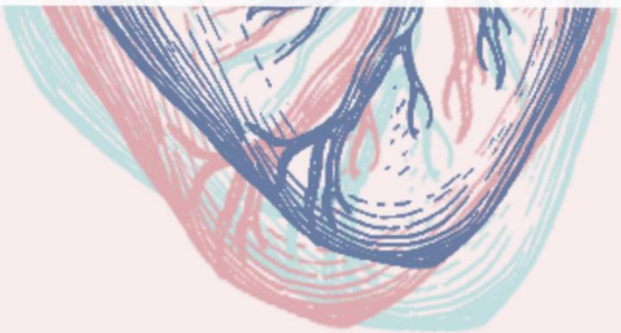
Cardio-Vascular System

5

Pharmacology



Writer: Leen Hajeer

S.corrector: Mohammad Alsayed

F.corrector: Dena Kofahi

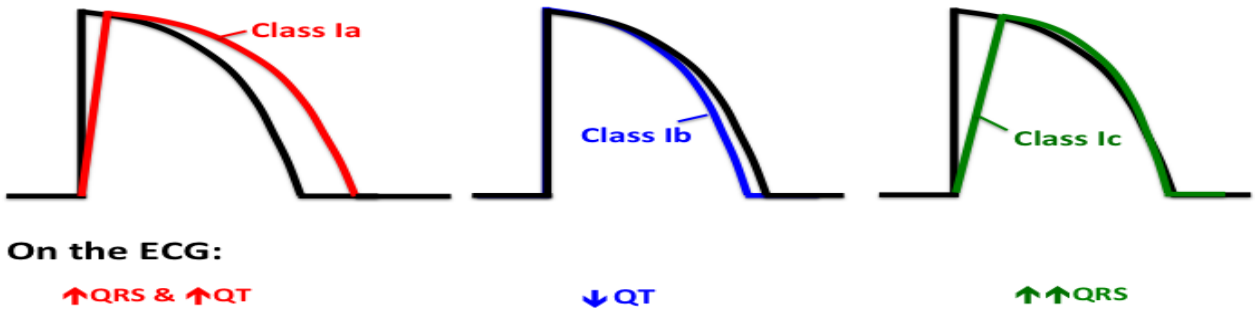
Doctor: Munir Gharaibeh

Antiarrhythmic Drugs

Last lecture we classified antiarrhythmic drugs according to their mechanism of action into four classes, now we are going to discuss drugs related to each class.

Class I: Na^+ channels blockers

They are classified according to their effects on the ventricular action potential into three subcategories:



Class 1A drugs:

Quinidine

- Prototype, related to quinine.
- Derived from the Cinchona tree, which was discovered to have antipyretic, antimalarial (Quinine), and antiarrhythmic activity (Quinidine).
- Inhibits α and muscarinic receptors. However, its antiarrhythmic activity is related to inhibition of Na channels.
- It slows upstroke and conduction and prolongs action potential duration, QRS duration and QT interval (prolongation of QT interval is dangerous and related to side effects).
- Use nowadays restricted to patients with **normal hearts** with no histopathologic abnormalities (no failure, ischemia, hypertrophy) but have **atrial or ventricular tachycardia**.

- **Side effects: Toxic**
  -Nausea (18%), Diarrhea (33%)
  -Headache, dizziness, and tinnitus = *Cinchonism*
  -Hypersensitivity, fever, rash, and angioedema
  -Thrombocytopenia
  -Excessive prolongation of QT interval, slowed conduction
  -Hypotension
  -↑Serum Digoxin levels (due to drug interaction)
  -↑ Warfarin effects
  -Sudden death (that's why the use of this drug is very limited nowadays.)

Procainamide

- Oral, but has short t½.
- Causes **Lupus Erythematosus** in 30% of patients with treatment over 6 months.
- It is acetylated into the metabolite NAPA (n-acetyl procainamide), which has Class III action (no longer class 1A).

Disopyramide

- Related to quinidine with more anticholinergic effects but less diarrhea than seen with quinidine.

Class 1B drugs:

Lidocaine (Lignocaine, or Xylcaine)

- A local anesthetic that also has antiarrhythmic activity.
- It has high affinity for binding to activated and inactivated Na+ channels with rapid kinetics.
- Acts selectively in **ischemic ventricular tissue** to promote conduction & block re-entry (its selectivity makes it an effective drug in ischemia and MI).
- More effective with ↑ K+.
- **Not effective in atrial arrhythmias**, it's mainly used for **ventricular arrhythmias**.
- It was routinely given to all MI patients to **prevent ventricular arrhythmias** because these patients usually develop ventricular arrhythmias in the early phases of MI, such as extrasystoles or ventricular tachycardia, which exacerbate the problem.

- **Kinetics:**

  -Well absorbed after oral administration but ineffective orally due to significant first pass effect in the liver, so it's given through IV.

  -Well distributed in the body after reaching systemic circulation, including to the brain (so it causes central side effects).

- **Side Effects:**

  -Least cardiotoxic of the class except for **hypotension** with high doses due to depression of the myocardium.

  -Most important side effects are **related to the CNS** which include paresthesia, tremor, nausea, slurred speech, and convulsions.

Tocainide

- Oral analog of lidocaine.

- Causes CNS and GI side effects and blood dyscrasia (so it's not a successful replacement of lidocaine).

Mexiletine

- Oral analog of lidocaine.
- Causes neurologic side effects.

Phenytoin

- Antiepileptic drug whose chemistry is not related to lidocaine and has antiarrhythmic activity.
- Used for **digitalis-induced arrhythmias** due to its selectivity for these arrhythmias. (Although digitalis is used to treat atrial arrhythmias, it can induce ventricular arrhythmias).
- Used for **arrhythmias after congenital heart surgery** (any cardiac surgery may induce cardiac arrhythmias).
- Also used for **congenital prolonged QT interval.**

Class 1C drugs:

Flecainide

- Potent blocker of Na + and K+ channels.
- It has negative inotropic effect.
- Proarrhythmic → Causes ventricular arrhythmias.
- Effective in **supraventricular tachycardia in those with normal hearts**.
- **Side Effects:** Ventricular arrhythmias, CNS effects, and sudden death.

Propafenone

- Blocks Na+ channels but also has beta blocking activity (class II) and Ca++ blocking activity (class IV).
- No effect on QT interval. 😃
- Used for **supraventricular arrhythmias**.
- **Side effects:** metallic taste, constipation, and arrhythmias.

Class II: Beta blockers

Propranolol

- The prototype of the group. It is used to treat hypertension, IHD, and it was accidentally found to have antiarrhythmic activity.

- Besides beta blocking, they have **membrane stabilizing activity** (independent of beta blockade), and **intrinsic sympathomimetic activities**.
- Very effective, well tolerated, and documented to reduce mortality after acute myocardial infarction by **reducing arrhythmias**, besides **reducing myocardial oxygen requirements.**

✓ Remember that its effect in the treatment of IHD is by reducing myocardial oxygen requirements, while its effect as an antihypertensive drug is by reducing HR, contractility and cardiac output.

Esmolol , Acebutolol

- β1 selective drugs (free of bronchospasm side effect).
- Short acting and given by IV, so they are used in **intraoperative arrythmias** and **acute arrhythmias** (general anesthesia can trigger the occurrence of cardiac arrhythmias).

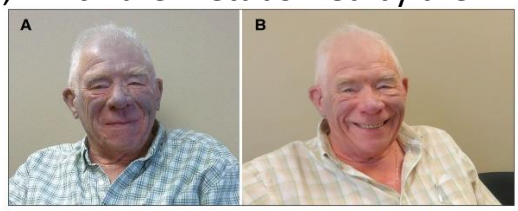
Class III: K^+ channel blockers

Amiodarone

- It's a pure antiarrhythmic drug, and not used in other conditions.
- It blocks K+ channels and markedly prolongs AP duration (the main action).
- It also has other actions: Class I actions (blocking Na+ channels), blocks α and β receptors, and blocks Ca++ channels.
- Effect is due to alteration of the lipid membranes of cardiac electrical cells.
- Reserved for life-threatening **atrial and ventricular arrhythmias** (broad spectrum).
- Slows heart rate and AV conduction.
- Low incidence of TdP (torsade de pointes) despite significant QT prolongation. (remember that TdP is caused by prolonged QT interval).
- Peripheral vasodilator (only with IV).
- It has slow kinetics and long half-life (t½ 25-110 days), thus it's given as a loading dose of 10 gm over a short period, as well as orally, then continued with oral doses.
- Metabolized by CYP3A4 enzymes, which are susceptible for many drugs and food interactions, thus this drug is highly subjected to drug interactions.

- **Toxicity:** Relatively safe drug, mainly causes extracardiac and dose related side effects (occurs only with high doses).
  -Lung fibrosis (1%) – The most serious and severe side effect, but it's reversible after stopping the drug.
  -CNS
  -Thyroid problems (hypothyroidism and hyperthyroidism) due to the presence of

iodine in its structure.
- GI and liver problems
- Corneal deposits
- Skin: photodermatitis and discoloration (blue man syndrome), reversible after stopping the treatment. (Notice the man in the figure under amiodarone treatment and after stopping the treatment).
-Drug interactions with digoxin & anticoagulants, which are metabolized by the CYP3A4 system.



Bretylium Tosylate

- Originally an antihypertensive drug that was used long ago, but tolerance developed and the blood pressure raised again to pretreatment levels, so its use was stopped.
- It works on sympathetic nerve endings and causes the release of NE, then it decreases the release and reuptake of NE.
- It's given orally.
- It was discovered to have antiarrhythmic activity, but nowadays it's rarely used except for prevention of ventricular fibrillation after failure of cardioversion and lidocaine , and repeated recurrent attacks of ventricular fibrillation persist (lidocaine is given by IV and therefore cannot be continued). Remember that ventricular fibrillation is an emergency and if it persists for a few minutes it will result in death.
- **Side effects:** Hypotension, Parotid swelling.

Sotalol

- It's a beta blocker, but it has Class III actions (K+ channel blocking).
- A broad spectrum antiarrhythmic drug used for **atrial and ventricular arrhythmias.**
- **Side effects:** bradycardia, HF, and prolongation of QT. (so amiodarone remains a better choice).

Ibutilide
Dofetilide

Newer drugs but amiodarone is still a better choice.

Class IV: Ca^{+2} channel blockers

Verapamil, Diltiazem

- They have good selectivity toward activated and inactivated L-type Ca++ channels which are responsible for phase 2 depolarization.
- As we know they are used for the treatment of hypertension, IHD, and they also have antiarrhythmic activity. DHPs (like nifedipine) are not used for this purpose because

they are potent vasodilators and elicit a baroreceptor reflex which results in stimulation of the SNS.

- The effects are more marked in tissues that fire frequently, are less completely polarized at rest, and those dependent on Ca++ (SA node and AV node), which make them effective in the treatment of atrial arrhythmias.
- Verapamil is widely used in the treatment of **Paroxysmal Supraventricular Tachycardia**, which is a common condition that affects young people, and can be due to sympathetic overactivity after stress or tension, or after giving PDE inhibitors like coffee and tea (theophylline derivatives). It usually self-terminates, but if it persists it can be managed by drugs such as verapamil and adenosine.
- They are vasodilators and have negative inotropic effects.
- Can cause severe AV block in diseased hearts.
- **Side effects:** Relatively safe, but with prolonged use they can cause constipation, gastric discomfort, vertigo, headache, nervousness, and pruritis.
- ↑ Digoxin levels. (digoxin is a very sensitive drug with low therapeutic index, and its levels are affected by many drugs interactions).

Miscellaneous drugs (unclassified)

Table 21.1 Antidysrhythmic drugs unclassified in the Vaughan Williams system

Drug	Use
Atropine	Sinus bradycardia
Adrenaline (epinephrine)	Cardiac arrest
Isoprenaline	Heart block
Digoxin	Rapid atrial fibrillation
Adenosine	Supraventricular tachycardia
Calcium chloride	Ventricular tachycardia due to hyperkalaemia
Magnesium chloride	Ventricular fibrillation, digoxin toxicity

⇒ Note that the last two drugs are normal salts which are found normally in our bodies, but reduction in calcium and magnesium levels will affect the contractility and the electrical activity of the heart.

Digoxin

- An old fashioned agent used for heart failure and atrial arrhythmias. It has been widely used for more than two centuries, but nowadays it's very narrowly used.

- It has direct actions. It causes vagotonic effects, such as SA suppression and increased AV refractoriness, so it blocks conduction (it's used in the treatment of heart failure and we'll talk about it in details later on).
- Its use is restricted for very rapid atrial arrhythmias with the presence of heart failure.

Magnesium

- It works on Na+/K+ ATPase, Na+ channels, certain K+ channels and Ca++ channels.
- Magnesium counteracts the effect of calcium, so increased levels of magnesium results in reduced activity of calcium channels.
- Effective through IV in refractory **digitalis-induced ventricular arrhythmias**, but only in hypomagnesemic patients (phenytoin is also used for this condition).
- Effective in **TdP** patients even if serum Mg++ is normal.

Potassium salts

- Used for **digitalis-induced arrhythmias** with hypokalemia.
  Digitalis can induce hypokalemia, so patients must be supplied with potassium salts to prevent the occurrence of cardiac arrhythmias.
- Depress ectopic pacemakers and slow conduction.

Adenosine

- Naturally occurring nucleoside.
- Stimulates purinergic (P1) receptors.
- Activates inward rectifier K+ current and inhibits Ca++ current.
- Very short acting (t1/2 = 10 seconds).
- ↓ Phase 4 depolarization in SA node.
- ↓ AV conduction.
- No effect on ventricles.
- 90-95% effective in **supraventricular tachycardia**. It replaced verapamil (which has 80-85% effectivity), so nowadays it's the drug of choice for the treatment of this condition.
- Less effective in the presence of adenosine receptor blockers, e.g. theophylline and caffeine.
- **Side effects:** It can cause transient flushing (20%) that is benign and lasts for only a few seconds, chest tightness, AV block, headache, hypotension, nausea, and paresthesia. (all these symptoms will disappear a few minutes after administration).

Good luck