Antiarrhythmic Drugs (slide#1)

*** Causes of some Arrhythmias :**

1) **Torsade de Pointes** : Familial long QT interval, Drug - Induced (drugs which prolong action potential duration), 300 different mutations in at least 8 ion channel genes.
****Treatment**: K+, Drugs that decrease triggered upstrokes (β Blockers or Mg++),Drugs that decrease action potential duration (Pacemaker or isoproterenol).
2) **Short QT Syndrome**: gain function mutations in three potassium channel genes(**KCNH2, KCNQ1,** and **KCNJ2).**
3) **Chatecholaminergic Polymorphic Ventricular Tachycardia (CPVT):** mutations in **sarcoplasmic proteins** that control calcium. - Casuse stress or emotion-induced syncope.
4) **Sick Sinus Syndrome**: mutations in **HCN4** and **SCN5A**
5) **Brugada Syndrome**: loss function mutations in **SCN5A**
6) **Familial Atrial Fibrillation**: gain fucntion mutation in the potassium channel gene, **KCNQ1**.

* **Arrhythmias non-pharmacologic Therapy**: Surgery, Radiofrequency Catheter Ablation, Implantable Cardioverter- Defibrillator (ICD) and Gene therapy.

Antiarrhythmic Drugs

A)Vaughan Williams classification

1) Class IA Drugs

a) Quinidine: Antipyretic, Anti-malarial , Inhibits α and muscarinic receptors , Slows upstroke, conduction, and prolongs action potential and QRS duration.
Uses: restricted to patients with normal hearts(no failure, no ischemia), but have atrial or ventricular arrhythmias , acute severe malaria.
Side Effects: cinchonism, angioedema, diarrhea, thrombocytopenia, excessive prolongation of QT interval, slowed conduction and sudden death, increase **Digoxin** levels , increase **Warfarin** effects.
b) Procainamide: for lupus erythematosus
Acetylated Procainamide ➔ NAPA (Antiarrhythmic Drugs Class III) action.
c) Disopyramide(Na+ blocker): More anticholinergic effects but less diarrhea than quinidine.

2) Class IB Drugs

a) Lidocaine(Na+ blocker):
- Acts selectively in ischemic tissue to promote conduction & block reentry.
- More effective with K+. - Not effective in atrial arrhythmias (used in ventricular arrhythmias)

***Side Effects**: Least cardiotoxic of the class, except for hypotension with high doses due to depression of the myocardium.
***Oral analogs**:
i) Tocainide: side effects➔ CNS, GI and blood dyscrasia,
ii) Mexiletine: side effects➔CNS

b) Phenytoin:
Uses: Digitalis induced arrhythmias,Epilepsy, Arrhythmias after congenital heart surgery, Congenital prolonged QT interval.

3) Classy IC Drugs
a) Flecainide(Na + and K+ blocker):
- Effective in supra-ventricular tachycardia with normal hearts.
*__Side Effects__: Ventricular arrhythmias, CNS, and sudden death.
b)Propafenone
-Used for supra-ventricular arrhythmias.
* **Side effects**: metallic taste, constipation, and arrhythmias.

4) Classy II Drugs (β blockers)
a) Propranolol:
-Very effective, well tolerated, and documented to reduce mortality after acute myocardial infarction by reducing arrhythmias , membrane stabilization effect.
b) Esmolol (β1 selective)
- Short acting, used in intraoperative and acute arrhythmias , no membrane stabilization effect.
c) Acebutolol (β1 selective)
- Short acting, used in intraoperative and acute arrhythmias, membrane stabilization effect.

5) Class III Drugs
a) Amiodarone: given IV (Loading dose 10gm) and orally, slow kinetics (t½ 25-110 days), metabolized by **CYP3A4 enzymes**.
- Toxicity: mainly extracardiac and dose related.
-Side effects: Lung fibrosis , GI and liver, corneal deposits, photodermatitis and discoloration of the skin, increase **Digoxin** levels.
b) Sotalol:
-Used for atrial and ventricular arrhythmias.
*Sides effects: Bradycardia, Heart failure, Prolongation of QT.
c) Bretylium Tosylate:
- Originally an antihypertensive, but tolerance develops.
- Rarely used except in the prevention of ventricular fibrillation after failure of cardiversion and lidocaine.
***Side effects**: Hypotension, Parotid swelling.
d) Ibutilide
e) Dofetilide

6) Class IV Drugs (Ca++ Channel Blockers)

Verapamil and **Diltiazem**

- Used for Paroxysmal Supraventricular Tachycardia.

*Side effects: Can cause severe AV block in diseased hearts , increase **Digoxin** levels , Constipation, gastric discomfort, vertigo, headache, nervousness, pruritis.

B) Miscellaneous Drugs

1) Digoxin:

- Used in atrial arrhythmias , Vagotonic Effects, increases AV refractory period

2) Magnesium:

- Effective IV in refractory digitalis- induced ventricular arrhythmias only in hypomagnesemic patients.
- Effective in Torsade de Pointes patients even if serum Mg++ is normal.

3) Potassium salts:

- For digitalis-induced arrhythmias with hypokalemia
- Depress ectopic pacemakers and slow conduction.

4) Adenosine:

- Effective in supraventricular tachycardia, replaced verapamil.
- Less effective in the presence of adenosine receptor blockers, e.g. theophylline and caffeine.

***Side effects**: transient flushing (20%), chest tightness, AV block, headache, hypotension, nausea, and paresthesia , decreases phase 4 depolarization in SA node. decreases AV conduction, No effect on ventricles.

Table 17.1 The mechanism of action, the electrophysiological actions and clinical uses of selected antidysrhythmic drugs

		Example	Mechanism of action	Electrophysiological actions	Clinical use
Vaughan Williams classification	Class Ia	Disopyramide	Na^+ channel block	Reduced rate of depolarisation of action potential, increased ERP, decreased AV conduction	Ventricular fibrillation, especially associated with myocardial infarction
	Class Ib	Lidocaine			
	Class II	Propranolol, atenolol	β-Adrenoceptor antagonism	Slowed pacemaker activity, increased AV refractory period	Dysrhythmia prevention in myocardial infarction; paroxysmal atrial fibrillation due to sympathetic activity
	Class III	Amiodarone, sotalol	K^+ channel block	Increased action potential duration and increased ERP	Atrial fibrillation; ventricular fibrillation
	Class IV	Verapamil	Ca^{2+} channel block	Decreased APD, slowed AV conduction	Supraventricular tachycardias; atrial fibrillation
Not classified by system		Adenosine	K^+ channel activation	Slowed pacemaker activity, slowed AV conduction	Given i.v. for supraventricular tachycardias
		Digoxin	K^+ channel activation (vagal action)	Slowed AV conduction (block)	Atrial fibrillation
		Magnesium chloride	? Ca^{2+} channel block		Ventricular fibrillation; digoxin toxicity