PHARMACOLOGY

بسم الله الرحمن الرحيم

FINAL | Lecture 3

Antiarrhythmic Drugs (Pt.3)

وَلَقَدْ خَلَقْنَا الْإِنسَانَ وَنَعْلَمُ مَا تُوَسْوِسُ بِهِ نَفْسُهُ ۖ وَنَحْنُ أَقْرَبُ إِلَيْهِ مِنْ حَبْلِ الْوَرِيدِ

اللهم إنّا نعوذ بك من شرور أنفسنا ومن سيئات أعمالنا

Written by: Omar Ibrahim

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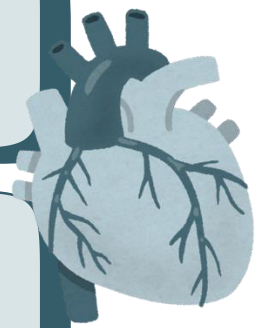

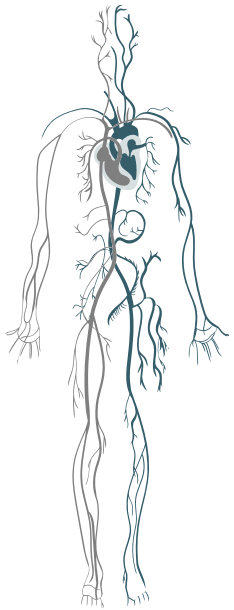

وَلِلَّهِ الْأَسْمَاءُ الْحُسْنَى فَادْعُوهُ بِهَا

المعنى: العظيم ذو الكبرياء، المتعالي عن صفات خلقه، القاهر لعتاتهم، ولا يوصف بهذا الاسم على سبيل المدح سواه سبحانه وتعالى.

الورود: ورد مرة واحدة في القرآن.

الشاهد: ﴿ٱلْعَزِيزُ ٱلْجَبَّارُ ٱلْمُتَكَبِّرُ ۚ سُبْحَٰنَ ٱللَّهِ عَمَّا يُشْرِكُونَ﴾ [الحشر:٢٣].

٣٣

اضغط هنا لشرحٍ أكثر تفصيلًا

Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

- Cardiovascular Effects:
- It markedly prolongs the action potential duration (and the QT interval on the ECG) by blockade of multiple potassium channels, including the rapid component of the delayed rectifier potassium current (I_{Kr}), as well as ATP-sensitive potassium channels (K_{ATP}) and the inward rectifier potassium channel (I_{K1}).
- It also affects the slow component of the delayed rectifier (I_{Ks}) and ultra-rapid delayed rectifier (I_{Kur}).

Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

- In addition to the K+ channel blokage effect, Amiodarone also secondarly blocks the following channels:
  - It blocks inactivated sodium channels.
  - It blocks calcium channels.
  - It blocks α- and β-adrenergic receptors.
- Consequences of these actions include slowing of the heart rate and AV node conduction.
- Amiodarone is primarily a K+ channel blocker (Class III antiarrhythmic). However, it possesses properties of Classes I, II, III, and IV, as it blocks sodium channels, calcium channels, and beta-adrenergic receptors in addition to K+ channels.

Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

- The broad spectrum of actions may account for its relatively high efficacy and its low incidence of torsades de pointes (Polymorphic Ventricular Tachycardia) despite significant QT-interval prolongation.
- This strongly suggests that **QT prolongation alone does not trigger TdP**. Instead, TdP is a specific arrhythmogenic mechanism that **often involves QT prolongation**, but it is **not a direct consequence of drug-induced QT prolongation**.
- It causes peripheral vasodilation, primarily after intravenous administration and may be related to the action of the vehicle or α-adrenergic receptor blockade. Therefore, it will induce hypotension directly after administration.

Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3) Adverse Reactions:

1. Symptomatic bradycardia and heart block in patients with preexisting sinus or AV node disease (Contraindicated).
2. The drug accumulates in many tissues (10 - 50 times more than plasma) including the heart, lung, liver, and skin, and is concentrated in tears.
   - This high tendency to accumulate in tissues causes the drug to have a very high **volume of distribution (Vd)** and **half-life** and can also **induce adverse effects in the tissues where it accumulates**.
3. Dose-related pulmonary toxicity is the most important adverse effect. → Fatal pulmonary fibrosis in 1% of patients.
   - Might cause a complete Pulmonary Crisis.

Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3) Adverse Reactions:

4. Abnormal liver function tests as well as hyperbilirubinemia induced by hypersensitivity hepatitis (Cholestatic Hepatitis) may develop during amiodarone treatment. Liver function tests should be monitored regularly.
5. Skin deposits result in a photo-dermatitis and a gray-blue skin discoloration in sun exposed areas and the malar regions.
6. Asymptomatic corneal micro-deposits, disturbing the clearance of the cornea and affecting vision, occur in all patients treated with amiodarone after a few weeks of treatment.
7. Halos may develop in the peripheral visual fields.

Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3) Adverse Reactions:

8. Rarely, an optic neuritis (Inflammation of the Optic Nerve) may progress to blindness.
9. It blocks the peripheral conversion–Activation–of thyroxine (T4) to triiodothyronine (T3).
10. It is also a potential source of large amounts of inorganic iodine, response to excess amounts of iodine **varies between patients**, and:
    A. It may result in either hypothyroidism or hyperthyroidism (Type I or II). In either **situation**, a goiter can develop.
    B. Type 1 amiodarone-induced thyrotoxicosis is due to excessive thyroxine production.
    C. Type 2 amiodarone-induced thyroiditis is due to destructive thyroiditis.

Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

- Treatment of each form of thyroiditis is different:
  - Type 1 is treated with thionamides.
    - Anti-Thyroid drug, to reduce thyroxine production
  - Type 2 is treated with prednisolone.
    - Anti-Inflammatory drug, to reduce inflammation and destruction.
- Thyroid function should be evaluated before starting treatment and should be monitored periodically.

Amiodarone Pharmacokinetics:

- Amiodarone bioavailability is 35-65%.
- It undergoes hepatic metabolism by CYP3A4, and the major metabolite, desethylamiodarone, is bioactive.
- The elimination half-life is complex and biphasic, with:
- A rapid component of 3–10 days (50% of the drug), when the drug is still mostly in plasma, and
- A slower component of several weeks, once tissue stores dominate (average terminal half-life ≈ 50 days).
- After discontinuation of the drug, both therapeutic effects and adverse reactions can persist for 1–3 months, due to the drug's high tendency to accumulate in tissues.

Amiodarone Pharmacokinetics:

- Measurable tissue levels may be observed up to 1 year after discontinuation.
- It has many important drug interactions, and all medications should be reviewed when the drug is initiated and when the dose is adjusted.
- Because CYP3A4 is one of the most commonly used metabolic pathways in the liver, amiodarone **can interact with many widely prescribed medications**.
  - It is a substrate for liver cytochrome CYP3A4, and its levels are **increased** by drugs that **inhibit** this enzyme.
  - Drugs that **induce** CYP3A4, (rifampin), **decrease** amiodarone concentration

Amiodarone Adverse Reactions:

- It **inhibits several cytochrome P450 enzymes**, just like isoniazid, as a **direct adverse effect** rather than due to its metabolism by CYP3A4, and **may increase the plasma levels of many drugs**, including statins, digoxin, and warfarin, which are commonly used in patients with **heart failure** and **arrhythmias** and are **metabolized** by cytochrome P450 enzymes.
- The dose of warfarin should be reduced by ⅓–½ following initiation of amiodarone, and prothrombin times (INR) should be closely monitored.
- Knowing all these adverse reactions is essential, as amiodarone is **the most commonly used anti-arrhythmic drug today** due to its various mechanisms of action.

Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3), Sotalol:

- Sotalol is a β-adrenergic receptor-blocker and prolongs the duration of the action potential (class 3).
- The drug is formulated as a racemic mixture of **D- and L-sotalol**.
- All the **β-adrenergic–blocking activity** resides in the **L-isomer** while the **D- and L-isomers** share **action potential prolonging** effects.
- It is **not** cardio-selective.

Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3), Sotalol:

- Sotalol antiarrhythmic effects involve **ion channel blockade** in addition to its β-blocking action.
- It is a potent inhibitor of the rapid component of the delayed rectifier potassium current (I_{Kr}). This blockade slows the efflux of potassium ions, which prolongs the cardiac action potential duration and the effective refractory period in the atrium and ventricle.
- **Cardiac Adverse Effects:**
  - A dose-related incidence of torsades de pointes.
  - Patients with overt heart failure may experience further depression of left ventricular function.
  - β-blockers used in heart failure are: **carvedilol, metoprolol and bisoprolol** – only these three are evidence-based and mortality reducing in patients with heart failure.

Sotalol Therapeutic Uses:

1. Life-threatening ventricular arrhythmias
2. Maintenance of sinus rhythm in patients with treated atrial fibrillation.
3. Treatment of supraventricular and ventricular arrhythmias in the pediatric age group. An alternative for Amiodarone in young patients with arrhythmias as they could be highly affected by its adverse effects.

Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3), Dofetilide:

- It prolongs the action potential duration.
- This action is affected by a dose-dependent blockade of the rapid component of the delayed rectifier potassium current (I_{Kr}) which increases in hypokalemia.
- It does not block other potassium channels or the sodium and calcium channels; or adrenergic receptors.

Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3), Dofetilide:

- It is 100% bioavailable.
- **Verapamil** increases peak plasma concentration of **dofetilide** by **increasing** intestinal blood flow, thus increasing the rate of its absorption.
- Mainly eliminated by the kidney.
- Inhibitors of the renal cation secretion mechanisms prolong its half-life as it is actively eliminated by the kidneys.
- QT prolongation and the risk of ventricular arrhythmias is concentration dependent; thus, dosing should be according to creatinine clearance.

Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3), Dofetilide:

- It is mainly indicated for the maintenance and restoration of normal sinus rhythm in patients with atrial fibrillation.
- Treatment with dofetilide should be initiated in hospital after baseline measurement of the rate-corrected QT interval (QTc) and serum K^+, and Mg^{2+}.
  - Because low K^+ or Mg^{2+}, or a prolonged QTc, significantly increases the risk of dofetilide-induced QT prolongation and Torsades de Pointes.
- During loading, the QTc is measured before the second and subsequent doses; an increase in the QTc to ≥500 ms is an indication to reduce the dose or discontinue the drug.

Dofetilide Relative Contraindications:

1. A baseline QTc of greater than 450 ms (500 ms in the presence of an intraventricular conduction delay)
2. Bradycardia of less than 50 bpm
3. Hypokalemia until corrected

Calcium Channel-Blocking Drugs (Class 4)

- Verapamil and diltiazem **block L-type calcium channels not only in cardiac muscle (reducing inotropy) but also in the SA and AV nodal cells**, slowing both heart rate and conduction, **producing a cardio-suppressive effect similar to that of β-blockers**.
- **Verapamil is preferred for arrhythmias** because it is **more cardio-selective**, causing less vasodilation — and therefore less reflex sympathetic activation — than diltiazem.
- Verapamil and diltiazem, but not the **dihdropyridines**, have antiarrhythmic effects.
- Verapamil Cardiac Effects:
  - It blocks both activated and inactivated L-type calcium channels.
  - Thus, its effect is more marked in tissues that **fire frequently**, those that are less completely polarized at rest, and those in which activation depends exclusively on the calcium current, such as the SA and AV nodes.

Calcium Channel-Blocking Drugs (Class 4)

- It prolongs AV nodal conduction time and its effective refractory period.
- It usually slows the SA node by its direct action, but its hypotensive action may occasionally result in a small reflex increase of SA rate.
- Verapamil can suppress both early and delayed after-depolarizations and may abolish slow responses arising in severely depolarized tissue.
- Because verapamil mainly **slows SA node firing** and **AV nodal conduction**, it is **primarily** used to **treat supraventricular arrhythmias**.

Calcium Channel-Blocking Drugs (Class 4)

- Ventricular arrhythmias usually present with a **wide QRS complex**, while supraventricular arrhythmias typically produce a **narrow QRS**. However, in rare cases, a ventricular arrhythmia can appear with a narrow QRS, which may lead clinicians to **misdiagnose it as supraventricular tachycardia**.
- A common error has been to administer intravenous verapamil to a patient with ventricular tachycardia **misdiagnosed** as supraventricular tachycardia.
- In this setting, it can worsen the ventricular arrhythmia, because verapamil's **vasodilatory and hypotensive effects** can destabilize the already compromised ventricular rhythm and hypotension and ventricular fibrillation can occur.

Calcium Channel-Blocking Drugs (Class 4)

- It may precipitate **heart failure**.
- It can induce AV block when used in large doses or in patients with AV nodal disease.
  - This block can be treated with **atropine** and **β-receptor stimulants**.
- May produce constipation, and peripheral edema.
  - Common in all Ca^{+2} Channel blockers, due to vasodilation and the relaxation of GIT muscles respectively.

Calcium Channel-Blocking Drugs (Class 4)

Therapeutic Uses:

1. Supraventricular tachycardia.
2. To reduce the ventricular rate in atrial fibrillation or flutter — by slowing the number of rapid atrial impulses that pass through the AV node to the ventricles.

- It only rarely converts atrial flutter and fibrillation to sinus rhythm, because it **only slows AV nodal conduction**, not the atrial reentry circuits or ectopic foci that cause the arrhythmia (**not dependent on calcium channels**).
- It should be avoided in arrhythmias induced by digoxin because it increases digoxin concentration and enhances its AV block.
- Non-DHP CCBs, β-blockers, and digoxin should not be used together because their combined AV-node–blocking effects can cause severe bradycardia, AV block, and hypotension.

Other Antiarrhythmic Agents: Adenosine

- Mechanism & Clinical Use:
- Adenosine is a nucleoside that occurs naturally throughout the body.
- Its half-life in the blood is less than 10 seconds, therefore given as an IV fusion.
- It activates K^+ efflux from the cell.
- It reduces Ca^{++} influx into the cell.
  - Might cause vasodilatory effects.
- The results of these actions are marked hyperpolarization and suppression of calcium-dependent action potentials.

Other Antiarrhythmic Agents: Adenosine

- With a bolus dose, it directly inhibits AV nodal conduction and increases its refractory period but has lesser effects on the SA node, therefore it is given as an infusion instead of a bolus administration.
- Adenosine is currently the drug of choice for prompt conversion of paroxysmal supraventricular tachycardia to sinus rhythm (high efficacy and very short duration of action).
- It is less effective in the presence of adenosine receptor blockers (theophylline or caffeine), and its effects are potentiated by adenosine uptake inhibitors such as dipyridamole.

Adenosine Adverse Reactions:

- Flushing in about 20% of patients (due to vasodilation) and shortness of breath or chest burning (perhaps related to bronchospasm) in over 10%, making this drug contraindicated in Respiratory deficient patients, ex: patients with asthma.
- Induction of very short-lived, high-grade AV block (due to its high but short duration efficacy).
- Less common toxicities include headache, hypotension, nausea, and paresthesias.
- Its very short duration of action (half-life < 10 seconds), causes any side effects to disappear quickly, making this drug highly safe and effective.

Other Antiarrhythmic Agents: Ivabradine

- Ivabradine is a selective blocker of "funny" current (I_f) in the SA node and is useful for heart rate control. It only has a negative chronotropic effect without any inotropic or dromotropic effects.
- It slows pacemaker activity by decreasing diastolic depolarization of sinus node cells.
- It is an open channel blocker that shows use-dependent block.
- Unlike other heart rate-lowering agents such as β-blockers, it reduces heart rate without affecting myocardial contractility, ventricular repolarization, or intracardiac conduction.

Other Antiarrhythmic Agents: Ivabradine

- At **therapeutic concentrations**, block of I_f is not complete, and thus, the autonomic control of the SA node rate is retained. Because the inhibition is incomplete, the SA node can still respond to sympathetic and parasympathetic input, preserving normal physiological control of heart rate while reducing its baseline frequency.
- **Elevated heart rate** is an important determinant of the ischemic threshold in patients with coronary artery disease (CAD) and a prognostic indicator in patients with congestive heart failure (CHF).
- It has **antianginal** and **anti-ischemic effects** in patients with **coronary artery disease** and **chronic stable angina**.

Other Antiarrhythmic Agents: Ivabradine

- In patients with left ventricular dysfunction and heart rates greater than 70 bpm, it reduces mean heart rate. Especially when **β-blockers** are not effective enough or inappropriate.
- Also used for patients with Inappropriate sinus tachycardia is an uncommon disorder characterized by multiple symptoms, including palpitations, dizziness, and orthostatic intolerance.
- Visual disturbances attributable to the block of the I_f channels in the retina have been described.

Other Antiarrhythmic Agents: Magnesium

- Originally used for patients with digitalis-induced arrhythmias who were hypomagnesemic. (Replacement Therapy)
- It influences Na^+/K^+ATPase, sodium channels, certain potassium channels, and calcium channels.
- Magnesium therapy may be indicated in patients with torsades de pointes even if serum magnesium is normal.

Quick heads-up—do NOT skip the next slide! The doctor did not go over it, but it will make the rest of the lecture way clearer.

Arrhythmic Effects of Potassium Disorders:

- **Hypokalemia (↓ K^+ outside the cell)**
  - ↑ K^+ efflux → membrane becomes more negative (**hyperpolarized**)
  - Although counterintuitive, hyperpolarization **facilitates the re-activation of voltage-gated Na^+ channels**, making more Na^+ channels available → cells become more excitable and reach threshold more easily.
  - **Result:** ↑ automaticity → ectopic beats, SVT, VT, and torsades de pointes
- **Hyperkalemia (↑ K^+ outside the cell)**
  - ↓ K^+ efflux → membrane becomes less negative (**partial depolarization**)
  - Partial depolarization **prevents full repolarization to the resting membrane potential (RMP)** → ↓ Na^+ channel re-activation → cells become less excitable and conduction slows
  - **Result:** bradycardia, AV block, wide QRS, and possible asystole
- **Key Clinical Reminder:**
  - Always correct potassium abnormalities before giving antiarrhythmic drugs. **Uncorrected K^+ disturbances can cause arrhythmias, worsen existing arrhythmias, or make antiarrhythmic drugs dangerous.**

Other Antiarrhythmic Agents: Potassium

- The effects of increasing serum potassium are:
  1. A resting potential depolarizing action
  2. A membrane potential stabilizing action (less nodal depolarization), the latter caused by increased potassium permeability.
- Hypokalemia results in an increased risk of early and delayed after-depolarizations, and ectopic pacemaker activity, especially in the presence of digitalis.

Other Antiarrhythmic Agents: Potassium

- Hyperkalemia depresses ectopic pacemakers (severe hyperkalemia is required to suppress the SA node) and slows conduction.
- Because both insufficient and excess potassium are potentially arrhythmogenic, potassium therapy is directed toward normalizing potassium gradients and pools in the body.

Summary Table of the Lecture:

Drug / Class	Mechanism of Action	Main Clinical Uses	Major Adverse Effects / Dangers	Important Notes
Amiodarone (Class III, broad-spectrum)	Blocks multiple K^+ channels (IKr, IKs, IKur, IK1, KATP); also blocks Na^+, Ca^{2+}, α, β receptors → ↑ AP duration & QT	Most supraventricular & ventricular arrhythmias	Pulmonary fibrosis, thyroid dysfunction (↑ or ↓), blue-gray skin, photosensitivity, hepatotoxicity, corneal deposits, optic neuritis, bradycardia, AV block	Very long half-life (weeks–months), massive tissue accumulation, CYP3A4 interactions; ↑ digoxin/warfarin/statins; reduce warfarin dose 33–50%
Sotalol (Class III + β-blocker)	Non-selective β-blocker + IKr blockade → prolongs AP & ERP	VT, AF maintenance, SVT/VT in pediatrics	**Dose-dependent torsades de pointes**, worsened LV function	Not cardio-selective; alternative to amiodarone in young patients
Dofetilide (Pure Class III)	**Pure IKr blocker**; dose-dependent QT prolongation	Restoration + maintenance of sinus rhythm in AF	Torsades de pointes, severe QT prolongation	Must be started in hospital; avoid if QTc > 450–500 ms; avoid bradycardia < 50 bpm; correct K^+/Mg^{2+} first; renally eliminated → dose by CrCl
Verapamil (Class IV)	Blocks L-type Ca^{2+} channels → slows SA firing, slows AV conduction, ↓ contractility	SVT; control ventricular rate in AF/flutter	Hypotension, AV block, HF worsening, constipation, peripheral edema	DO NOT give in VT (can cause VF); avoid combination with β-blockers & digoxin (risk of severe bradycardia/AV block)
Diltiazem (Class IV)	Same as verapamil but less cardio-selective	Same as verapamil; rate control	Same as verapamil	Slightly more vasodilation than verapamil
Adenosine	↑ K^+ efflux; ↓ Ca^{2+} influx → strong AV nodal block; hyperpolarization	**Drug of choice for acute PSVT**	Flushing, dyspnea/bronchospasm, chest burning, very transient AV block, hypotension	Very short half-life (< 10 sec); less effective with caffeine/theophylline; potentiated by dipyridamole; avoid in asthma
Ivabradine	Selective **If (funny current) blocker** in SA node → ↓ HR (pure chronotropic effect)	Stable angina, CAD, HF with HR > 70, inappropriate sinus tachycardia	Visual brightness phenomena (phosphenes)	**Does NOT fully block If**, so autonomic regulation (SNS/PNS) still works → HR can still increase when needed
Magnesium	Modulates Na^+/K^+ ATPase, Na^+, K^+, and Ca^{2+} channels	Digitalis-induced arrhythmias; **torsades de pointes**	Very safe; flushing or hypotension possible	Works even if magnesium level is normal
Potassium (Clinical effect)	Changes resting membrane potential and excitability	Correction of hypo/hyperkalemia to prevent arrhythmias	Hypokalemia → SVT, VT, TdP; Hyperkalemia → bradycardia, AV block, wide QRS	ALWAYS correct K^+ abnormalities before giving antiarrhythmics

PHARMACOLOGY QUIZ LECTURE 3

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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			