بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 4

Cholinergic drugs pt.2

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وَلِلَّهِ الْأَسْمَاءُ الْحُسْنَى فَادْعُوهُ بِهَا

المعنى: الباقي بعد فناء الخلق والمسترد أملاكهم ومواريثهم بعد موتهم، ولم يزل الله باقيًا مالكًا للأشياء كلها يورثها من يشاء، ويستخلف فيها من أحب.

الورود: ورد في القرآن (٣) مرات.

الشاهد: ﴿ وَإِنَّا لَنَحْنُ نُحْيِۦ وَنُمِيتُ وَنَحْنُ ٱلْوَٰرِثُونَ ﴾ [الحجر:٢٣].

٢١

اضغط هنا لشرحٍ أكثر تفصيلًا

Direct-Acting Cholinomimetics

The endothelium of blood vessels contains muscarinic receptors despite the lack of parasympathetic innervation in these vessels.

5. Stimulation of M_3 and M_5 receptors in the endothelium of blood vessels increases the synthesis and release of endothelium- dependent relaxing factor (EDRF) (which is NO, Nitric Oxide which is gas and lipid soluble and diffuses through membranes and reach the smooth muscle and relax it) which mediates vasodilation, and reduction of blood pressure.

- Cholinomimetics have NO direct effect on blood vessels because of lack of parasympathetic innervation of blood vessels

We have some drugs (we will take it in the pharmacology of cardiovascular system) they act by releasing nitric oxide, which will dilate or relax the vascular smooth muscle and cause vasodilation. Nitric oxide is a vasodilator released from endothelial cells as a result of stimulation of muscarinic receptors there and go to the smooth muscle to relax it

Direct-Acting Cholinomimetics

Note :Pilocarpine which are available in eye drops for treatment of glaucoma (treatment of glaucoma is the main use of Pilocarpine),,, This is known as Local administration But pharmacologically if we give

6. **Pilocarpine (**IntraVenous **IV) which is known as systemic administration has different effects on blood pressure: after the initial reduction in blood pressure, blood pressure will be elevated (hypertension) due to sympathetic ganglionic discharge caused by activation of M_1 receptors on sympathetic ganglia.**

Pilocarpine given intravenously produces biphasic **effects on blood pressure**. Initially, it causes a **decrease in blood pressure** due to vasodilation. This occurs because pilocarpine stimulates muscarinic receptors on the endothelium, leading to nitric oxide release and relaxation of vascular smooth muscle.

However, after this initial fall, **blood pressure may rise (hypertension).** This later increase is due to **sympathetic ganglionic discharge** caused by activation of **M1 receptors on autonomic (sympathetic) ganglia.**

There are **two types of autoreceptors** involved in acetylcholine (Ach) regulation:
Inhibitory autoreceptors, which reduce Ach release (negative feedback)
Facilitatory **autoreceptors**, which increase Ach release (positive feedback)

These autoreceptors are present both in peripheral nerve endings and in **autonomic ganglia**.

When inhibitory autoreceptors are activated, **less acetylcholine is released**, resulting in **reduced muscarinic stimulation**, less vasodilation, and therefore **relative vasoconstriction**, which raises blood pressure.

Autonomic ganglia include both **sympathetic and parasympathetic ganglia**, and **both use acetylcholine as their neurotransmitter**. Stimulation of ganglionic M1 receptors—especially in sympathetic ganglia—enhances catecholamine release, leading to **increased vascular tone and elevated blood pressure**.

Because ganglionic effects are complex, they can sometimes **oppose the direct effects of muscarinic receptor stimulation** on target organs. For this reason, pilocarpine is **not used intravenously in clinical practice today**. Instead, it is used topically **as eye drops** for the treatment of **glaucoma** . For more explanation **click here**

Direct-Acting Cholinomimetics

Respiratory System: [M_3 receptors]

1. **Contraction of smooth muscle of the bronchial tree → bronchoconstriction and exacerbation of bronchial asthma**

AS a matter of fact, in chronic smokers with chronic bronchitis, the bronchi and their mucosa are damaged. Despite this structural damage, bronchoconstriction is present. This bronchoconstriction is mediated by the parasympathetic nervous system through activation of M3 muscarinic receptors, which cause contraction of bronchial smooth muscle. Therefore, these patients are treated with anticholinergic drugs to antagonize M3 receptors and relieve bronchoconstriction. In general, muscarinic receptors mediate smooth-muscle contraction throughout the body, except in blood vessels, where activation of muscarinic receptors on the endothelium causes vasodilation

2. **Stimulation of secretions of glands in tracheobronchial mucosa**

Exocrine glands are stimulated by acetylcholine acting on muscarinic receptors. The parasympathetic nervous system is therefore referred to as the secretomotor system, as it increases glandular secretions and causes smooth-muscle contraction

Direct-Acting Cholinomimetics

Gastrointestinal Tract: [M_3 receptors]

1. **Increased gastric secretions.**
2. **Peristaltic activity is increased throughout the gut and most sphincters are relaxed.**

In the GI tract, parasympathetic stimulation causes contraction of the smooth muscle in the bowel wall while simultaneously causing relaxation of the sphincters. This coordination is essential because parasympathetic activity mediates the defecation reflex. Effective defecation requires peristaltic contractions of the bowel along with relaxation of the sphincters at the right time. A similar mechanism occurs in the genitourinary tract, where parasympathetic stimulation coordinates smooth muscle contraction and sphincter relaxation

Direct-Acting Cholinomimetics

Genitourinary tract: [M_3 receptors]

1. **Stimulation of detrusor muscle of the urinary bladder → contraction for Urination**
2. **Relaxation of bladder sphincter.**

- **Both promote voiding (urination).**

3. **Human uterus contacts and its vessels dilate in response to muscarinic agonists, but pregnant uterus is not affected.**

The pregnant uterus is generally not affected by sympathomimetics, but toward the end of pregnancy, β2 receptors increase, which mediate relaxation of the uterus to help maintain the fetus. Premature contractions at this stage could lead to fetal loss, whereas contractions during labor are normal.

Summary: The human uterus and its viscera normally contract in response to muscarinic agonists, but the pregnant uterus is largely unresponsive to parasympathetic stimulation or cholinomimetics. In contrast, activation of the sympathetic nervous system can influence the pregnant uterus

Direct-Acting Cholinomimetics

4. Erection (M receptors)

erection is a function of the parasympathetic nervous system through muscarinic receptor stimulation

Secretory glands: [M_3 receptors]

1. Stimulation of secretions of salivary (M_1 also), sweat, lacrimal and nasopharyngeal glands.

Exocrine glands are stimulated by the parasympathetic system, which is why it is called the secretory system. At the same time, it causes smooth-muscle contraction, which is why it is also called the motor system. Together, this is referred to as the secretomotor system

Now, let's discuss a group of drugs that **inhibit cholinesterase** .
These drugs are **indirect-acting** dna **non-selective** eht tceffa yeht gninaem , **autonomic** ,**central** dna ,**musculoskeletal systems** esu eseht lla ecnis ,**acetylcholine** as a neurotransmitter.

These drugs are called **indirect-acting cholinomimetics** or **acetylcholinesterase inhibitors** si desu netfo mret retrohs A .**anti-cholinesterases** yb krow yehT . **inhibiting the hydrolysis of acetylcholine** sti ot gnidael ,**accumulation at the synapse** dna **prolonged pharmacological effects**.

There are **three main types** era srehto eht elihw ,yllacitupareht tnatropmi si eno :
sa dezingocer ylniam**toxins**

Indirect-Acting Cholinomimetics

- **Acetylcholinesterase inhibitors or anticholinesterases.**

1) **Edrophonium. Simple alcohol bearing a quaternary ammonium group**

What is a quaternary ammonium? A quaternary ammonium compound always carries a positive charge. This means it is water-soluble, cannot cross cell membranes, cannot be given orally, and does not cross the blood-brain barrier. These properties make quaternary ammonium compounds useful in the diagnosis of certain diseases, which we will discuss later.

2) **Carbamates:**

a. **Neostigmine. (ester of carbamic acid) and is a quaternary ammonium.**

Indirect-Acting Cholinomimetics

b. **Physostigmine. is a naturally occurring tertiary amine (lipid soluble) ,,,**so can pass through membranes and can go to the central nervous system and can be absorbed by the GI tract ,,,,.Physostigmine used as antitode (antagonist)

c. **Carbaryl. Very high lipid solubility, it is an insecticide.**

Insectحشرة

Cide قاتل

Mechanism of carbaryl:make inhibition of choline esterase then there will be a accumulation of acytel choline in their bodies and then the acytel choline make paralysis so they can't breath and eventually die

Indirect-Acting Cholinomimetics

Organophosphate

3. **Orphosphates:** these are insecticide and humancides which means nerve gases that is used in chemical warfare,, chemical weapon)

a. **Echothiophate** (thiocholine derivative of clinical value)

Metabolized in the body

b. **Parathion, Malathion → Paraoxon, Malaoxon** (Insecticides)

c. **Soman, Sarin** (nerve gases).

Used in chemical warfare

Note: Organophosphates are no longer approved for use as insecticides and their use is illegal. Using them as insecticides is punishable by law because they are highly toxic to humans and persist on vegetables even after washing, leading to potential poisoning. Therefore, in agriculture, carbamates are the preferred choice for insecticidal use instead of organophosphates

Indirect-Acting Cholinomimetics

- **These Anticholinesterases have similar pharmacodynamics but differ in chemical structure and pharmacokinetics.**
- **They also affect nicotinic transmission (why?)**

Indirect-Acting Cholinomimetics

Pharmacokinetics:

- **Absorption of neostigmine (quaternary ammonium carbamates) from the conjunctiva, skin and lungs is poor.**

Neostigmine is a carbamate from the physostigmine group. Carbamates include neostigmine, physostigmine, and carbaryl. When this drug (Neostigmine(is administrated to the eye, it is not systemically absorbed because it is ionized, and ionized compounds do not cross membranes easily, resulting in poor absorption.

- There is a problem if it was high in the CNS, so carbamate's **Distribution into the central nervous system (CNS) is negligible.**

Indirect-Acting Cholinomimetics

- **Physostigmine, in contrast, is well absorbed from all sites and can be used topically.**
- **It is also distributed to the CNS (why?).**
- **It is more toxic than more polar carbamates.**
- **Carbaryl is very well absorbed from all site and distributed to the CNS extensively**
  Because it's lipid soluble.

Indirect-Acting Cholinomimetics

Physostigmine is the exception to the other carbamates that are poorly absorbed because they are ionized. It is a tertiary amine, so it is absorbed from all sites and can be used topically. It is also distributed to the CNS because it is lipid-soluble and can cross biological membranes. Physostigmine is more toxic than the more polar carbamates and is more toxic than neostigmine, which is a quaternary ammonium compound.

Drug	Chemical type	CNS penetration	Toxicity	Explanation
Neostigmine	Quaternary ammonium	❌ Does NOT enter CNS	⬇️ Lower	Ionized, polar → poor membrane crossing
Physostigmine	Tertiary amine	✅ Enters CNS	⬆️ Higher	Lipid-soluble → crosses BBB
Carbaryl	Carbamate (lipophilic)	✅ Enters CNS extensively	⬆️ High	Very well absorbed, highly lipid-soluble

Indirect-Acting Cholinomimetics

- **The organophosphates (except echothiophate) are well absorbed from skin, lung, gut and conjunctiva. They are extensively distributed to all parts of the body including CNS.**

  We have previously stated that cholinergic, or cholinomimetic, drugs facilitate the drainage of aqueous humor. These indirect cholinomimetics increase acetylcholine, thereby enhancing aqueous humor drainage from the eye and reducing intraocular pressure. However, they are not as commonly used as timolol and pilocarpine. If there is a problem with the response, they can be used, as they have a more sustained effect.

Echothiophate is organophosphate that is **highly polar and is used topically in the conjunctiva to treat glaucoma.**

Glaucoma = increased intraocular pressure due to impaired aqueous humor drainage, leading to optic nerve damage.

Organophosphates are very dangerous because they are absorbed everywhere. Direct contact without gloves leads to absorption, and the substance can reach the brain. For this reason, their use in agriculture is prohibited. If they are to be used, complete body protection is required, including eye protection with a face mask and hand protection with gloves. Because this level of protection is difficult for some people to maintain, their agricultural use is prohibited.

Indirect-Acting Cholinomimetics

Pharmacodynamics:

- **Inhibition of cholinesterases increases the concentration of endogenous acetylcholine.**

1. **Edrophonium produces a short-lived and reversible inhibition of the enzyme (2-10 minutes).**
2. **Carbamates produce a reversible and prolonged inhibition (0.5-6 hours) .**

Edrophonium is used for diagnosis because of its very short half-life. The condition involved is myasthenia gravis (the doctor said this condition isn't required but he explained it), which results from antibodies against acetylcholine receptors. As a result, the activity of these receptors is decreased. It is an immune-mediated disease. When an acetylcholinesterase inhibitor is given, the level of acetylcholine increases, allowing it to compete with the antibodies. These antibodies act like a drug by preventing activation of acetylcholine receptors. Increasing the concentration of acetylcholine overcomes the muscle relaxation, allowing muscle movement.

Muscle weakness can have many causes because myopathies include different diseases, so the underlying reason may not be clear. If a patient is given edrophonium and shows improvement, such as being unable to walk properly and then being able to walk after intravenous administration, this suggests myasthenia gravis. However, after 10–15 minutes, the patient returns to the original condition. This confirms the diagnosis of myasthenia gravis.

Therefore, **edrophonium is used only for diagnosis** and not for treatment. The treatment involves using drugs with a longer duration of action, mainly anticholinesterases.

Due to carbamates' prolonged inhibition, we use neostigmine & physostigmine to treat myasthenia gravis, approximately we need to give the patient the drug 4 times a day, every 6 hours or at least 3 times to keep muscles functioning.

Indirect-Acting Cholinomimetics

3. **Organophosphates phosphorylate the active site** In the acetylcholinesterase enzyme **covalently and irreversibly.**

- **The effect is long-lasting (hundreds of hours).**
- **Later on, one oxygen-phosphorus bonds is broken leading to strengthening of the phosphorus-enzyme bond, a process called aging of the enzyme (24-48 hours after exposure).**

Indirect-Acting Cholinomimetics

3. **Organophosphates phosphorylate the active site** In the acetylcholinesterase enzyme **covalently and irreversibly.**

The first splash of organophosphate we immediately lose all the acetylcholinesterase in the body, when the activity is back?? When new acetylcholinesterase is synthesized because the enzyme is inhibited irreversibly by covalent binding (it cancels the presence of the enzyme in the body) and this is why we should not use them in agriculture as insecticides, due to their high toxicity.

Indirect-Acting Cholinomimetics

- **The effect is long-lasting (hundreds of hours).**

The reason for the prolonged effects of organophosphates is twofold. First, the synthesis of new enzymes takes time: it requires 3–4 days for the process to occur, starting from the gene and continuing until the enzyme is fully produced. Second, organophosphates accumulate in the body by binding to fat. They are then slowly released from fat over several months, meaning their toxicity persists even after exposure has stopped. This gradual release explains why their effects can continue for an extended period, as in cases where they do not cause death. The half-life may be around 100 hours (approximately 4 days), but in some cases, it can extend to 40–50 days.

Indirect-Acting Cholinomimetics

- **Later on, one oxygen-phosphorus bonds is broken leading to strengthening of the phosphorus-enzyme bond, a process called aging of the enzyme (24-48 hours after exposure).**

The problem arises because, over time, one oxygen–phosphorus bond in the organophosphate molecule is broken, which leads to a strengthening of the phosphorus–enzyme bond in a process called aging. Aging means that the enzyme, acetylcholinesterase, becomes permanently inactivated. If aging occurs while organophosphates are still stored in body fat, this situation becomes very dangerous. However, there are interventions that can be attempted to counteract this effect, and they may be successful. The explanation of how this can be done is presented after two slides.

Indirect-Acting Cholinomimetics

- **Oximes (pralidoxime) are nucleophiles and are able to break the phosphorus-enzyme bond before aging occurs, and are called "Cholinesterase regenerators".**
- **They are part of the treatment of organophosphate but not carbamate poisoning. When? & Why?**

Indirect-Acting Cholinomimetics

- **Oximes (pralidoxime) are nucleophiles and are able to break the phosphorus-enzyme bond before aging occurs, and are called "Cholinesterase regenerators".**

Oximes work by freeing the enzyme from the organophosphate, allowing it to function again. However, the problem is not completely resolved because organophosphates are highly soluble and remain in the body for long periods. If aging has occurred, pralidoxime becomes ineffective and cannot reverse the enzyme inhibition. Therefore, patients exposed to organophosphates require immediate medical attention. They should be treated promptly with pralidoxime as well as an anticholinergic drug such as atropine, because the toxicity results from excessive acetylcholine due to inhibition of acetylcholinesterase.

Indirect-Acting Cholinomimetics

- **They are part of the treatment of organophosphate but not carbamate poisoning. When? & Why?**

When? Oximes should be given before aging of the organophosphate–enzyme bond occurs.

Why? In the case of carbamate poisoning, the binding of carbamates to acetylcholinesterase is reversible, so the enzyme regenerates automatically. This happens because part of the enzyme hydrolyzes and releases the carbamate, while another part remains temporarily inhibited. In contrast, organophosphates bind irreversibly to the enzyme, forming covalent bonds throughout the body and causing permanent inhibition.

Indirect-Acting Cholinomimetics

Organ-system effects:

- **These effects are due to accumulation of acetylcholine at all cholinergic sites** (Brain, CNS, and skeletal muscles).
- **Therefore, the actions are similar, but not identical, to those of the direct-acting cholinomimetic agonists.**
- Why? The effects are similar but not identical to those of direct-acting cholinomimetic agonists because, in addition to the autonomic nervous system, acetylcholine also acts on the central nervous system and skeletal muscles.

1. **Actions on eye, GIT, respiratory tract and urinary tract are similar to the direct-acting cholinomimetic agonists.**

Indirect-Acting Cholinomimetics

2. **CNS (both muscarinic and nicotinic receptors):**

- **Low concentrations cause diffuse activation of CNS and an alerting response** So if someone touched organophosphate with his hand so it arrived the CNS he feels awake, but 👇
- **In higher concentrations, they produce generalized convulsions followed by coma and death.**

This phenomenon is called initial stimulation followed by inhibition. At first, stimulation of CNS receptors leads to alertness. As the concentration of acetylcholine increases, it can cause convulsions. A further increase results in coma (representing depression of CNS activity), and an even higher concentration can lead to death (severe depression). This pattern—early activation followed by depression—is characteristic of CNS receptors in general. Therefore, patients exposed to organophosphates often die from convulsions and coma, because to stop breathing, the function of the entire CNS must be suppressed.

هون معناها تثبيط

Indirect-Acting Cholinomimetics

3. **CVS:**

- **They can stimulate both parasympathetic and sympathetic ganglia (nicotinic receptors), although parasympathetic activation predominates.**
- **Sympathetic ganglia stimulation may counteract the effects of acetylcholine on vascular beds → vasoconstriction. At toxic doses these agents may cause tachycardia, instead of bradycardia.**

Indirect-Acting Cholinomimetics

3. **CVS:**

- **They can stimulate both parasympathetic and sympathetic ganglia (nicotinic receptors), although parasympathetic activation predominates.**

Nicotinic receptors are present at the ganglia and are normally activated by acetylcholine. Organophosphates do not act solely on muscarinic receptors of the parasympathetic system; they also affect nicotinic receptors, which are activated due to the accumulation of acetylcholine. However, parasympathetic effects generally predominate.
Regarding autonomic innervation, each organ is influenced predominantly by either the sympathetic or parasympathetic system. For example:
•In the heart, parasympathetic activity predominates.
•In blood vessels, sympathetic activity predominates.
•In exocrine glands, parasympathetic activity is dominant.
This explains why the effects of organophosphates vary depending on the target organ.

Indirect-Acting Cholinomimetics

- **Sympathetic ganglia stimulation may counteract the effects of acetylcholine on vascular beds → vasoconstriction.** When the sympathetic ganglia are stimulated, catecholamines are released, causing vasoconstriction.

- **At toxic doses these agents may cause tachycardia, instead of bradycardia.**

As mentioned, sympathetic stimulation leads to tachycardia. However, parasympathetic stimulation can also occur, which may reduce the heart rate and cause bradycardia.

Indirect-Acting Cholinomimetics

4. **Neuromuscular junction (nicotinic receptors):**

- **Low concentration increases the strength of contraction in skeletal muscle.**
- **High concentration leads to fibrillation of the muscle fibers, muscular fasciculation may also occur.**
- **Marked inhibition of acetylcholinesterase my produce neuromuscular blockade.**

Initially, muscle contractility increases due to the elevated levels of acetylcholine. With continued stimulation, excessive contractility occurs, leading to muscle fibrillation. This means the muscles undergo fatigue (exhaustion), rupture of muscle fibers, release of potassium, and ultimately weakness.

Organophosphate exposure may cause paralysis. Why? Because the muscle undergoes sustained depolarization. Normally, muscle contraction involves depolarization followed by repolarization, but in this case, the muscle does not have time to repolarize. This sustained depolarization prevents further contraction, leading to paralysis or relaxation of the muscle, as it loses its ability to contract.

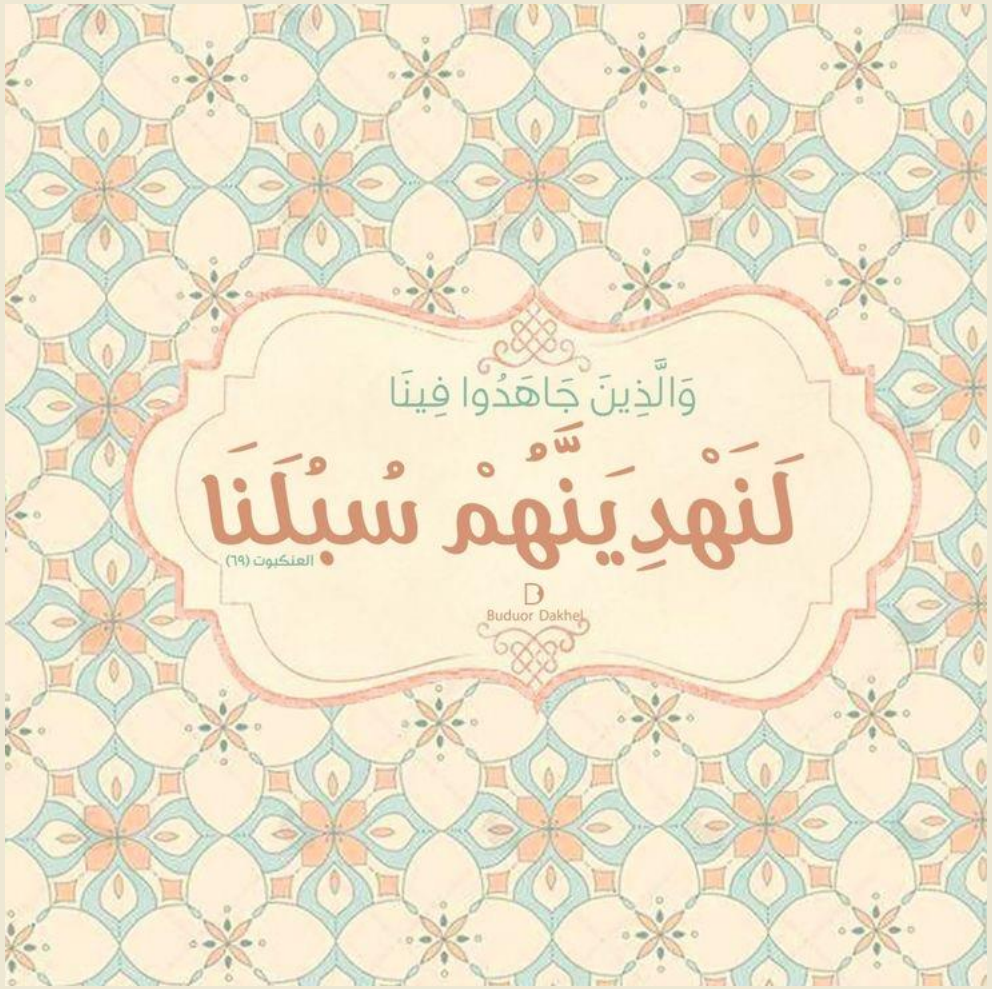
⚠️ **CAUTION:**

DO NOT READ THIS UNLESS YOU ARE DONE WITH THIS MODIFIED:

Dr. Yacoub: "I know this lecture is not easy but it’s important because you’re gonna face poisoned patients (with insecticides or herbicides and other toxins or overdoses of drugs) in the emergency room, this will be explained to you in more details when you take toxicology with forensic medicine (الطب الشرعي) in 5th year."

إن شاء الله على خير:)

رسالة من الفريق العلمي:



ويقول ابن القيّم رحمه الله: إنّما يجد المشقّة في ترك المألوفات والعوائد من تركها لغير الله، فأما من تركها صادقًا مخلصًا من قلبه لله فإنه لا يجد في تركها مشقّةً إلّا في أوّل وهلةٍ، ليُمتَحَنَ أصادقٌ هو في تركها أم كاذبٌ، فإن صبر على تلك المشقّة قليلًا استحالت لذّةً.

لا تنسَونا من صالحِ دُعائِكُم

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide #**7**	In the GI tract, parasympathetic stimulation causes relaxation of the smooth muscle in the bowel wall while simultaneously causing contraction of the sphincters.	In the GI tract, parasympathetic stimulation causes Contraction of the smooth muscle in the bowel wall while simultaneously causing Relaxation of the sphincters.
V1 → V2			