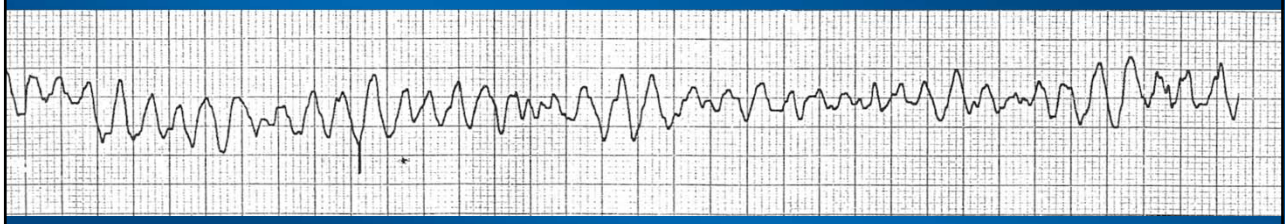
Antiarrhythmic Agents



MEDICINE of THE HIGHEST ORDER

UR MEDICINE

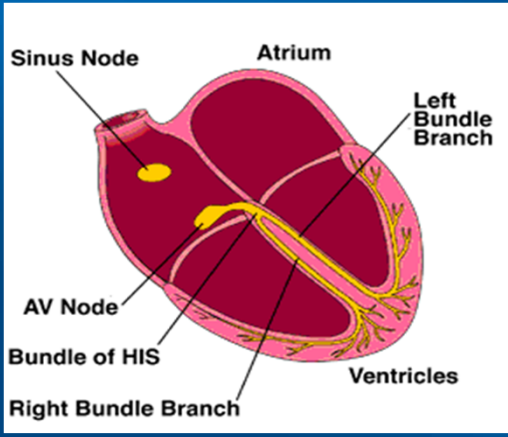
Objectives

- Describe indications of, and mechanism of action for, the various classes of antiarrhythmic dugs
- Describe adverse reactions, precautions, and contraindications of antiarrhythmic agents
- Discuss considerations when choosing an antiarrhythmic to treat supraventricular and ventricular tachyarrhythmias

MEDICINE of THE HIGHEST ORDER

UR MEDICINE

Electrical conduction



Pacemaker cells
- Possess automaticity
- SA node, AV node, and ventricular conduction system (bundle of His, bundle branches, and Purkinje fibers)

•Non-pacemaker cells
- Do not possess automaticity (normally)
- Atrial and ventricular myocytes

Action Potentials

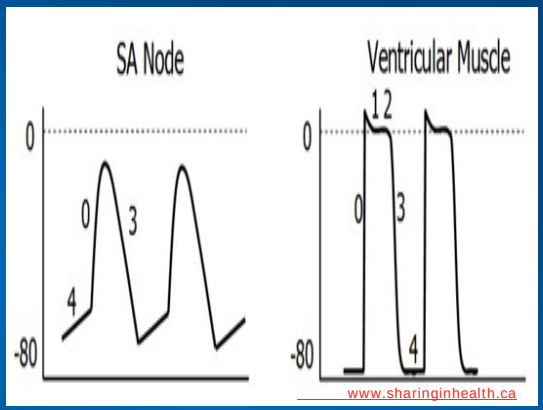
Phase 0=rapid depolarization

Phase 1= early repolarization

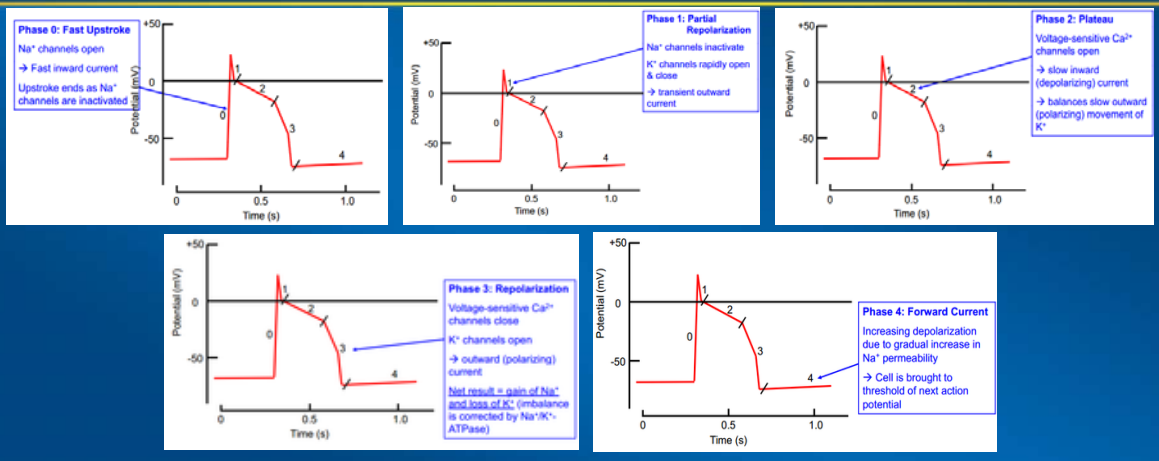
Phase 2= plateau phase

Phase 3= rapid repolarization

Phase 4= resting phase



Ion Channels



Images: Quizlet.com

Electrical dysfunction

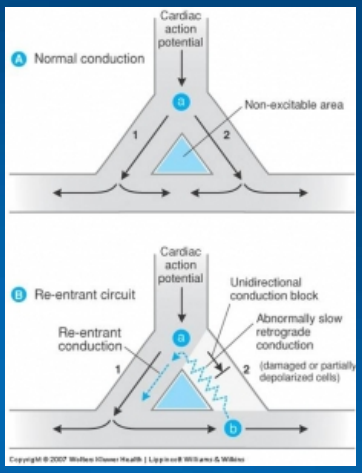
1) **Abnormal impulse formation**
   - **Impaired or enhanced automaticity of the SA node**
   - **Ectopic beats**
2) Impulse conduction defects
   - Conduction Blocks
   - Re-entry
   - Accessory Tract Pathways
3) Triggered activity
   - A normal action potential "triggers" abnormal depolarizations

Electrical dysfunction

1) Abnormal impulse formation
   - Impaired or enhanced automaticity of the SA node
   - Ectopic beats
2) **Impulse conduction defects**
   - **Conduction Blocks**
   - **Re-entry**
   - **Accessory Tract Pathways**
3) Triggered activity
   - A normal action potential "triggers" abnormal depolarizations

Re-entry

Mechanism responsible for the majority of arrhythmias
- *Atrial fibrillation*
- *Atrial flutter*
- *Atrioventricular nodal reentrant tachycardia (AVNRT)*
- *AV re-entrant tachycardia (AVRT)*
- *Ventricular tachycardia (after MI, with presence of scar)*
- *Ventricular fibrillation*

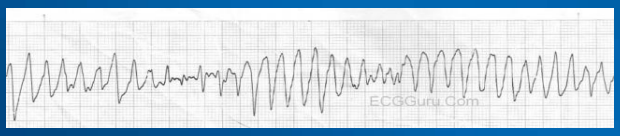


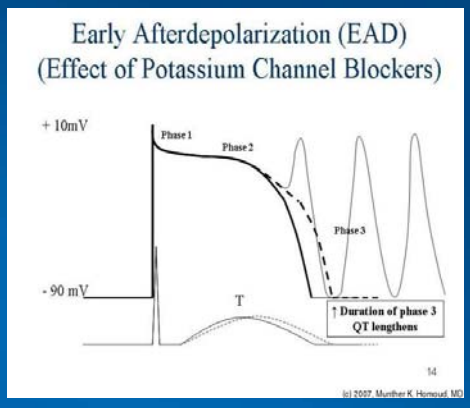
Electrical dysfunction

1) Abnormal impulse formation
   - Impaired or enhanced automaticity of the SA node
   - Ectopic beats
2) Impulse conduction defects
   - Conduction Blocks
   - Re-entry
   - Accessory Tract Pathways
3) **Triggered activity**
   - **A normal action potential "triggers" abnormal depolarizations**

Triggered Activity

- Sustained (early) afterdepolarizations can lead to Torsade de Pointe





MEDICINE of THE HIGHEST ORDER
UR MEDICINE

Vaughn-Williams Classification

Class I (1A, 1B and 1C): Na+ Channel Blockers

Class II: Beta Blockers

Class III: K+ Channel Blockers

Class IV: Ca+ Channel Blockers

{And (Class V): Others}

Anti-Arrhythmics Classified by Cardiac Tissue on which they Act

Cardiac Tissue	Antiarrhythmic
SA Node	β-blockers (II), calcium-channel blockers (IV) & digoxin
AV Node	Class IC, calcium-channel blockers (IV), β-blockers (II) & digoxin
Atria	Class's IA & IC, K^+ channels blockers (III) & β-blockers (II)
Ventricles	Na^+ channel blockers (I) & K^+ channel blockers (III)
Accessory Pathways	Class IA & K^+ channel blockers (III)

99

Image: Quizlet.com

MEDICINE of THE HIGHEST ORDER

UR MEDICINE

Beta Blockers (Class II)

- Decrease automaticity by decreasing slope of phase 4 depolarization and by inhibiting sympathetic stimulation of receptors in the SA and AV node
- Prolong repolarization which decreases incidence of re-entry

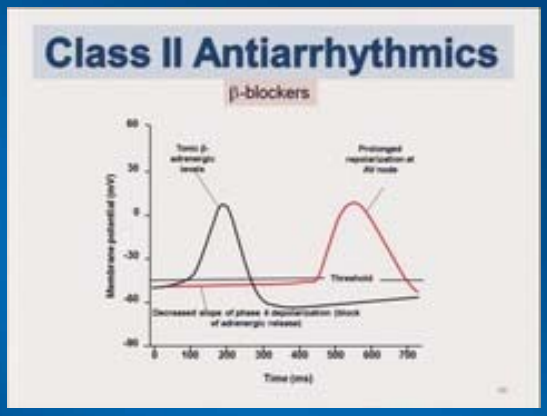


Image: quizlet.com

Beta Blockers (Class II)

	Selectivity	Drugs	Lipophilicity
First Generation	Non-selective (beta-1 and beta-2)	Propranolol Nadolol	High Low
Second Generation	Relatively beta-1 selective	Atenolol Metoprolol Bisoprolol	Low Moderate Moderate
Third Generation	Beta-1 selective	Labetolol Carvedilol	Moderate High

MEDICINE of THE HIGHEST ORDER
UR MEDICINE

Beta blocker properties

Drug	Alpha blockade	Beta-1 selectivity	ISA	MSA	Lipophilicity	Usual dose*	Half life, hours*	Elimination
Acebutolol	No	Yes	Yes	Yes	Low	100 to 400 mg twice per day	3 to 4	Hepatic (primary) Renal (secondary)
Atenolol	No	Yes	No	No	Low	50 to 200 mg once daily	6 to 9	Renal
Betaxolol	No	Yes	No	Yes	Low	10 to 20 mg once daily	14 to 22	Hepatic (primary) Renal (secondary)
Bisoprolol	No	Yes	No	No	Moderate	2.5 to 20 mg once daily	9 to 12	Renal and hepatic
Carteolol	No	No	Yes	No	Low	2.5 to 5 mg once daily	6	Renal
Carvedilol	Yes	No	No	Yes	High	3.125 to 25 mg twice per day	7 to 10	Biliary (primary) Hepatic (secondary)
Esmolol	No	Yes	No	No	Low	IV only 250 to 500 micrograms/kg over one minute (loading dose); 50 micrograms/kg per minute as IV infusion; titrate incrementally up to maximum of 300 microgram/kg per minute^	9 minutes	Blood esterases
Labetalol	Yes	No	Yes ($Beta_2$)	Low	Moderate	IV 20 mg^ Orally 100-400 mg two or three times per day	3 to 4	Hepatic
Metoprolol tartrate	No	Yes	No	Low	Moderate	IV 1.25 to 5 mg^ Orally 25 to 100 mg two or three times per day	3 to 4 (7 to 9 hours in poor metabolizers)	Hepatic via CYP2D6 (polymorphic)
Metoprolol succinate (extended release)	No	Yes	No	Low	Moderate	Orally 50 to 400 mg once daily	Apparent half-life prolonged by continuous osmotic release over ~20 hours	Hepatic via CYP2D6 (polymorphic)
Nadolol	No	No	No	No	Low	40 to 160 mg once daily	20 to 24	Renal
Nebivolol	No	Yes	No	No	High	5 to 40 mg once daily	10 to 12 (19 to 32 poor metabolizers)	Hepatic
Oxprenolol~	No	No	Yes	Yes	Moderate	40 to 80 mg three times per day	1.5	Hepatic
Penbutolol	No	No	Yes	No	High	10 to 40 mg once daily	5	Hepatic
Pindolol	No	No	Yes	Low	Moderate	5 to 30 mg twice per day	3 to 4	Hepatic (primary) Renal (secondary)
Propranolol	No	No	No	Yes	High	IV 1 to 5 mg^ Orally 10 to 80 mg two to four times daily	3 to 4	Hepatic
Sotalol§	No	No	No	No	Low	80 to 160 mg twice per day	12	Renal
Timolol	No	No	No	No	Moderate	10 to 30 mg twice per day	4 to 5	Hepatic (primary) Renal (secondary)

ISA: intrinsic sympathomimetic activity; MSA: membrane stabilizing activity; IV: Intravenous.
* Range of usual, oral, anti-hypertensive dose, unless "IV" noted.
~ Half-life of active metabolite. Subsequent dosing generally needed. See drug monograph for detail.
^ Usual initial IV dose. Subsequent dosing generally needed. See drug monograph for detail.
◇ Not available in US.
§ Sotalol has independent class III antiarrhythmic activity.

Prepared with data from:
Frishman WH, Alvarshetty M. β-Adrenergic blockers in systemic hypertension pharmacokinetic considerations related to current guidelines. Clin Pharmacokinet 2002; 41:505.
Brubacher JR. β-Adrenergic Antagonists. In: Goldfrank's Toxicologic Emergencies, 9th ed, Nelson LS (Ed), McGraw-Hill, New York 2010.

UpToDate

MEDICINE of THE HIGHEST ORDER

UR MEDICINE

Calcium channel blockers (Class IV)

- Effect pacemaker cells at the SA and AV node
- Slow the rise of Phase 0
- Prolong the repolarization of AV nodal cells
- Overall effect is prolonged AV nodal conduction
- Especially useful for arrhythmias that involve re-entry through the AV node

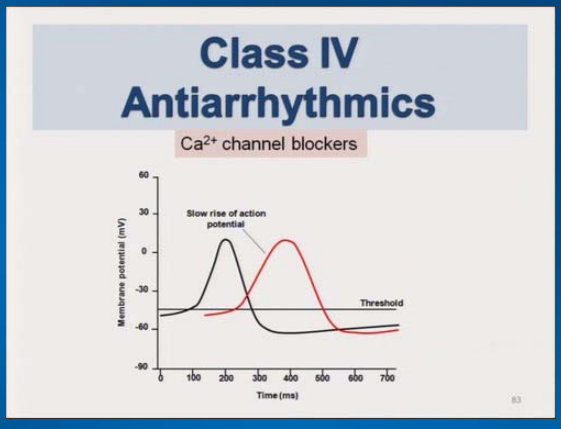


Image: Quizlet.com

MEDICINE of THE HIGHEST ORDER

UR MEDICINE

Calcium Channel Blockers (Class IV)

	Drugs	Action	Side effects / precautions
Dihydropyridines	Nefidepine Amlodipine	Greater effect on calcium channels in smooth muscle, cause vasodilation	Pedal edema
Non-dihydropyridines	Verapamil Diltiazem	Greater effect on cardiac tissues	Avoid in CHF patients Constipation

Digoxin (Other, Class V)

Cardiac glycoside
- Selective inhibitor of the plasma membrane sodium pump

Has effects on cardiac myocytes
- Overall rise in intracellular calcium concentration increases myocardial contractility

Has direct effects on conduction system in the heart
- Decreases automaticity at the AV node
- Decreases conduction velocity through the AV node

Also inhibits sympathetic output and increases vagal tone by binding to neurons in the central and peripheral nervous systems

Keep in mind:
- Narrow therapeutic window
- Digoxin toxicity
- Drug interactions

The "Real" Antiarrhythmic Agents

Class IA	Class IB	Class IC	Class III
Quinidine Procainamide Disopyramide	**Lidocaine** Mexiletine	**Flecainide** **Propafenone**	**Amiodarone** **Dronedarone** **Dofetilide** **Sotalol** Ibutilide
AF, AFL, AT, SVT, VT	VT	AF, AFL, AT, SVT, WPW, PVC's	AF, AFL, AT, SVT, VT

Class I agents

- All Class 1 (A, B, and C) agents have similar effects on the SA node action potential resulting in decreased automaticity
- The difference between classes is effect on the ventricular action potential

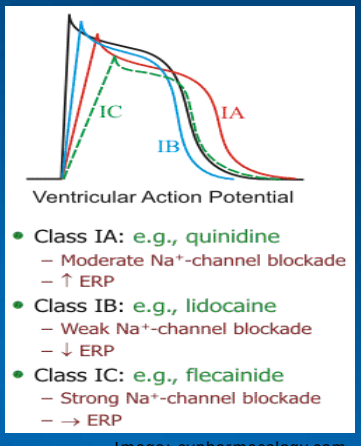


Image: cvpharmacology.com

Class IA Antiarrhythmics

Quinidine, Procainamide, Disopyramide

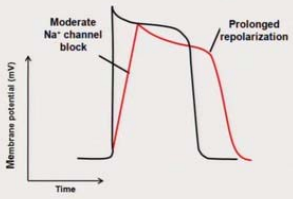


Image: Quizlet.com

- Moderate Na+ channel blockers
- Decrease conduction velocity through the myocardium
- Also block K+ channels resulting in prolonged repolarization

Quinidine (Class IA)

- Also has vagolytic effects which cause increased conduction velocity through the AV node
  - Can be dangerous in patient's with aflutter
    - Atrial firing rate decreases due to class I decreased conduction velocity through the myocardium BUT increases AV nodal conduction can encourage 1:1 A:V ratio
    - Should be used with an AV nodal blocker
  - *Used infrequently, Class III agents have replaced it for treatment of Afib/Flutter*
- Side effects difficult to tolerate
  - Diarrhea, nausea, headache, dizziness, rash
  - Cinchonism=decreased hearing, tinnitus, blurred vision, delirium
- Contraindicated in patients with prolonged QT
- Increases digoxin levels
- Careful monitoring of K+ levels
  - Hypokalemia decreases efficacy, exacerbates QT prolongation and contributes to development of Torsades

Procainamide (Class IA)

- Used for supraventricular and rarely ventricular tachyarrhythmias
- Can be used safely in setting of acute MI to decrease likelihood of re-entrant rhythms
- Unlike Quinidine, has few anticholinergic effects and does not alter digoxin levels
- Hepatic metabolism results in an active metabolite (NAPA)
- Class III antiarrhythmic effects prolongs refractory period and causes QT prolongation
- Limiting side effects: (reversible) lupus-like syndrome and gi side effects
- "Procainamide Challenge"-used to unmask Brugada pattern

Disopyramide (Class IA)

- Similar to quinidine in action
- Side effects:
  - Less gi side effects that quinidine but more profound anticholinergic effects
- Contraindications:
  - Sinus node dysfunction, heart blocks
  - CHF
- Strong negative inotropic effects
  - Role in HOCM
- *Trend is toward Class III agents (and ICDs)*

Class IB Antiarrhythmics

Lidocaine, Mexiletine

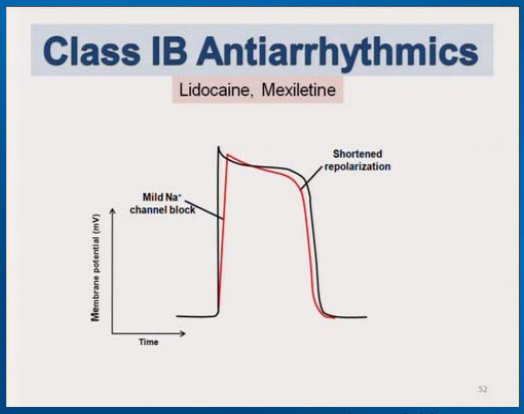


Image: Quizlet.com

- Little effect on normal cardiac tissue
- Exhibit use dependent block in diseased myocardium
- Do not prolong QT

Lidocaine (Class IB)

- Used for freq PVCs or VT/VF that causes hemodynamic compromise (IV)
- Can be used in combination with amiodarone
- Short half-life (20 min)
- CNS effects:
  - Block Na+ channels in the CNS too
  - Confusion, dizziness, seizures

Mexiletine (Class IB)

- Developed originally as anticonvulsant
- Used for VT
  - May be given with amiodarone
- Little effect on HR, BP, CO, or intracardiac pressures
- 90% metabolized in the liver
- Can be difficult to obtain

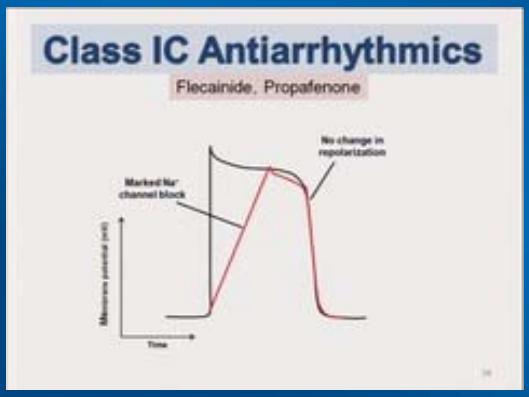


Image: Quizlet.com

- Strongest Na+ channel blockers
- Decrease rate of phase 0 upstroke in atrial and ventricular cells
- can cause widening of QRS (esp. with exercise)
- Use for atrial arrhythmias and frequent PVCs
- CAST (Cardiac Arrhythmia Suppression Trial)
  - Proarrhythmic effects in patients with pre-existing tachyarrhythmias or MI
- "Pill-in-the-pocket" or daily
- Use with an AV nodal blocker to prevent organization into 1:1 flutter (especially flecainide)

Class 1C antiarrhythmics

Flecainide

- Use with beta blocker
- 40% excreted in urine, rest metabolized by the liver
- Can have CNS effects: blurred vision, headache, ataxia

Propafenone

- Has some beta blocking properties
- Metabolized by the liver
- Side effects: nausea, dizziness, metallic taste (especially with dairy products), blurred vision, paresthesia, constipation, increased LFTs

Class III antiarrhythmics

- Potassium channel blockers
  - Dofetilide (Class III)
  - Sotalol (mixed Class II and Class III)
  - Amiodarone (mainly Class III, has properties of Class I, II, and IV antiarrhythmics too)
  - Dronedarone (mainly Class III, has properties of Class I, II, and IV antiarrhythmics too)
- Prolonged repolarization decreases the incidence of re-entry
- QT prolongation, risk of of torsades de pointes

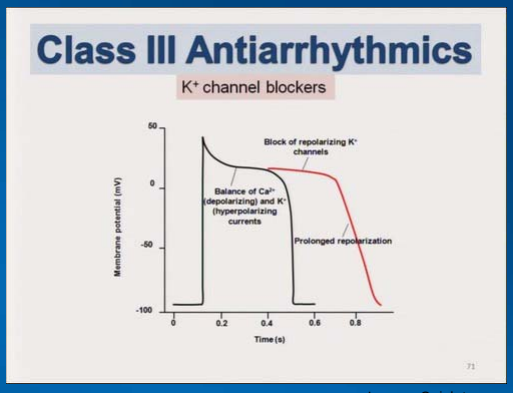


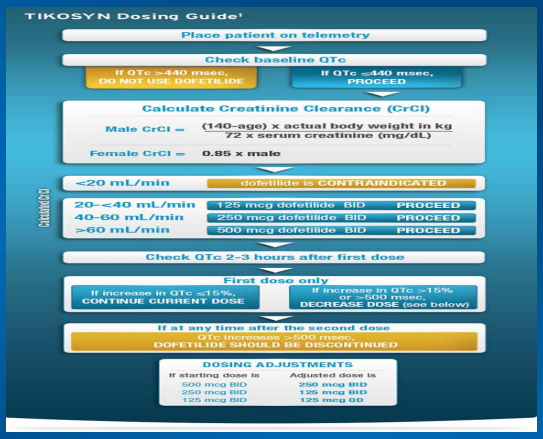
Image: Quizlet.com

MEDICINE of THE HIGHEST ORDER

UR MEDICINE

Dofetilide (Class III)

- 3 day hospitalization
- Dose adjusted
  - Kidney function
  - QTc
- Must be a registered provider



www1.pfizerpro.com

Measuring the corrected QT (QTc)

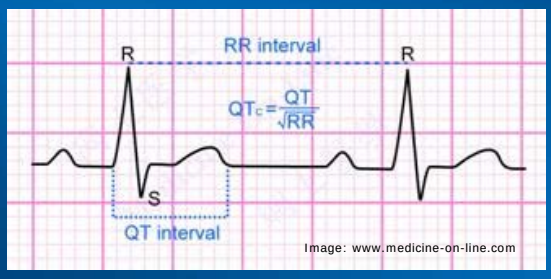


Image: www.medicine-on-line.com

QT= 0.32 sec (320 msec)
RR= 0.8 sec (800 msec, 75 bpm)
QTc= 0.358 (358 msec)

QT intervals vary with heart rate

Normal QTc:

- *adult men </=440 msec*
- *adult women </=460 msec*

QTc >500 msec highly abnormal for men and women

Dofetilide (Class III)

- Ongoing surveillance monitoring as an outpatient for QTc and kidney function/electrolytes
- Risk of Torsade due to QT prolongation
- Multiple drug interactions

Drug Contraindications:

- **HCTZ (alone or in combination drugs)**
- **Verapamil**
- Cimetidine
- Ketoconazole
- Trimethoprim
- Prochlorperazine
- Megestrol
- Dolutegravir

Also:

- Macrolide and fluoroquinolone antibiotics
- Anti-depressants

Sotalol (Mixed Class II and Class III)

- Non-selectively antagonizes Beta-adrenergic receptors (Class II action)
  - can cause significant bradycardia and hypotension
- K+ channel blocker (Class III action)
- Used to treat atrial and ventricular arrhythmias
- Started either in hospital setting or with close EKG monitoring as an outpatient (for QTc monitoring)
- Renally excreted, may require dose adjustment based on kidney function

Amiodarone

- Mainly a Class III agent but also acts as a class I, II, and IV agent
  - K+ channel blocker (Class III): lengthens refractory period in all cardiac tissues (which decreases re-entry)
  - Na+ channel blocker (Class I): decreases rate of firing in pacemaker cells
  - Alpha and beta blocker (Class II): inhibits sympathetic stimulation
  - Ca++ channel blocker (Class IV): AV node blockade/bradycardia
- Diverse effects attributed to ability to alter the lipid membrane where ion channels and receptors are located
- Onset of action with oral amiodarone takes 2-3 days
- Elimination half-life 25 to 100 days

Type and incidence of major side effects associated with amiodarone therapy

Side effect	Incidence, percent
Lung	
Cough, especially with infiltrates on chest radiography and reduced DLCO	5 to 15 (>400 mg/day) 1 to 2 (≤400 mg/day)
Thyroid	
Hypothyroidism and hyperthyroidism	2 to 24 3 to 4 (≤400 mg/day)
Heart	
Bradycardia and atrioventricular block	3 to 5
Proarrhythmia	<1
Liver	
Serum AST or ALT more than two times normal	15 to 50 1 to 2 (≤400 mg/day)
Hepatitis and cirrhosis	<3
Eye	
Corneal microdeposits	>90
Halo vision, especially at night	<5
Optic neuritis	1
Skin	
Photosensitivity	25 to 75
Blue discoloration	<10
Gastrointestinal tract	
Nausea, anorexia, and constipation	30 4 to 5 (≤400 mg/day)
Central nervous system	
Varied manifestations including ataxia, paresthesias, peripheral neuropathy, sleep disturbance, impaired memory, and tremor	3 to 30 4 to 5 (≤400 mg/day)
Genitourinary tract	
Epididymitis and erectile dysfunction	<1

Data from Goldschlager, N, Epstein, AE, Naccarelli, G, et al. Practical guidelines for clinicians who treat patients with amiodarone. Practice Guidelines Subcommittee, North American Society of Pacing and Electrophysiology. Arch Intern Med 2000; 160:1741; Vorperian, VR, Havighurst, TC, Miller, S, et al. Adverse effects of low dose amiodarone: A meta-analysis. J Am Coll Cardiol 1997; 30:791; and Harjai, KJ, Licata, AA. Effects of amiodarone on thyroid function. Ann Intern Med 1997; 126:63.

UpToDate

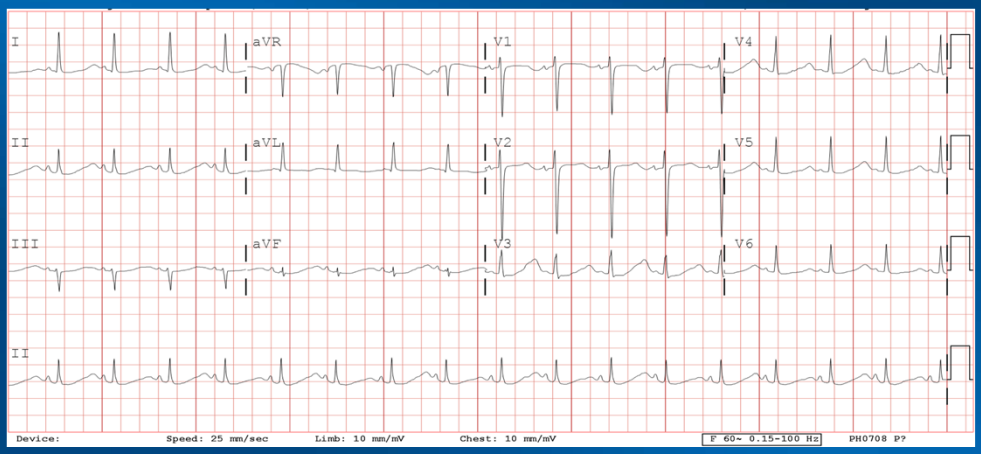
Amiodarone

- Diverse side effects
- Ongoing monitoring:
  - LFTs
  - TFTs
  - Annual eye exam
  - PFTs
- Little correlation between plasma concentration and drug efficacy or toxicity
- Can be used safely in patients with CHF and post MI
- Warfarin dose will likely need to be reduced

MEDICINE of THE HIGHEST ORDER

UR MEDICINE

Amiodarone QT prolongation



Dronederone

- Derivative of amiodarone
- Class III agent, also has Class I, II and IV actions
- Less lipophilic, less associated toxicities
- Half-life about 24 hours (amiodarone=up to 50 days)
- Hepatic metabolism

Dronedarone

- ANDROMEDA Trial, 2012 meta-analysis
- **Contraindicated in patients with CHF**
- **Associated liver injury**
- Should not be used as a rate controlling agent
- Only rarely effective for the chemical cardioversion of AF or atrial flutter to sinus rhythm

Dronedarone

- Monitoring:
  - Baseline LFTs and then within 6 months, then yearly
  - Yearly ECG
- Drug interactions:
  - Avoid CYP3A4 inhibitors (ketoconazole, macrolide antibiotics, also grapefruit juice)
  - Diltiazem, Digoxin, statins require dose adjustment
  - Warfarin may require dose adjustment, not as significant as with amiodarone
- Common side effects:
  - crampy abdominal pain, diarrhea, nausea, and rash.

AAD	Arrhythmia	Outpatient Initiation	Monitoring	Adjustments
Class IC – Na channel blockers				
Flecainide *Tambocor*	AF/AFL, AT, PVC's, WPW	Yes	ETT CAD	D/C in CAD and structural heart disease Add AV nodal blocker
Propafenone *Rythmol (SR)*	AF/AFL, AT, PVC's	Yes	ETT CAD	D/C in CAD and structural heart disease Add AV nodal blocker ⇓ warfarin clearance
Class III – K channel blockers				
Amiodarone *Cordarone* *Pacerone*	SVT, VT	Yes	LFT, PFT, TFT Yearly eye exam QT	Use lowest effective dose ⇓warfarin dose Halve digoxin
Sotalol *Betapace*	AF/AFL, VT	No	CrCl QT	⇓ Dose in renal dysfunction
Dronedarone *Multaq*	AF/AFL	Yes	LFT Heart Failure	Avoid as rate control drug D/C if recent CHF
Dofetilide *Tikosyn*	AF/AFL, PVC's	No	QT CrCl Electrolytes	Dose adjust according to protocol

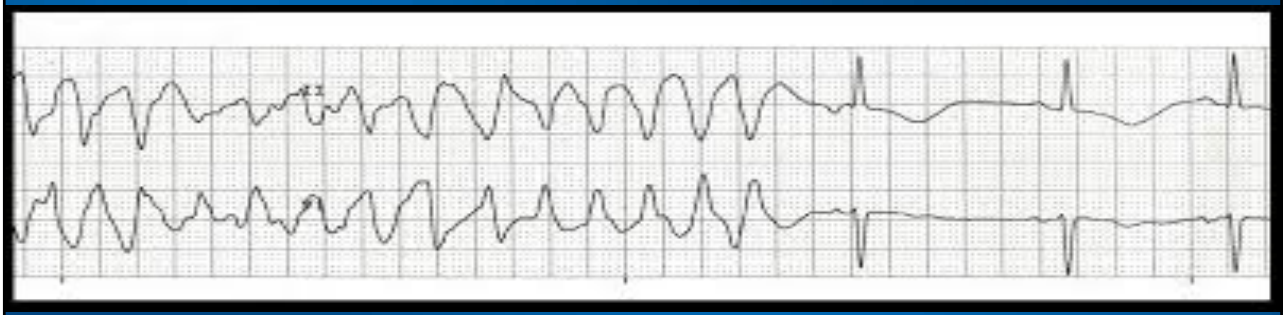
Summary

- **Goal of antiarrhythmic agents:**
  - To restore and maintain sinus rhythm without development of worse conduction or rhythm disturbances
- **Achieved by:**
  - Suppressing enhanced automaticity
  - Decreasing conduction velocity
  - Changing the effective refractory period to suppress re-entry

Remember….”Some Block Potassium Channels”

Class I	“**S**ome”	**S**odium Channel Blockers
Class II	“**B**lock”	**B**eta-Blockers
Class III	“**P**otassium”	**P**otassium Channel Blockers
Class IV	“**C**hannels”	**C**alcium Channel Blockers

Questions?



Kristi Filmore, NP
Dr. David Huang
URMC Electrophysiology
275-4775

MEDICINE of THE HIGHEST ORDER
UR MEDICINE

References

Blomstrom-Lundqvist et al. ACC/AHA/ESC Practice Guidelines (2003). ACC/AHA/ESC Guidelines for the Management of Patients with Supraventricular Arrhythmias-Executive Summary. doi: 10.1016/j.jack.2003.08.013

Golan, DE., Tashjian Jr., AH., Armstrong, EJ., Galanter, JM., Wang Armstrong, A., Aranout, RA., and Rose, HS. Principles of Pharmacology-The Pathophysiologic Basics of Drug Therapy. 2005 Lippincott Williams & Wilkins.

Ferri, Fred F. Practical Guide to the Care of the Medical Patient. 7th Edition. 2007. Elsevier Mosby.

Torp Pederson et al. EHRA/HRS/APHRS Expert Consesus on Ventricular Arrhythmias. Heart Rhythm, Vol 11, No 10, October 2014.

Up to Date