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Pharmacology- Anti-arrhythmic drugs

CVS Block

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Anti-arrhythmic drugs

Cardiac arrhythmia: An Abnormality in *heart rate.*

High HR = tachycardia low HR = bradycardia

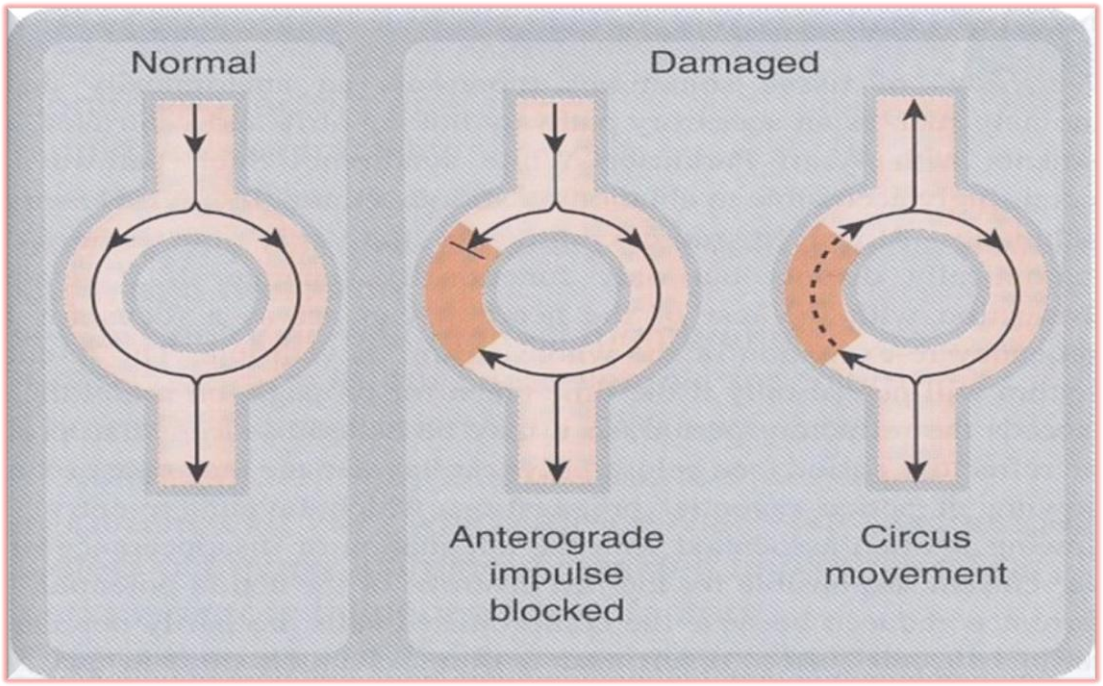
AT regular state: the interval between every impulse is the same.
extrasystoles: is an impulse that originates from a site other than SA node

, e.g. "AV or Purkiniji Fibers "

PAC (premature atrial contraction)

PVC (premature Ventricle contraction)

Circus Movement (Re-entry phenomenon)



CLASSIFICATION OF ANTIARRHYTHMIC DRUGS:

Vaughn Williams's classification" "

CLASS I: Na^+ channel blockers (membrane stabilizing drugs)

CLASS II: β-adrenoceptor blockers

CLASS III: K^+ channel blockers

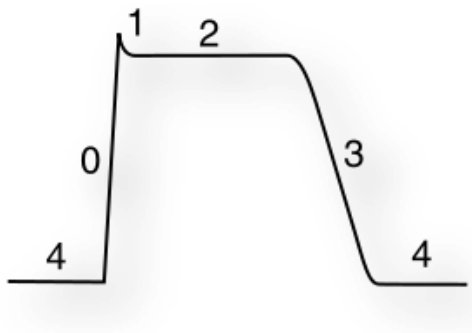
CLASS IV: Ca^{++} channel blockers

CLASS V: miscellaneous anti-arrhythmic agent

Class 1:

Drugs that block the rapid inflow of Na+ ions and thus:

- decrease the rate of rise of depolarization (Phase O)
- decrease phase 4 diastolic depolarization (suppress pacemaker activity)
- (membrane stabilizing effect)
- At high concentration they have local anaesthetic effect
- -Ve inotropic effect (cardiac depression)



For your information: The sodium channel is part of the membrane (wall) surrounding every cell that allows sodium to pass through into the cell, making the cells excitable and able to contract. Thus, the flow of sodium through these channels is necessary for the muscle cells of the heart to be stimulated to contract, and Class I antiarrhythmics decrease the electrical stimulation of the muscle cells.

Class I agents are divided into three groups (1A, 1B and 1C) based upon their effect on the length of the action potential:

- **1A LENGTHENS** the action potential, e.g.: quinidine & procainamide.
- **1B SHORTENS** the action potential, e.g.: lidocaine & mexiletine.
- **1C DOES NOT** significantly affect the action potential, e.g.: flecainide & propafenone.

Drug of Class 1A :

(Na^+ Channel Blocker lengthens the action potential)

First : QUINIDINE

Mechanism :

- Membrane stabilizing effect .
- Block potassium channels leading to prolongation of action potential duration (prolong phase 3) which causes Prolongation of atrial and ventricular refractory period.
- Anticholinergic effect by Increasing conduction through the A.V. node, this may lead to high ventricular rate in atrial flutter which can be prevented by prior administration of a drug that slow A.V conduction such as digoxin, B adrenoceptor, ca channel blocker .

- Depress cardiac contractility (- intropic action).
- Cause α-adrenergic blocking effect which cause vasodilatation and reflex sinus tachycardia. This effect is seen more after i.v. dose.

ECG changes:

- prolongation of P-R and Q-T interval
- Widens QRS complex (QRS: represents the ventricular excitation) .

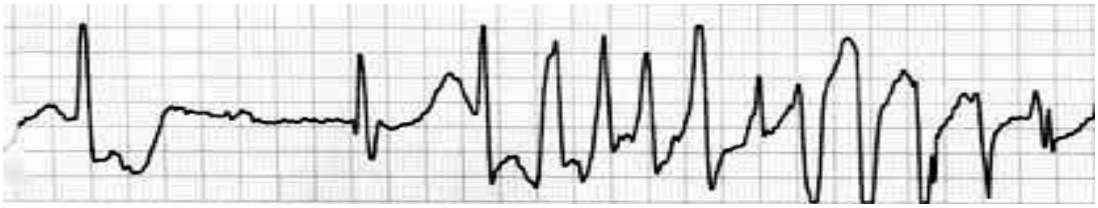
Clinical uses:

- In almost all types of arrhythmias
  Common uses: atrial flutter & fibrillation
  Can be used for ventricular tachycardia
- Maintaining sinus rhythm after D.C cardioversion.
  D.C (direct current): It is a defibulator that generate a shock to the heart.

Adverse effects:

- **GIT**: anorexia (loss of appetite) , nausea, vomiting, diarrhea .
- Anticholinergic adverse effects .
- **Cinchonism:** (only in large doses and is very rare, but important): **tinnitus** (ear ringing) **, headache & dizziness .**
- Hypotension .
- **Cardic** : quinidine syncope (episodes of fainting) due to torsades de pointes developing at therapeutic plasma levels . may terminate spontaneously or lead to fatal ventricular fibrillation .
- At toxic concentrations, can precipitate arrhythmia and produce asystole (cardiac arrest) if serum concentrations exceed 5 µg/ml or in high potassium levels (> 5mmol/L).

torsades de pointes



torsades de pointes : a polymorphous ventricular tachycardia in which the morphology of the QRS complexes varies from beat to beat. The ventricular rate can range from 150 beats per minute (bpm) to 250 bpm. This ventricular tachycardia will lead to ventricular fibrelation, which is the most serious life threatening arrhythmia

important in general, any drug prolong the AP (Q-T interval) cause torsades de pointes

Drug interactions :

- With digoxin: it will Increase the concentration of digoxin, displacement from plasma proteins, inhibition of digoxin renal clearance .

Important : Given orally, rarely given I.V. because of toxicity and hypotension due to α-blocking effect.

Second : PROCAINAMIDE

Similar to quinidine except :

1- less toxic on the heart, can be given I.V.

2- more effective in ventricular than in atrial arrhythmias

3- less depression of contractility

4- No anticholinergic or α-blocking actions

Therapeutic uses:

- Effective against most atrial and ventricular arrhythmias
- Second choice (after lidocaine) in ventricular arrhythmias after acute myocardial infarction .

Adverse Effects :

- In long term therapy it cause reversible lupus erythematosus-like syndrome in 5-15%(High incidence) of patients
- Hypotension
- Torsades de pointes
- Hallucination & psychosis

Class I B

(Na^+ Channel Blocker + Shorten AP Duration)

Lidocaine and Mexiletine

*Lidocaine:

1) USES :

-Treatment of Acute Ventricular Arrhythmias in emergency like: (cardiac surgery, acute myocardial infarction).

-NOT effective in Atrial Arrhythmias.

2) ADVERSE EFFECTS:

-Hypotension (low blood pressure).

-Neurological: Paresthesia(a sensation of tingling, pricking, or numbness of a person's skin), **Tremor**(involuntary rhythmic muscle contraction and relaxation), **Dysarthria**(slurred speech) **and Convulsions**(a medical condition where body muscles contract and relax rapidly and repeatedly, resulting in an uncontrolled shaking of the body).

3) PHARMACOKINETICS:

-NOT effective orally (3% bioavailability).

-GIVEN by I.V. bolus (direct injection) **or slow infusion** (Drop by drop in the IV line)**.**

-T1/2(half life) = **2hrs.**

*Mexiletine:

1) USES:

-Chronic Ventricular Arrhythmia.

-Digitalis-induced arrhythmias.

-Chronic pain e.g. diabetic neuropathy and nerve injury.

2) ADVERSE EFFECTS:

-Nausea, Vomiting.

-Neurological effects.

-Hypotension.

tremor , drowsiness, diplopia (double vision)

Arrhythmia -

3) PHARMACOKINETICS:

-Effective Orally.

-T1/2= 10 hr.

1B

Acute ventricular arrhythmias >> lidocaine

Chronic ventricular arrhythmias >> Mexiletine

Class I C

(Na^+ Channel Blocker + Do NOT effect AP Duration)

Flecainide and Propafenone

*Flecainide:

1) USES:

-Used in Supraventricular Arrhythmias in patients with NORMAL hearts.

-Wolff-Parkinson-White syndrome:

(Pre-excitation of the ventricles of the heart due to an accessory pathway (known as the Bundle of Kent).This accessory pathway is an abnormal electrical communication from the atria to the ventricles.

- Very effective in Ventricular Arrhythmias.

2) ADVERSE EFFECTS:

-CNS: Dizziness, tremor, blurred vision, abnormal taste sensations and paraesthesia.

-It is a PROARRHYTHMIC drug (a drug that will cause cardiac arrhythmia) **so it should be reserved for resistant arrhythmias.**

-Arrhythmias (because of the proarrhythmic effect).

-Heart failure due to -ve inotropic effect (A decrease in the rate of cardiac muscle contraction).

*Propafenone:

-Chemical structure similar to Propranolol.

- Has weak Beta-blocking action.

- Causes metallic taste and constipation (bowel movements that are infrequent and/or hard to pass).

CLASS I : Na Channel Blocker

Classes	Drugs	How it's given	Uses	Adverse effects
IA	-Quinidine →	Orally	→ 1- Atrial flutter & Atrial fibrillation it returns the rhythm back to normal sinus rhythm. 2- in treatment of ventricular arrhythmias.	→ - Hypotension - Cinchonism (headache, tinnitus, blurred vision - GIT(diarrhea, nausea,vomiting)
	Procainamid→	IV	→ 1- ventricular arrhythmias . 2- second drug of choice after lidocaine in the treatment of acute ventricular tachycardia associated with an acute myocardial infarction	→ - Systemic lupus erythematosus like syndrome. - Torsade de pointes
IB	Lidocaine →	IV	→ First drug of choice in the treatment of acute ventricular tachycardia associated with acute myocardial infarction	→ Neurological effects:Tremors,nausea of central origin, convulsions
	Mexiletine→	orally	→ in chronic treatment of ventricular arrhythmias.	→Neurologic effects as lidocain
IC	Flecainide →	Orally and IV	→Only approved for refractory ventricular arrhythmias	Severe proarrhythmic drugs Life- threatening ventricular tachycardia
	Propafenone →	Orally and IV	→ Used in atrial flutter or fibrillation	Flecainide increase the mortality rate in patients with premature ventricular contractions following myocardial infarction.

CLASS II DRUGS

β- ADRENOCEPTOR BLOCKERS

PHARMACOLOGICAL ACTIONS:

Block β_1- receptors in the heart → reduce the sympathetic effect on the heart causing:

- decrease automaticity of S.A. node and ectopic pacemakers

- prolong refractory period (slow conduction) of the A.V node → help prevent re-entry arrhythmias.

In brief: - Decrease heart rate & cardiac contractility.

-Suppress abnormal automaticity & decrease A-V conduction.

The sympathetic effect on the heart includes an increase of:
heart rate, force of contraction and blood pressure

Ectopic pacemakers: is an excitable group of cells that causes a premature heart beat outside the normally functioning SA node of the human heart.

Re-entry arrhythmias: are responsible for atrial flutter, most paroxysmal supraventricular tachycardia and ventricular tachycardia. It occurs when an electrical impulse recurrently travels in a tight circle within the heart, rather than moving from one end of the heart to the other and then stopping.

CLINICAL USES:

1- atrial arrhythmias associated with emotion, exercise and thyrotoxicosis. 2- WPW. 3- digitalis-induced arrhythmias.

Thyrotoxicosis: A toxic condition resulting from excessive amounts of thyroid hormones in the body, as that occurring in hyperthyroidism (over activity of the thyroid gland) causing a variety of symptoms that include rapid heartbeat, sweating, anxiety and tremor.

WPW (Wolff–Parkinson–White syndrome): is a syndrome of pre-excitation of ventricles of the heart due to an abnormal electrical communication from the atria to the ventricles. WPW is a type of atrioventricular reentrant tachycardia.

Digitalis: is also known as digoxin, it's a drug that strengthens the contraction of the heart muscle, slows the heart rate and helps eliminate fluid from body tissues. It's often used to treat congestive heart failure and is also used to treat certain arrhythmias when taking the therapeutic dose.

CLASS II DRUGS:

-**Propranolol**: it has an ability to prevent ventricular arrhythmias, that's why it used for reducing the incidence of sudden arrhythmic death after myocardial infarction

CLASS III DRUGS

(K^+ channels blockers)

Prolong phase 3 (the rapid repolarization phase) → prolong AP & refractory period.

Drugs of Class III:

- Amiodarone.

- Ibutilide (Pure Class III).

AMIODARONE

PHARMACOLOGICAL ACTIONS:

-Main effect is to prolong action potential duration → prolong refractory period -
Additional actions of classes: 1, 2 & 4. -
has a vasodilating effects (due to α- and β-adrenoceptor blocking effects and calcium channel blocking effects).

USES:

(Broad spectrum antiarrhythmic)
1- Main use: serious resistant ventricular arrhythmias.
(It's very effective in many types of arrhythmias)
2- Maintenance of sinus rhythm after D.C. cardioversion of atrial flutter and fibrillation.

3- Resistant supraventricular arrhythmias e.g. WPW.
4- useful in re-entry arrhythmias.

ADVERSE EFFECTS:

1-bradycardia, heart block and heart failure.
2- Pulmonary fibrosis.
3- hyper- or hypothyroidism (since Amiodarone contains iodine).
4- photodermatitis and skin deposits (patients should avoid exposure to the sun).
It may cause bluish discoloration of the skin.
5- Tremor, headache, ataxia (loss of muscles coordination, especially in extremities), paresthesia.
6- Constipation.
7- corneal microdeposits.
In long use:
8- Hepatocellular necrosis.
9- peripheral neuropathy.

Pharmacokinetics:

Extremely long t1/2 = 13 - 103 DAYS.

Drug Interactions:

Reduce clearance of several drugs e.g. quinidine, warfarin, procaiamide, lecainide.

PURE CLASS III
Ibutilide

-Given by a rapid I.V. infusion.

- Causes QT interval prolongation → precipitates torsades de pointes.

USES:

For the acute conversion of atrial flutter or atrial fibrillation to normal sinus rhythm.

Contraindications:

In patients suffering from torsades de pointes**.**

Torsades de pointes: is a polymorphous ventricular tachycardia in which the morphology of the QRS complexes varies from beat to beat; it is a malignant ventricular arrhythmia that is associated with syncope and sudden death.

drug	comment	use	Adverse effect
Amiodarone	Given orally Have a long half life And have a broad actions	In maintaining sinus rhythm in patients with atrial fibrillation Re-entry arrhythmia (Circus movement)	pulmonary fibrosis - Hypo or hyperthyroidism blue skin discoloration photodermatitis
Ibutilide	Given by a rapid I.V. infusion	Used for the acute conversion of atrial flutter or atrial fibrillation to normal sinus rhythm.	QT interval prolongation , so it precipitates torsade de pointes.

Class I V **(Calcium channel blockers)**

Drugs

1-Verapamil 2-Diltiazem

Site of Action

A.V.Node & S.A.Node (in the atria)

(Because **A.V.N & S.A.N** depend on Ca influx to do their work)

MOA

1- Calcium channel blocker
2- slow conduction

3- prolong effective refractory period

Uses

1- atrial arrhythmias

2- re-entry supraventricular

Arrhythmias, e.g.WPW

3- NOT effective in ventricular arrhythmias (because the SA node & the AV node are located in the atrium)

Class V

ADENOSINE (naturally occurring nucleoside)

Site of Action

AV node & ventricles

MOA

1- enhance potassium conductance

(K+channel opener) inhibit cAMP induced calcium influx leading to marked hyperpolarization , cause marked slowing of AV-conduction and prolongation of AV node refractory period

Uses

First choice for the treatment of paroxysmal supraventricular tachycardia

Adverse effects

1- flushing
2- shortness of breath and chest burning (in patients with bronchospasm)
3- brief AV block (contraindicated in heart block)
4- rarely: hypotesion, nausea, paresthesias and headache

** Notes :

- **ADENOSINE preferred over verapamil - safer and does not depress contractility**
- **It's given by I.V. bolus.**
- **half-life= less than 10 sec.**
- **MISCELLENIOUS ANTIARRHYTHMIC DRUGS + DIGITALIS**

BRADYARRHYTHMIAS

ATROPINE:

- **Can be used in sinus bradycardia after myocardial infarction and in heart block.**
- **In emergency heart block isoprenaline may be combined with atropine.**

NONPHARMACOLOGIC THERAPY OF ARRHYTHMIAS

Implantable Cardiac Defibrillator (ICD) جهاز لتنظيم ضربات القلب:

- **Can automatically detect and treat fatal arrhythmias such as ventricular fibrillation.**