PHARMACOLOGY

Antiarrhythmic Drugs

OBJECTIVES:

- Understand definition of arrhythmias and their different types
- describe different classes of Antiarrhythmic drugs and their mechanism of action
- understand their pharmacological actions, clinical uses, adverse effects and their interactions with other drugs.

Before studying this lecture, We advise you to study physiology lectures of: contractile mechanism of cardiac muscle - cardiac electrical activity – arrhythmias

PHARMACOLOGY
435

- Important.
- Extra notes.

Antiarrhythmic Drugs

Introduction: (remember)

Within the heart there is a conduction system which is responsible for generating and conducting the impulses to all parts of the heart. Normally, the impulses generated in the SA node passing the inter-nodal pathways reaching the AV node (and because there are few gap junctions, there will be what's called "AV nodal delay") then passing through bundle of His to right and lift bundle branches and finally reaching Purkinje fibers. **The arrhythmias** are conceptually simple. Dysfunctions cause abnormalities in impulse formation and conduction in the myocardium **(arrhythmias)**

Definition:

Arrhythmia is an abnormality in the heart's rhythm, or heartbeat pattern

So **arrhythmia** is an abnormality in the:

- **Rate**
  - >100= "tachycardia"
  - <60= "bradycardia"
- **Regularity**
  - e.g. extrasystole.
  - Extrasystole is a premature contraction of the heart that is independent of the normal rhythm, as (PAC, PVC)
- **Site of origin**
  - e.g. ectopic pacemaker.
  - When the pacemaker is not the SA node.
- **Disturbance in conduction**
  - Slower/ blocked AV node

The ultimate goals of antiarrhythmic drugs:

1- Maintenance of normal rhythm.

2- Prevention of more serious arrhythmias.

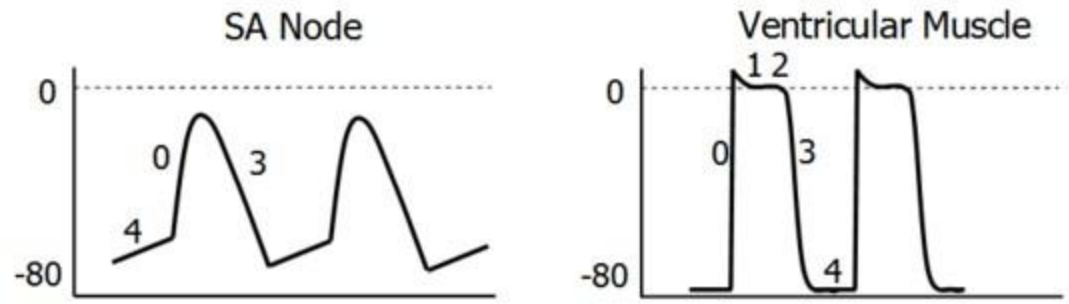
How antiarrhythmic drugs produce their effects?

1- Slow conduction velocity.

2- Altering the excitability of cardiac cells by prolonging the effective refractory period

3- Suppressing ectopic pacemaker activity by inhibiting phase 4 (slow depolarization)

Classification of the antiarrhythmic drug:



Vaughn-Williams CLASSIFICATION	MECHANISM OF ACTION	Effect on pacemaker (SA node) action potential
IA	Na+ channel blocker (Membrane stabilizing drugs)	Slow phase 0,4 & prolong phase 3
IB		Slow phase 0,4 & shorten phase 3
IC		Markedly Slow phase 0
II	b-Adrenoreceptor blocker	Slow phase 4 depolarization
III	K+ channel blocker	Prolongs Phase 3
IV	Ca2+ channel blocker	Slow Phase 4 spontaneous depolarization and conduction
V	Miscellenious antiarrhythmics	

Class I :

❖ Drugs that **block the influx of Na** ions through Na channels (membrane stabilizing effect) , they have the following effects on the cardiac action potential:

1- decrease the rate of rise of rapid depolarization (Phase O)

2- decrease phase 4 slow diastolic depolarization (suppress pacemaker activity)

❖ Sub classified according to their effect on action potential duration (phase 3), and subsequently affect effective refractory period:

- **IA** : prolong action potential duration by inhibiting potassium efflux (Class III activity)
- **IB** : shorten action potential duration
- **IC** : no effect on action potential duration

Class I Drugs

CLASS IA (prolong action potential duration)

Drug	QUINIDINE		PROCAINAMIDE
Pharmacological action	Cardiac effects (direct)	Actions on ANS (indirect)	Similar to Quinidine except : 1- less toxic on the heart 2- there is **No** anticholinergic or α-blocking actions
	1- Membrane stabilizing effect 2- Blocking of K channels: - cause prolongation of action potential duration (refractory period) 3- ECG changes: -prolongs P-R and Q-T interval - widens QRS complex	1- Anticholinergic effect: -Increase conduction through the A.V. node (risk of ventricular tachycardia) 2- α-adrenergic blocking effect: -cause vasodilatation & reflex sinus tachycardia (seen more after I.V dose)	
Clinical use	1- common uses: **atrial flutter & fibrillation** 2- can be used for ventricular tachycardia 3- maintaining sinus rhythm after D.C. cardio version (direct current cardiac version-الإنعاش)		more effective in **ventricular** than in atrial arrhythmias
ADRs	**1-Torsades de pointes** **2- Anticholinergic adverse effects:** -Dry mouth -Blurred vision -Urinary retention -constipation **3-Hypotension** - due to depressing contractility & vasodilatation		1- In long term therapy it causes reversible lupus erythematosus-like syndrome 2- Hypotension 3- Torsades de pointes 4- Hallucination & psychosis
administration	GIVEN ORALLY (Rarely given I.V.)		I.V.

❖ Torsades de pointes (twisting of the spikes) :

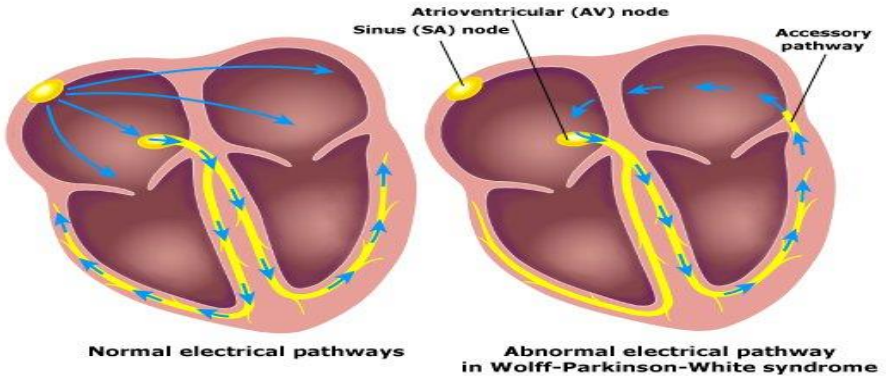
- It is the cause of quinidine syncope which is episodes of fainting develop at therapeutic plasma levels.
- may terminate spontaneously or lead to fatal ventricular fibrillation.

Class I Drugs

CLASS	CLASS IB (reduce action potential duration)		CLASS IC
Drug	Lidocaine	Mexiletine	Flecainide
Clinical use	Treatment of emergency ventricular arrhythmias e.g.: - during surgery as a local anesthetic - following acute myocardial infarction NOT effective in atrial arrhythmias	1- ventricular arrhythmia 2- digitalis-induced arrhythmias (Digitalis are drugs used for congestive heart failure and atrial arrhythmias, yet cause ventricular and other types of arrhythmia as side effect)	1- **supraventricular arrhythmias** 2- Wolff-Parkinson-White syndrome (WPW) 3-very effective in **ventricular arrhythmias**, but very high risk of proarrhythmia 4- should be reserved for resistant arrhythmias
ADRs	1- hypotension 2- CNS ADRs (similar to other local anesthetics): - paresthesia - tremor - dysarthria (slurred speech) - tinnitus - confusion - convulsions	1- GIT: - nausea , vomiting 2- CNS: - tremor, drowsiness, diplopia 3- CVS: - arrhythmias & hypotension	1- proarrhythmia 2- CNS : dizziness , tremor, blurred vision, abnormal taste sensations (*Dysgeusia*), paraesthesia 3- heart failure due to -ve inotropic effect
administration	- given I.V. bolus or slow infusion (NOT effective orally due to only 3% bioavailability)	Effective ORALLY	-
$t_{1/2}$	2 hours	10 hours	-

❖ Wolff-Parkinson-White syndrome (WPW):

It is the Pre-excitation of the ventricles due to an accessory pathway known as the Bundle of Kent. (it is a re-entry arrhythmia, where the electrical signal re-enters the AV node)



Class II Drugs

Pharmacological action: β_1 Blockers → Reduce sympathetic effect →

1- ↓ **S.A Node automaticity** (Bradycardia)

2- ↑ **refractory period of A.V Node** (Slow conduction)

Clinical uses of Class II Drugs :

- **Atrial arrhythmia**
- **Digitalis induced arrhythmias**
- **WPW**
  Wolf Parkinson White syndrome
- **Arrhythmia** caused by sympathetic excessive discharge (emotion , exercise , thyrotoxicosis)

Drug	Clinical use
Esmolol	- Very short acting ($t_{1/2}$ = 10min). - Given I.V. - Rapid control of ventricular rate in patients with atrial fibrillation or flutter (Tachycardia)
Propranolol, Atenolol, metoprolol	-used in patients who had myocardial infarction to reduce incidence of sudden death due to ventricular arrhythmias

Class III Drugs

Amiodarone
(prototype)

Pharmacological action

Main effect: prolong action potential duration and prolong refractory period by prolonging phase 3 repolarization (blocking K channels)
Additional effect:
- Class 1A (Membrane stability + α-adrenergic blocking effect)
- Class 2 (β_1 Blocker)
- Class 4 (Ca Block)
- vasodilating effects (due to its α- & β-adrenoceptor blocking effects and its calcium channel blocking effects)

Pharmacokinetic

- Extremely long t1/2 (13 - 103 DAYS)
-metabolized to its major active metabolite N-desethylamiodarone by cytochrome P450 (CYP3A4 and CYP2C8)
- eliminated primarily by **hepatic metabolism**
- **Can cross placenta,** and appear in breast milk

Clinical use

- main use: **serious resistant ventricular arrhythmias.**
- maintenance of sinus rhythm after D.C. cardio version (as quinidine)
- resistant supraventricular arrhythmiasm e.g. WPW: (useful in re-entry arrhythmias) (as Flecainide)

This drug should be reserved and only used for patients not responding to other drugs, due to it's many side effect

ADRs

Many side effect:
1-pulmonary fibrosis (common)
2-photodermatitis (avoid the sun)
3-hepatocellular necrosis (long use)
4-cardiac bradycardia, heart failure.
5-prephiral nephropathy
6-constipation
7-hyper/hypo thyroidism
8-bluish discoloration of skin
9- corneal micro deposits
10-CNS: headache, tremor, ataxia, paresthesia

Drug interaction

Enzymes inhibitor → Increase serum concentration of Amiodarone e.g. Loratadine, Ritonavir, Trazodone, Cimetidine, Grapefruit juice	Enzymes inducers → Decrease serum concentration of Amiodarone e.g. Rifampin	Amiodarone reduces clearance of several drugs e.g. Quinidine, warfarin, procainamide, flecainide

Class III Drugs cont. & class IV drugs

	Pharmacological action	Route of administration	Clinical use	ADRS
Ibutilide (Pure class III, with no additional effects)	QT interval prolongation (phase 3)	Given I.V. rapid infusion	acute conversion of **Atrial flutter or fibrillation** to normal sinus rhythm	**Torsades de pointes**

Class IV Drugs:

	Mechanism of action	Clinical use
-Verapamil -Diltiazem	Main site of action in the S.A and A.V Node leads to → slowing of conduction and prolong effective refractory period	- Effective in **atrial arrhythmia** - Re-entry supraventricular arrhythmias (e.g. WPW) - Not effective in ventricular arrhythmia

CLASSIFICATION OF DRUG	MECHANISM OF ACTION	COMMENT
IA	Na^+ channel blocker	Slows Phase 0 depolarization in ventricular muscle fibers
IB	Na^+ channel blocker	Shortens Phase 3 repolarization in ventricular muscle fibers
IC	Na^+ channel blocker	Markedly slows Phase 0 depolarization in ventricular muscle fibers
II	β-Adrenoreceptor blocker	Inhibits Phase 4 depolarization in SA and AV nodes
III	K^+ channel blocker	Prolongs Phase 3 repolarization in ventricular muscle fibers
IV	Ca^{2+} channel blocker	Inhibits action potential in SA and AV nodes

Class V Drugs

MISCELLENIOUS ANTIARRHYTHMIC DRUGS:

1- Adenosine **2-Digitalis** (will be studied later in heart failure treatment)

	Adenosine (Endogenous nucleoside)
Mechanism of action	Inhibits cAMP by binding to adenosine receptors (A1) causing:- 1-opening of potassium channels → hyperpolarization 2-Decreasing conduction velocity at A.V Node → Negative dromotropic effect 3-inhibiting phase 4 pacemaker action potential SA Node→ Negative chronotropic effect
Pharmacokinetics	Very short $t_{1/2}$ (less than 10 sec) Given I.V.
Clinical use	-Drug of choice for acute management of paroxysmal (متقطعه) **supraventricular tachycardia** - preferred over verapamil (because it's safer and does not depress contractility)
ADRs & contraindications	-flushing -bronchospasm (shortness of breath and chest burning), contraindicated in asthma -brief A.V block (thus contraindicated in heart block)

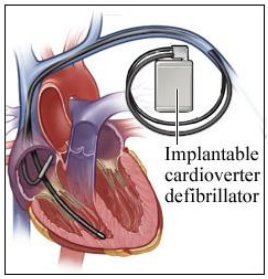
Bradyarrhythmias:

Atropine :-

- can be used in **sinus bradycardia** after myocardial infraction and in heart block .
- In emergency heart block isoprenaline may be combine with atropine (caution):
  isoprenaline is a β_1 Agonist and may cause serious tachycardia, when combined with atropine (which is an anticholinergic drug, also causes tachycardia) the result will be a very risky tachycardia and thus should be used with caution

Non-pharmacologic therapy of arrhythmias:

Implantable cardiac defibrillator (ICD):- can automatically detect and treat fatal arrhythmias such as ventricular fibrillation



Quiz

THANK YOU FOR CHECKING OUR WORK

THE PHARMACOLOGY TEAM

لولوه الصغير
شادن العمران
لمى الزامل
كوثر الموسى
ديمه الراجحي
جواهر الحربي
دلال الحزيمي
رنيم الدبيخي
نورة الصومالي
منيرة السلولي
منيرة العمري

شماء السعد
رهف بن عبّاد
سارة الخليفة
ساره المطوع
فاطمة الدين
آية غانم
أسرار باطرفي
نوف العبدالكريم
وضحى العتيبي
ريما الحيدان
نورة البصيص

عبدالرحمن السياري
أحمد اليحيى
خالد الزهراني
عبدالله الجنيدل
أحمد المصعبي
عبدالرحمن الزامل
عبدالرحمن الشمري
معاذ باعشن
عبدالعزيز الشعلان
محمد السحيباني
فارس المطيري
فوزان العتيبي
محمد ابونيان
عمر القحطاني
يوسف الصامل

For any correction, suggestion or any useful information do not hesitate to contact us :Pharmacology.med435@gmail.com

PHARMACOLOGY
435