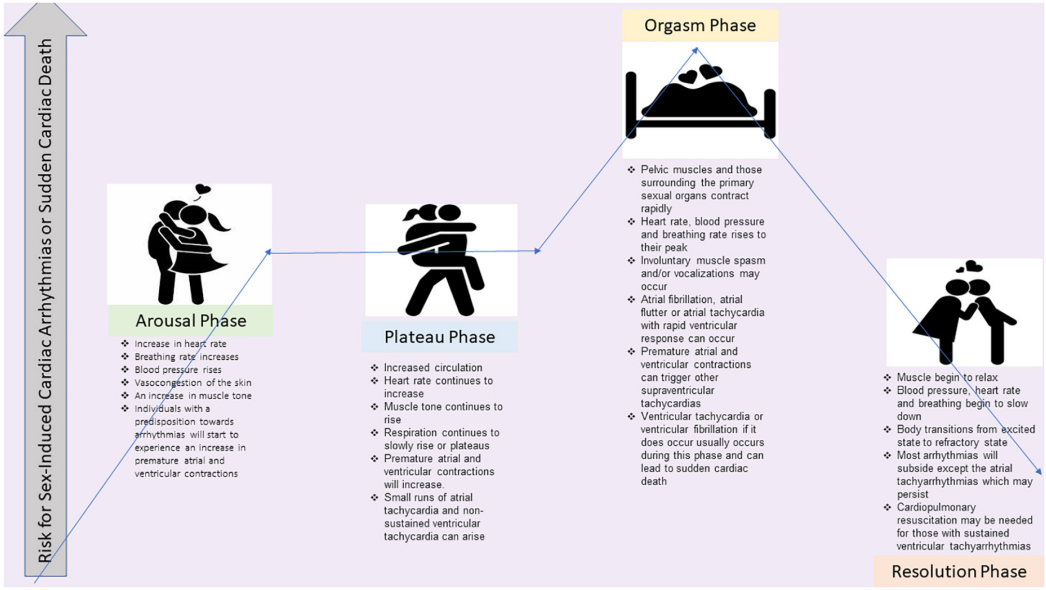
Sex, Rhythm & Death: The effect of sexual activity on cardiac arrhythmias and sudden cardiac death

Cicely Anne Dye*, Erica Engelstein, Sean Swearingen, Jeanine Murphy, Timothy Larsen and Annabelle Santos Volgman

Division of Cardiology, Rush University Medical Center, Chicago, IL, United States

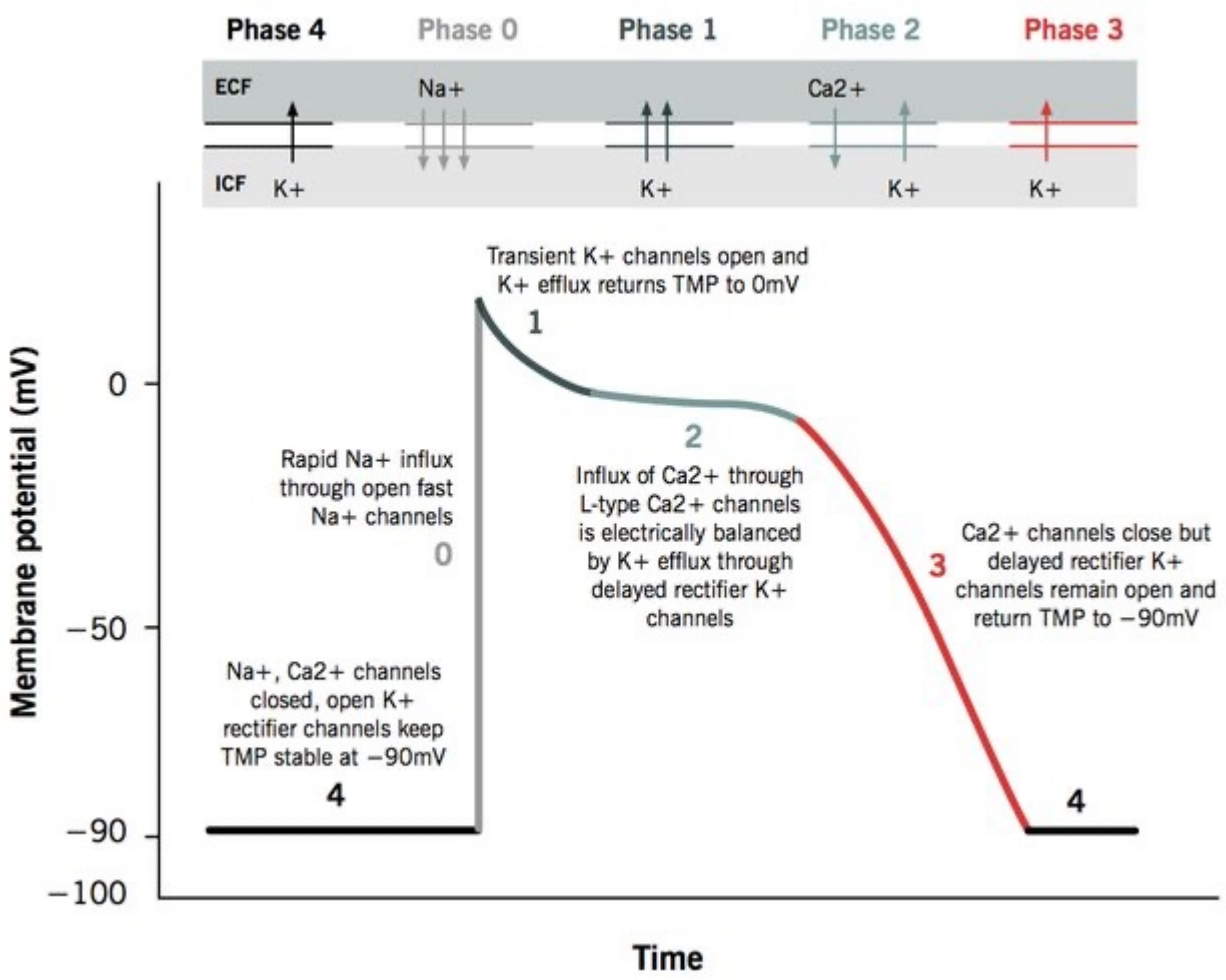


Pro-arrhythmic effects of anti-arrhythmic drugs

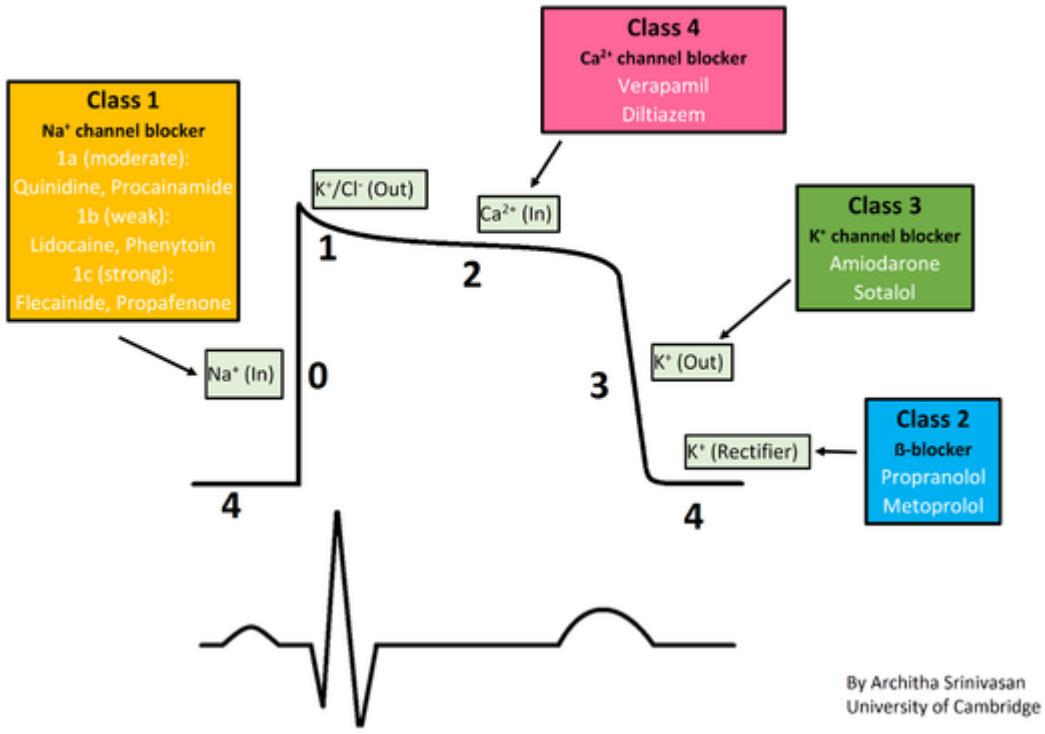
Effect	Drug	Incidence
Marked sinus bradycardia, sino-atrial blocks	Class IA, Class IC	Rare, except when latent sinus node disease is present
High-grade AV block	Class IA, Class IC	Rare
Conversion of AF to atrial flutter with higher ventricular rate	Quinidine and other Class IA	Rare with current dosages
Conversion of AF to atrial flutter with 1:1 AV conduction and wide QRS	Flecainide and propafenone	3.5–5%
Torsade de pointe	Quinidine and Class IA	1–8%
	Ibutilide, dofetilide, sotalol	Up to 8%
	Amiodarone	0.7%
Ventricular tachycardia or ventricular fibrillation	Potentially all AADs	Rare, except when LV dysfunction or heart failure are present

AAD, antiarrhythmic drugs; AF, atrial fibrillation; AV, atrioventricular; LV, left ventricular.

The cardiac action potential



Vaughan-Williams classes of anti-arrhythmic drugs



Class	Actions	Drugs
I	Sodium channel blockade	
IA	prolong repolarization	quinidine, procainamide, disopyramide
IB	shorten repolarization	lidocaine, mexiletine, tocainide, phenytoin
IC	little effect on repolarization	flecainide, encainide, propafenone
II	Beta-adrenergic blockade	propanolol, esmolol
III	Prolong repolarization potassium channel blockade	sotalol, amiodarone
IV	Calcium channel blockade	verapamil, diltiazem

I. Classes of anti-arrhythmic drugs

Class	Most Efficacious For	Channels Affected	Representative Drugs
IA	Atrial fibrillation Ventricular arrhythmias	Na^+ also prolong repolarization (prolong QT)	Quinidine, procainamide, disopyramide
IB	Ventricular arrhythmias	Na^+ Also shorten repolarization (shorten QT)	Lidocaine, mexiletine
IC	AV nodal reentry WPW-related arrhythmias Ventricular arrhythmias (? mortality)	Na^+ No significant effect on repolarization	Flecainide, propafenone
II	Atrial fibrillation/flutter (Ventricular arrhythmias)	Directly block beta adrenergic receptors; small Na^+ blocking effect	Propranolol, esmolol, acebutolol
III	Atrial fibrillation/flutter Ventricular arrhythmias	Prolong QT with little effect on repolarization (block either fast K^+ or slow Na^+ currents)	Amiodarone, sotalol, Ibutilide, dofetilide
IV	Atrial fibrillation/flutter Atrial automaticities AV nodal reentry	Block AV Node Ca^+ channels	Verapamil, diltiazem
Adenosine	AV nodal reentry Orthodromic tachycardia	Complete blockade of AV node conduction	
Digitalis	AV nodal reentry Atrial fibrillation/flutter	Reduces AV nodal conduction by blocking Na^+ - K^+ ATPase	
Magnesium	Torsades de pointes	Suppression of early afterdepolarizations through blockade of calcium or sodium channels	

II. Classes of anti-arrhythmic drugs

ANTIARRHYTHMIC DRUG ACTIONS

Vaughn-Williams Class	DRUG	ECG Changes	CHANNELS			RECEPTORS				Clinical Effects			
			Ca^{++}	Na^{+}	K^{+}	α	β	ACh	Ado	Pro-Arrhy	Extra Cardiac	LV FX	Heart Rate
I A	Quinidine	A		M	M	L		M		H	M		
	Procainamide			M	M					M	H		
	Disopyramide (Norpace)			M	M			M		L	M	↓↓	
I B	Lidocaine (Xylocaine)	B		L						L	M		
	Mexiletine (Mexitil)			L						L	M		
I C	Propafenone (Rythmol)	C		H			M			M	L	↓↓	↓
	Flecainide (Tambocor)			H						H	L	↓↓	
II	β-Adrenergic antagonists						H			L	L	↓	↓↓
III	Dronedarone (Multaq)		L	L	H	M	M	M		L	H	↓	↓
	Amiodarone (Cordarone)		L	L	H	M	M	M		L	H		↓
	Sotalol (Betapace)				H		H			H	L	↓	↓
	Ibutilide (Corvert)			△	H					H	L		
	Dofetilide (Tikosyn)				H					H	L		
IV	Verapamil (Calan, Isoptin)		M							L	L	↓↓	↓
	Diltiazem (Cardizem)		M							L	L	↓	↓
Misc	Adenosine (Adenocard)								△	L	L		↓

Antagonist relative potency
L = Low
M = Moderate
H = High

△ = Agonist
● = ECG Changes related to Ca^{++} channel block
● = ECG Changes related to Na^{+} channel block
● = ECG Changes related to K^{+} channel block

Anti-arrhythmic drugs I sub-classes

An easy way to remember…

- IA **D**isopyramide **Q**uinidine **P**rocainamide (**D**ouble **Q**uarter **P**ounder)

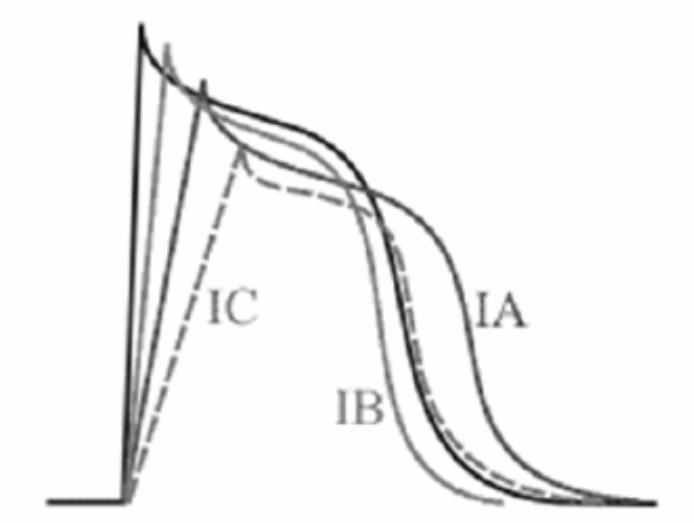
- IB **L**idocaine **M**exiletine (**L**etuce **M**ayo)

- IC **F**lecainide **P**ropafenone (**F**ries **P**lease)

Anti-arrhythmic drugs in Class I

❑ Anti-arrhythmic drugs included in the class I bind to and block the fast Na^+ channels that are responsible for the rapid depolarization (phase 0) of the cardiac action potential, although with differences in the efficacy.
Sub-class IC has the greatest effect on phase 0, IB drugs has the smallest, sub-class IA is intermediate in its effect on phase 0.
IC > IA > IB

❑ Some anti-arrhythmic drugs included in the class I can also block the K^+ channels responsible for phase 3, affecting the effective refractory period (ERP).
IA (increase ERP) > IC > IB (decrease ERP)



Class IA: *e.g.*, quinidine
- Moderate Na^+ channel blockade
- ↑ ERP

Class IB: *e.g.*, lidocaine
- Weak Na^+ channel blockade
- ↓ ERP

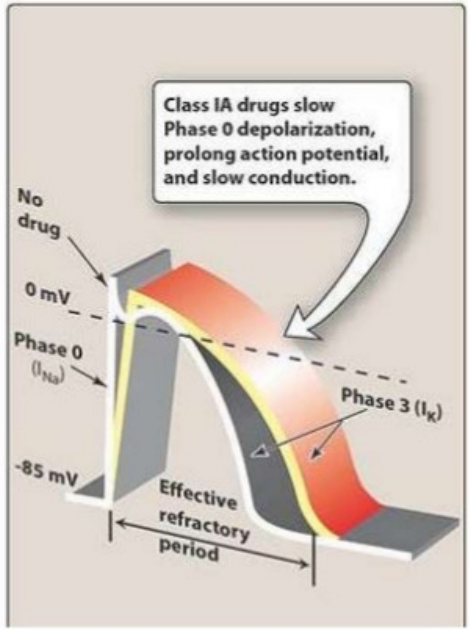
Class IC: *e.g.*, flecainide
- Strong Na^+ channel blockade
- → ERP

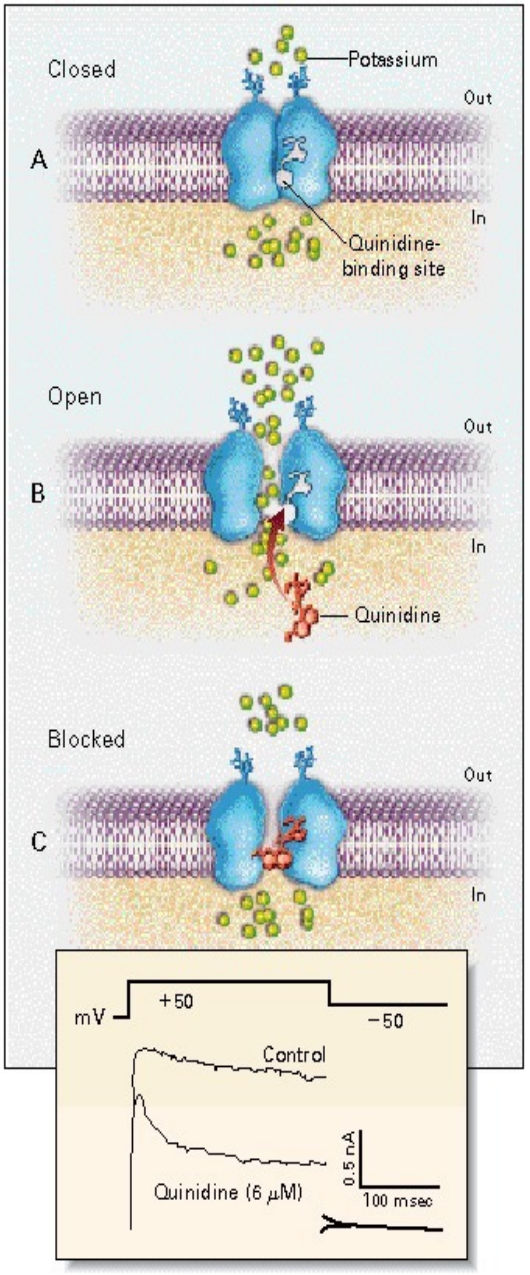
Anti-arrhythmic drugs: sub-class IA

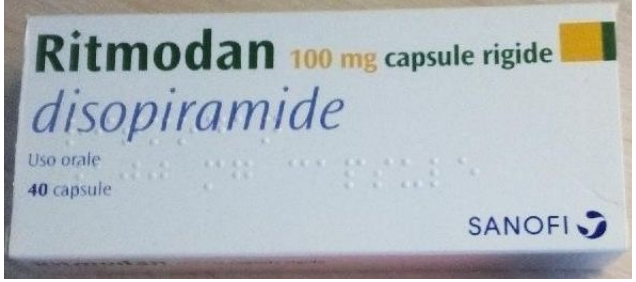
❑ Anti-arrhythmic drugs included in the sub-class IA **moderately** block the open rapid Na^+ channels;

❑ Anti-arrhythmic drugs included in the sub-class IA also block the K^+ channels, **increasing** the effective refractory period.

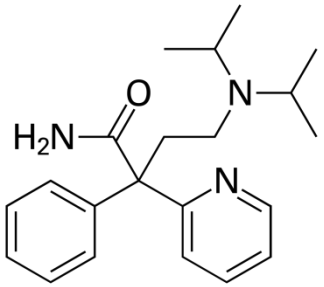
❑ These electrophysiological effects are manifested in both atrial and ventricular tissue, and therefore Class IA drugs have the potential of treating both <u>atrial and ventricular tachyarrhythmias.</u>







Disopyramide



- Disopyramide is an oral agent.

- Disopyramide is prescribed in order to **maintain the sinus rhythm** in presence of atrial flutter or atrial fibrillation and to prevent recurrence of ventricular tachycardia or fibrillation.

- Marked pro-arrhythmic effects (especially in patients with a history of congestive heart failure) and several drug-drug interactions.

0022-3565/93/2643-1425$03.00/0
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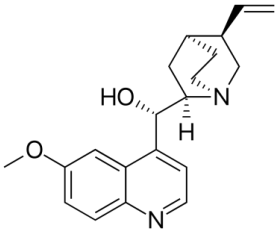
A Potent Inhibitory Effect of Erythromycin and Other Macrolide Antibiotics on the Mono-N-Dealkylation Metabolism of Disopyramide with Human Liver Microsomes[1]

HIROTOSHI ECHIZEN, HIROE KAWASAKI, KAN CHIBA, MASAYOSHI TANI and TAKASHI ISHIZAKI
Division of Geriatric Health and Nutrition, The National Institute of Nutrition (H.E.); Department of Pharmaceutical Science, Science University of Tokyo (H.K.); Division of Clinical Pharmacology, Clinical Research Institute (H.E., K.C., T.I.) and Division of General Surgery, (M.T.), National Medical Center, Tokyo, Japan
Accepted for publication October 29, 1992

Potentially Fatal Interaction Between Azithromycin and Disopyramide

ERIC V. GRANOWITZ, KENNETH J. TABOR,* and JAMES B. KIRCHHOFFER
From the Divisions of Infectious Disease and Cardiology, Department of Medicine, and the *Department of Clinical Pharmacy Services, Baystate Medical Center and Tufts University School of Medicine, Springfield, Massachusetts

Quinidine



❑ Quinidine is a stereoisomer of quinine, originally derived from the bark of the cinchona tree.

❑ Quinidine is administered orally as one of three salts (sulfate, gluconate, or polygalacturonate).

❑ Quinidine, combined with verapamil, is effective in treating **atrial fibrillation**.

European Heart Journal (2004) 25, 1385–1394

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Clinical research

Prevention of atrial fibrillation after cardioversion: results of the PAFAC trial

Thomas Fetsch[a], Peter Bauer[b], Rolf Engberding[c], Hans P. Koch[d], Jan Lukl[e], Thomas Meinertz[f], Michael Oeff[g], Ludger Seipel[h], Hans J. Trappe[i], Norbert Treese[j], Günter Breithardt[a,*], for The Prevention of Atrial Fibrillation after Cardioversion Investigators

European Heart Journal (2004) 25, 1395–1404

ELSEVIER

EUROPEAN SOCIETY OF CARDIOLOGY

Clinical research

Suppression of paroxysmal atrial tachyarrhythmias – results of the SOPAT trial

Monica Patten[a,*], Renke Maas[a], Peter Bauer[b], Berndt Lüderitz[c] Frank Sonntag[d], Miroslaw Dluzniewski[e], Robert Hatala[f], Grzegorz Opolski[g] Hans-Walter Müller[h], Thomas Meinertz[a], for the SOPAT Investigators[1]

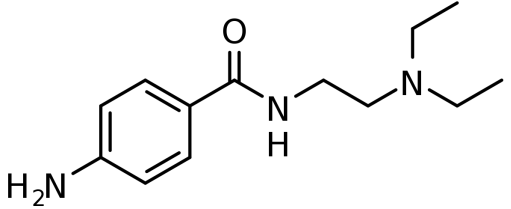
❑ The most common side effects are gastrointestinal, mainly diarrhea (30-50% of patients). Cinchonism, also after the first administration. Pro-arrhythmic effects.

Vol. 294 No. 13 QUINIDINE-ANTICONVULSANT INTERACTION — DATA ET AL. 699

INTERACTION OF QUINIDINE WITH ANTICONVULSANT DRUGS

JOANN L. DATA, M.D., GRANT R. WILKINSON, PH.D., AND ALAN S. NIES, M.D.

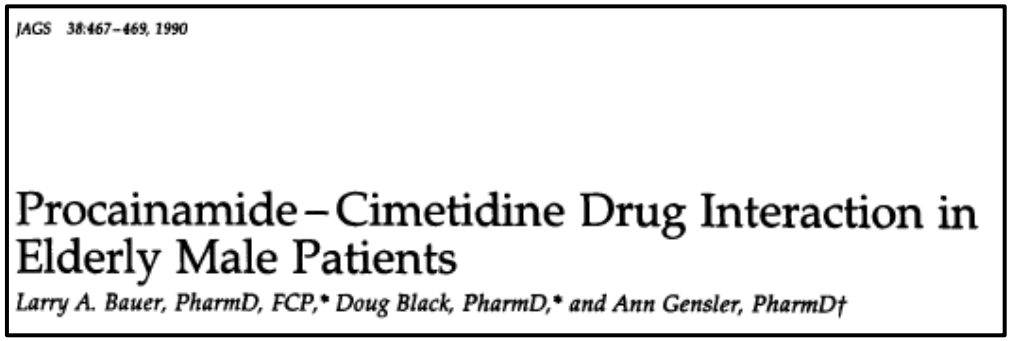
Procainamide



- Procainamide is a derivative of the local anesthetic agent procaine.

- Because procainamide is available for relatively rapid intravenous loading, it has often been used to treat **atrial fibrillation** or slow incessant ventricular tachycardias.

- The most common acute side effects are gastrointestinal (especially nausea, vomiting, and diarrhea), and hypotension (when the drug is administered intravenously). Chronic administration of procainamide can induce agranulocytosis (rare but mortality in 25% of patients) and lupus (frequent, 20% of patients). Several drug-drug interactions (cimetidine).


JAGS 38:467–469, 1990

Procainamide–Cimetidine Drug Interaction in Elderly Male Patients

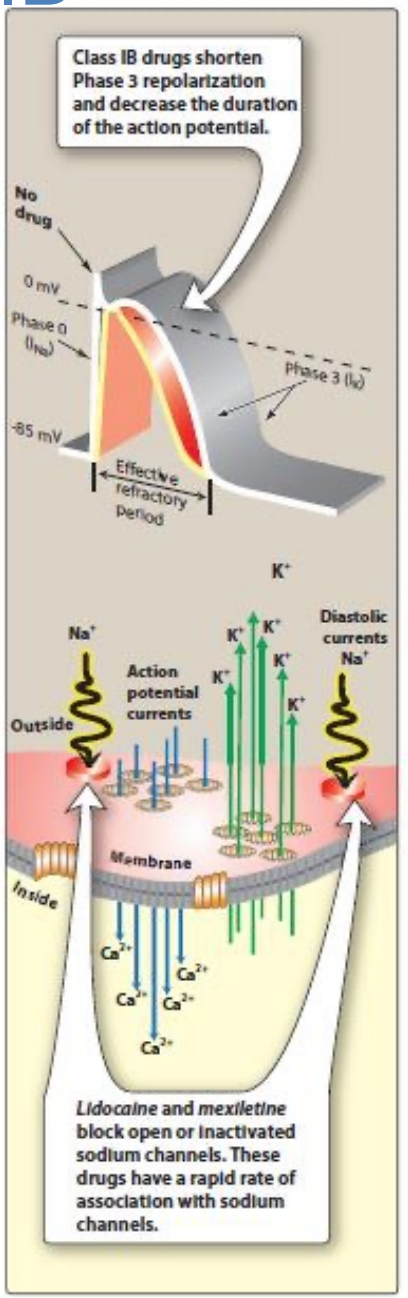
Larry A. Bauer, PharmD, FCP, Doug Black, PharmD,* and Ann Gensler, PharmD†*

Anti-arrhythmic drugs: subclass IB

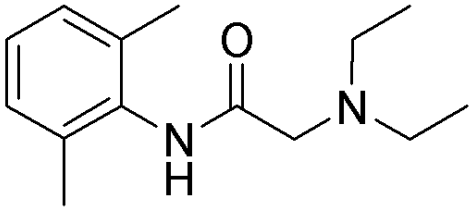
❑ Anti-arrhythmic drugs included in the sub-class IB **weakly** block Na^+ channels.

❑ Anti-arrhythmic drugs included in the sub-class IB **decrease** the effective refractory period.
This effect is more visible in fibers that have a longer action potential duration, like Purkinje fibers.

❑ Anti-arrhythmic drugs included in the sub-class IB have profound effects on conduction velocity in damaged myocardium, but they do not prolong conduction velocity in healthy cardiac tissue.



Lidocaine



❑ Lidocaine is a local anesthetic first introduced as an anti-arrhythmic drug in the 1950s.

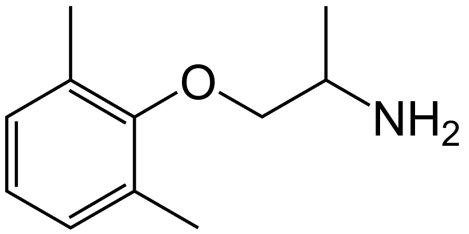
❑ Lidocaine is administered intravenously with a plasma half-life of 1–2 hours. For this trait, lidocaine is considered the drug of choice for **emergency therapy of arrhythmias**.

❑ Lidocaine is one of the least cardiotoxic Na^+ channel blockers. The predominant side effects relate to the CNS: 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. Nevertheless, lidocaine may be ineffective in hypokalemic patients.

Effects of Propranolol or Paracetamol on Lidocaine Concentrations in Serum and Tissues

*Theodosios Saranteas, MD, DDS, PhD,**
Costas Mourouzis, DDS,† Fanny Koumoura, DDS,‡
and Christina Tesseromatis, MD, DDS, PhD§

Mexiletine



❑ Mexiletine is a structural analog of lidocaine, is resistant to first-pass hepatic metabolism and effective by the oral route.

❑ The electrophysiological effects of mexiletine are virtually identical to those of lidocaine and it is frequently combined with quinidine to increase efficacy while decreasing the risk of pro-arrhythmia.

❑ Mexiletine is approved for treatment of ventricular arrhythmias.

❑ A very narrow therapeutic window limits mexiletine use. Tremor, dizziness, memory loss.

Clin. Cardiol. 13, 349-359 (1990)

Electrophysiology, Pacing, and Arrhythmia

This section edited by A. J. Camm, M.D., F.R.C.P., F.A.C.C.

Mexiletine: Pharmacology and Therapeutic Use

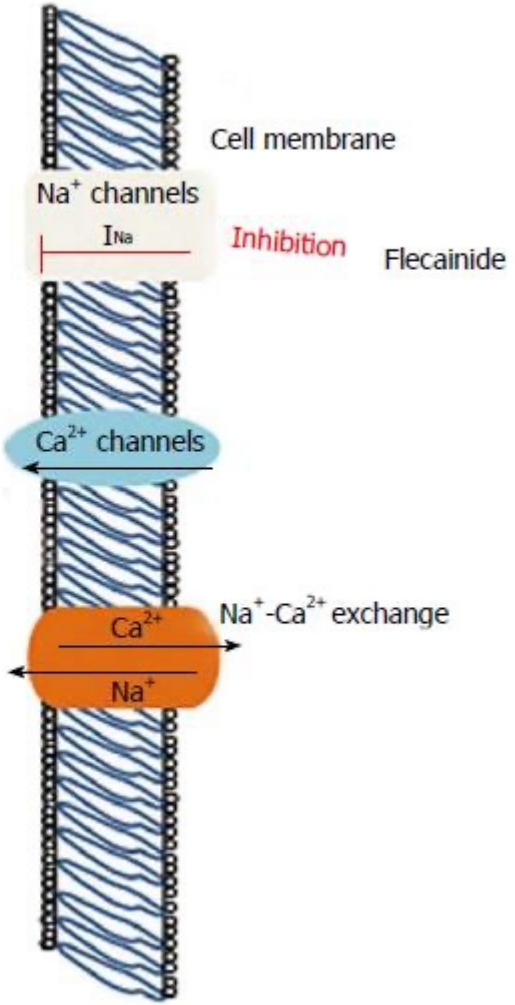
A. S. Manolis, M.D., T. F. Deering, M.D., J. Cameron, M.D., N. A. Mark Estes III, M.D.

Anti-arrhythmic drugs: subclass IC

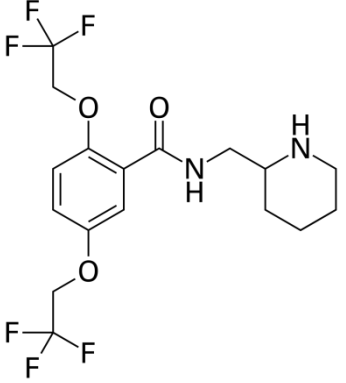
- Anti-arrhythmic drugs included in the sub-class IC produce a **potent and selective** blockade of the open rapid Na^+ channels.

- Anti-arrhythmic drugs included in the sub-class IC **have no effect** on the effective refractory period.

- Flecainide and propafenone are first-line drugs for most of the arrhythmias.



Flecainide



- Flecainide was synthesized in 1972 and approved by the FDA in 1984.

- Flecainide is recommended as one of the first line therapies for **pharmacological conversion as well as maintenance of sinus rhythm** in patients with atrial fibrillation and/or supraventricular tachycardias.

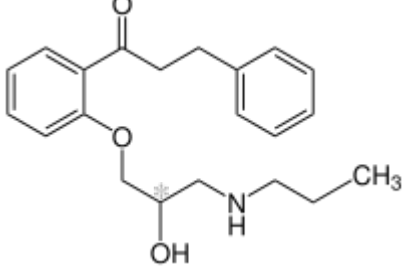
- Flecainide may cause severe exacerbation of arrhythmia. Flecainide may interact with cimetidine, fluconazole, certain HIV protease inhibitors (such as ritonavir, tipranavir), anticonvulsant drugs (such as phenytoin, phenobarbital), among others.

Br. J. clin. Pharmac. (1986), **22**, 108–110

Altered pharmacokinetics of oral flecainide by cimetidine

T. B. TJANDRA-MAGA, A. VAN HECKEN, P. VAN MELLE, R. VERBESSELT & P. J. DE SCHEPPER
Division of Clinical Pharmacology, K.U. Leuven, University Hospital Gasthuisberg (O & N) B-3000 Leuven, Belgium

Propafenone



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

❑ Propafenone is useful for the treatment of **supraventricular arrhythmias and life-threatening ventricular arrhythmias in the absence of structural heart disease**.

❑ Propafenone has pro-arrhythmic effects. The other side effects (neurological and gastrointestinal mainly) are usually well tolerated and often resolve with continued therapy or dosage reduction. Propafenone can cause a lupus-like facial rash, and also a condition called exanthematous pustulosis, which is a nasty rash accompanied by fever and a high white-blood-cell count. Numerous drug-drug interactions have been reported with propafenone.

Br. J. clin. Pharmac. (1987), **24**, 213–220

Drug interaction between propafenone and metoprolol

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Interaction Between Propranolol and Propafenone in Healthy Volunteers

Peter Russell Kowey, MD, Edward B. Kirsten, PhD, Chau-Hwei J. Fu, PhD, William D. Mason, PhD

Interaction between warfarin and propafenone in healthy volunteer subjects

The effect of propafenone on the pharmacokinetics and pharmacologic effects of warfarin was studied in healthy normal male volunteer subjects. Each drug was administered alone for 1 week followed by a combined administration for 1 additional week. Blood samples were analyzed for propafenone and warfarin concentrations and the effect of each treatment on the prothrombin time was assessed. The concurrent administration of warfarin did not produce any changes in the absorption or disposition kinetics of propafenone. Concurrent propafenone administration did lead to a reduction in the clearance of warfarin, resulting in an average increase of 38% in the mean steady-state plasma warfarin concentration. During the combined therapy phase, the prothrombin time increased significantly ($P < 0.01$) from the "warfarin alone" phase. We conclude from this study that the concomitant administration of propafenone and warfarin may lead to an enhanced anticoagulant effect that may require a reduction in the warfarin dose. (CLIN PHARMACOL THER 1987;42:305-11.)

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Anti-arrhythmic drugs class II: β-blockers

Agent	Mechanism of Action	Therapeutic use
Non-selective β-adrenergic antagonists (*first generation*):		
Propranolol	Equal affinity for β1 and β2. Membrane stabilizing effect.	Used for: hypertension, angina, supraventricular arrhythmia, ventricular arrhythmia, MI.
Nadolol	Equal affinity for β1 and β2. No sympathomimetic or membrane stabilizing activity.	Used for: Hypertension, angina, LQTS.
Timolol	Equal affinity for β1 and β2. No sympathomimetic or membrane stabilizing activity.	Hypertension, congestive HF, acute MI.
β_1-selective adrenergic antagonists (*second generation*):		
Metoprolol	No sympathomimetic or membrane stabilizing activity.	Used for: essential hypertension, angina, tachycardia, HF, vasovagal syncope, secondary prevention after MI
Atenolol	No sympathomimetic or membrane stabilizing activity.	Used for: hypertension, coronary heart disease, arrhythmias, angina, reduces risk of complications after MI
Esmolol	Little sympathomimetic activity, no membrane-stabilizing activity.	Used when short duration is desired or in critically ill patients where rapid withdrawal may be necessary.
Acebutolol	Some sympathomimetic and membrane stabilizing activity.	Used for hypertension, atrial and ventricular arrhythmias, acute MI in high-risk patients
Bisoprolol	No sympathomimetic or membrane stabilizing activity. Higher degree of β1 selectivity than metoprolol or atenolol.	Used for: HF, hypertension, MI, arrhythmias
β-adrenergic antagonists with additional cardiovascular effects (***third generation*** *- also possess vasodilatory actions*)		
Labetalol	Competitive antagonist to α1 and β receptors (β1 and β2). Partial agonist activity at β2 and also inhibits neuronal uptake of NE (cocaine-like).	Used for chronic hypertension or hypertensive emergencies
Carvedilol	Blocks α1, β1, and β2 similar to labetalol, but also has anti-oxidant and anti-inflammatory properties. Has membrane-stabilizing action, but no sympathomimetic activity.	Produces vasodilation and anti-inflammatory effects may help treatment of HF. Approved for use in hypertension, congestive HF, and LV dysfunction after MI
Celiprolol	β1 antagonist. β2 partial agonist. Also α2 antagonist and promotes NO production.	Reduces HR and blood pressure. Used to treat hypertension and angina
Nebivolol	β1 antagonist with endothelial NO-mediated vasodilatory action.	Also has antioxidant action and neutral or favorable effects on carbohydrate and lipid metabolism. Approved for the treatment of hypertension

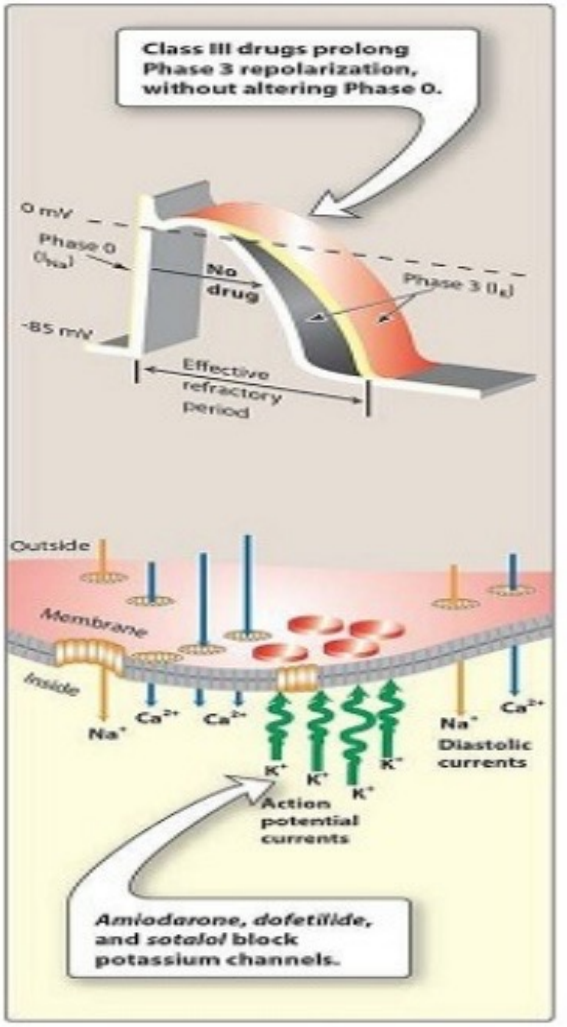
Features of β-blockers

- In both the SA and AV nodes, β-blockers slow the spontaneous firing rate by decreasing the slope of phase 4 and increasing the effective refractory period of the cardiac action potential;
- β-blockers have little effect on SA nodal conduction in normal individuals but they can markedly prolong SA nodal conduction in patients with intrinsic SA nodal disease;
- β-blockers can help to prevent the formation of reentrant arrhythmias in myocardium that has been damaged by ischemia;
- β-blockers depress the catecholamine-stimulated automaticity.

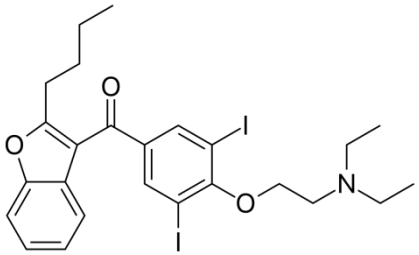
Anti-arrhythmic drugs class III: Agents that block K^+ channels and prolong repolarization

- Anti-arrhythmic drugs included in the class III block the K^+ channels that mediate repolarization, and thus increase the effective refractory period.

- Dronedarone and sotalol are first-line drugs for most of the arrhythmias.



Amiodarone



- Amiodarone is an iodine-containing benzofuran derivative.

- Intravenous amiodarone has been used to treat a wide range of arrhythmias, particularly in the post-operative period. Oral amiodarone is effective in most forms of **supraventricular and ventricular tachycardia** with its use limited by the frequency and severity of its adverse effects.

- The most significant adverse effects include thyroid dysfunction (hypo or hyper), chemical hepatitis, worsening sinus node dysfunction, and pulmonary fibrosis.

- Amiodarone inhibits hepatic metabolism, but it can also affect the bioavailability, protein binding and renal excretion of several clinically important coadministered drugs.

Drug interactions with amiodarone

There are a number of important drug interactions with amiodarone. This agent appears to have a marked effect on the kinetics of some commonly used cardiovascular drugs, such as warfarin, digoxin, quinidine, and procainamide, and has dynamic interactions with others, such as the beta blockers and some calcium antagonists. Bleeding has been reported, apparently caused by a potentiation of the anticoagulant effect of warfarin by amiodarone. *Torsades de pointes* has been observed when quinidine, propafenone, or mexiletine is given together with amiodarone. Furthermore, amiodarone may interact with beta-blocking agents and some of the calcium antagonists to produce symptomatic sinus bradycardia and sinus arrest, especially in a latent or overt sick sinus syndrome. During surgery, amiodarone may induce hypotension and an atropine-resistant bradycardia, possibly by interacting with anesthetic agents. A knowledge of the time of onset, extent, duration, and possible mechanisms of the interactions of amiodarone with other cardioactive drugs is still incomplete, but further studies are of great therapeutic importance. (Am Heart J 106:924, 1983.)

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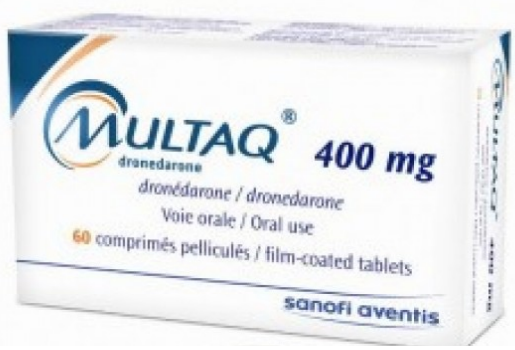
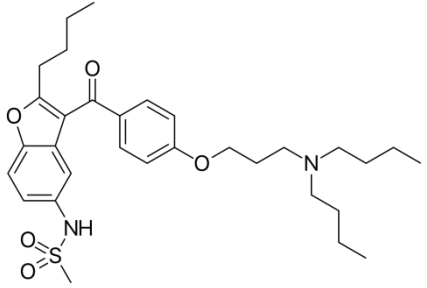


Dronedarone



❑ Dronedarone is a close analogue of amiodarone, but since it lacks the iodine moieties, dronedarone has fewer toxic effects on the thyroid and other organs. For these reasons, dronedarone is a first-line drug for several arrhythmias.

❑ Dronedarone was developed to treat **atrial fibrillation** and then started to be used as an antiarrhythmic drug.

❑ The most common side effects of dronedarone are gastrointestinal (diarrhea, nausea, abdominal pain, vomiting) and weakness.

❑ Dronedarone has fewer drug interactions comparing with amiodarone. Concomitant use with CYP3A4 inhibitors should be avoided (ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, nefazodone, verapamil, diltiazem & grapefruit juice).

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Dronedarone: una reale innovazione o solo una valida seconda scelta? Come districarsi tra linee guida, agenzie regolatorie e pratica clinica quotidiana

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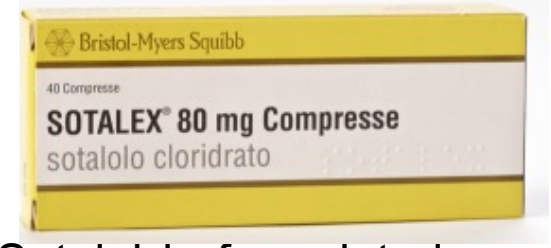
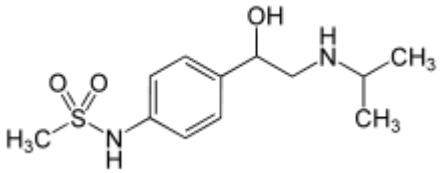


Sotalol



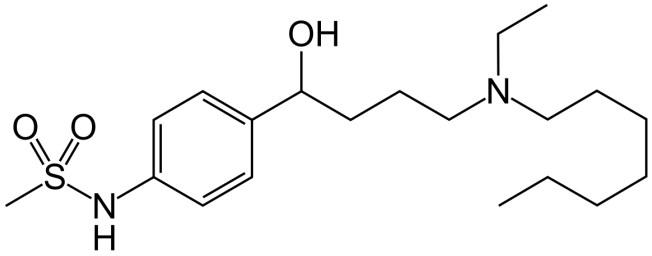
❑ Sotalol is formulated as a racemic mixture of d- and l-sotalol, because the l-isomer has β-blocking activity, whereas both the d- and l-isomers share action potential prolonging effects.

❑ Sotalol is approved for the treatment of **significant ventricular and supraventricular arrhythmias** but can be useful for treating all types of tachyarrhythmias. Sotalol can be usefull for the **maintenance of sinus rhythm in patients with atrial fibrillation**. It is also approved for treatment of supraventricular and ventricular arrhythmias in the pediatric age group. The drug is generally considered more effective than Class IA drugs but not as effective as amiodarone, although considered a first-line drug.

❑ Side effects include those attributed to both noncardioselective β-blockade and pro-arrhythmia. Other adverse effects of sotalol include, in decreasing order of frequency, fatigue, dyspnea, chest pain, headache, gastrointestinal disturbances (nausea and vomiting).

❑ Sotalol may interact with IA and other class III antiarrhythmic drugs, antacids, clonidine, diuretics, drugs prolonging the QT interval.

Ibutilide

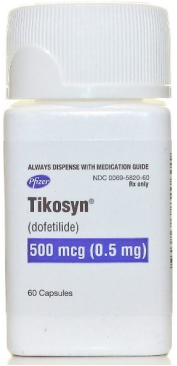


❑ Ibutilide is a new Class III antiarrhythmic agent, structurally analog of sotalol.

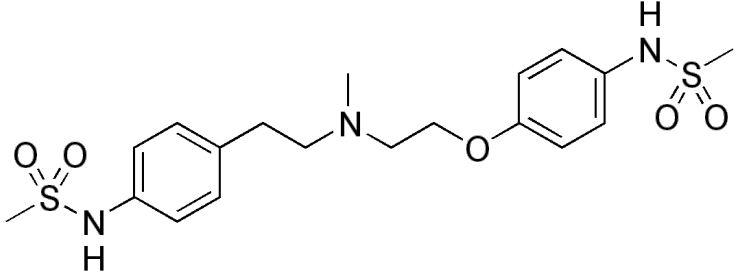
❑ Ibutilide is approved for intravenous chemical cardioversion of **recent onset atrial fibrillation and atrial flutter** in adults.

❑ The major adverse effect of ibutilide is its propensity to cause Torsades de pointes due to QT prolongation occurring in approximately 4% of adult patients, usually within 40 minutes of initiating the infusion.

❑ No specific drug interaction studies have been performed. Concomitant β-receptor or calcium channel antagonists apparently do not interact, although **data are limited** (Clinical Pharmacology of Antiarrhythmic Drugs. Raymond L. Woosley, Farshad Shirazi, in Cardiovascular Therapeutics (Third Edition), 2007).



Dofetilide



- Dofetilide is a “pure” class III drug.

- Dofetilide is approved for the maintenance/restoration of **normal sinus rhythm in patients with atrial fibrillation**.

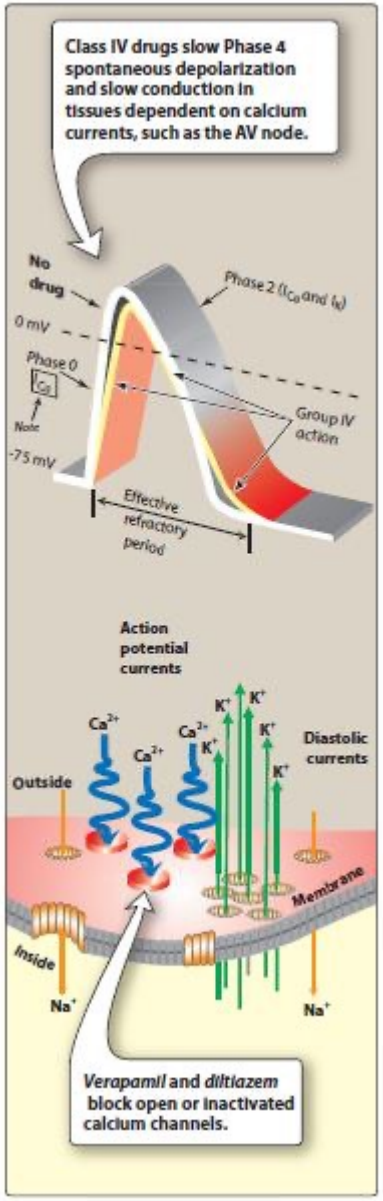
- The principal cardiac adverse effect is the risk of Torsades de pointes due to QT prolongation, which is approximately 3% in adult trials. Most pro-arrhythmic events are observed in the first 3 days. Dofetilide has been reported to cause occasional noncardiac symptoms, including headache, gastrointestinal disturbances, sleep disorders, and flulike symptoms.

- Concomitant use with CYP3A4 inhibitors should be avoided (ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, nefazodone, verapamil, diltiazem, and grapefruit juice).

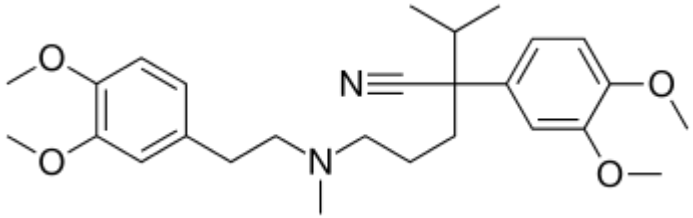
Anti-arrhythmic drugs class IV: Agents that block the slow inward Ca^{++} current

- Many Ca^{++}-blocking agents have been developed, but only two are commonly used (and have been approved) for the treatment of cardiac arrhythmias: **verapamil and diltiazem**.

- Verapamil and diltiazem both block the slow inward Ca^{++} current (L-type calcium channel). The administration of class IV drugs slows conduction velocity and increases the effective refractory period.



Verapamil



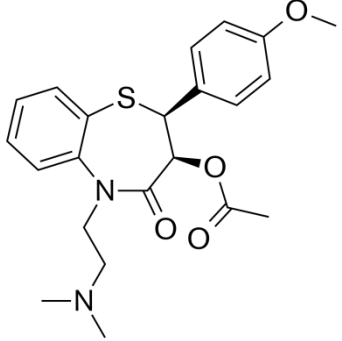
- Verapamil has a structure similar to that of papaverine.

- Verapamil is useful for slowing the ventricular response to **atrial tachyarrhythmias**. Verapamil is also effective in ectopic atrial tachycardia and supraventricular tachycardia. Finally, verapamil causes peripheral vasodilation, which may be beneficial in hypertension and peripheral vasospastic disorders.

- Orally administered verapamil is well tolerated by the majority of patients. Most complaints are with respect to gastrointestinal side effects (constipation and gastric discomfort). Other complaints include vertigo, headache, nervousness, and pruritus.

- Concomitant use with CYP3A4 inhibitors should be avoided (ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, nefazodone, diltiazem, and grapefruit juice).

Diltiazem



❑ Diltiazem is a benzothiazepine derivative that shares electrophysiological effect and clinical uses of verapamil.

❑ Diltiazem appears to be similar in efficacy to verapamil in the management of **atrial arrhythmias**.

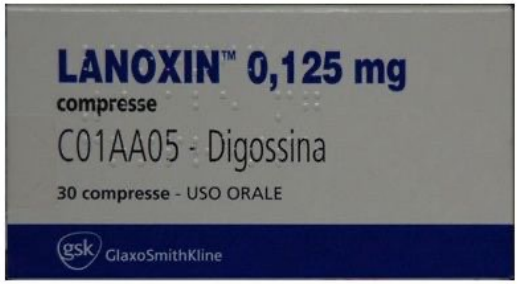
❑ The adverse effects are similar to verapamil with a lower incidence of ventricular depression.

❑ Diltiazem is extensively metabolized through the CYP450 system. For this reason, concomitant use with CYP450 inhibitors may increase diltiazem concentrations leading to adverse effects even at clinically recommended doses.

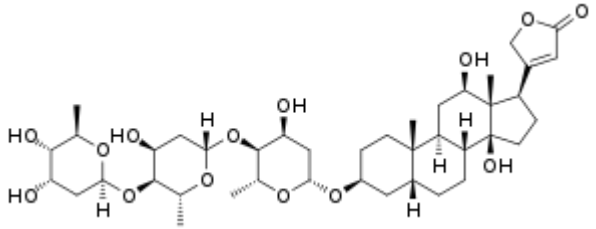
Miscellaneous anti-arrhythmic agents

❑ Certain agents used for the treatment of arrhythmias do not fit the conventional class 1–4 organization. These include:

1) Digoxin,
2) adenosine,
3) magnesium.



Digoxin



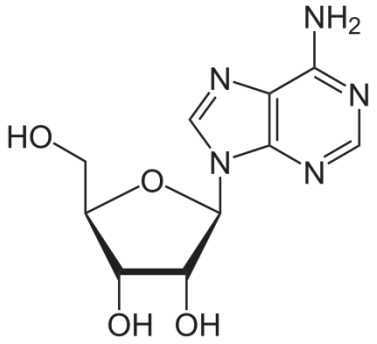
❑ Digitalis glycosides, especially digoxin, have been used in clinical medicine since the 1700s.

❑ The clinical utility of digoxin is twofold. First, it increases intracellular Ca^{++} during muscle contraction, thus increasing inotropy. Second, digoxin inhibits the membrane-bound Na^{+}-K^{+} ATPase enzyme.

❑ Since digoxin slows the conduction through the AV node, it can be administered for **significant ventricular arrhythmias.**

❑ Digoxin has a narrow therapeutical window and potentially life-threatening cardiac adverse effects. Gastrointestinal disorders (nausea, vomiting, anorexia, diarrhea, and cramps), neuropsychological disorders (visual disturbances, restlessness, and delirium), and bradycardia are warning signs. Some drug combinations can aggravate the cardiac adverse effects of digoxin, or reduce its efficacy (cholestyramine, antacid gels, kaolin-pectate, certain antimicrobial drugs and cancer chemotherapeutic agents).

Adenosine



- The nucleoside adenosine can activate the inward rectifier K^+ current and inhibit the Ca^{++} current.

- Intravenous adenosine is useful for the acute termination of supraventricular tachycardia that utilizes the AV node. Adenosine is also helpful for the diagnosis of narrow complex tachycardias by unmasking, such as atrial flutter and ectopic atrial tachycardia.

- Adverse reactions to the administration of adenosine are not uncommon; however, the short half-life of the drug limits the duration of such events.

- There are a few significant drug interactions with adenosine, in particular with dipyridamole (including combination preparations with aspirin), carbamazepine (which increases the action of adenosine), methylxanthine compounds (theophylline and caffeine).

Magnesium Sulfate

❑ Originally used for patients with digitalis-induced arrhythmias who were hypomagnesemic, magnesium infusion has been found to have antiarrhythmic effects in some patients with normal serum magnesium levels.

❑ The precise mechanism by which magnesium can ameliorate arrhythmias has not been established. Functionally, magnesium is required for the membrane-bound Na+/K+ ATPase, which is the principal enzyme that maintains normal intracellular potassium concentration.

❑ Magnesium sulfate can be administered orally, intramuscularly, or intravenously, when a rapid response is needed.

❑ The most well-established use of magnesium is in the therapy of Torsades de pointes.

❑ For the acute treatment of cardiac arrhythmias, the administration of intravenous magnesium has proven very safe. There is some potential of pushing magnesium levels into the toxic range in the presence of severe renal failure, but the overall risk of doing so is low.