◉Sheet ○Slides

number : 5

doctor : Hamzeh

done by : zaid alkhateeb

correction : ahmad tarefe

In this sheet we will continue in slides #2 then we will start with slides #3…

Toxicity

- Varies markedly depending on their **absorption**, access to the CNS, and metabolism.
- **Direct-Acting Muscarinic Stimulants**
- **Pilocarpine** and the **choline esters** over dosage cause:

  nausea, vomiting, diarrhea, urinary urgency, salivation, sweating, cutaneous vasodilation, and bronchial constriction.
- The effects are all blocked competitively by **atropine**

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Direct-Acting Muscarinic Stimulants :

-Such drugs (like ; Pilocarpine& Choline esters) can cause excessive parasympathetic effect (red in the slide) .

- in urinary urgency : you feel you have to go to urinate (or may be involuntary urination due to high doses)

- **Certain mushrooms** contain muscarinic alkaloids. (*Amanita muscaria,* the first source of muscarine, contains very low concentrations of the alkaloid.) Ingestion of these mushrooms causes typical signs of muscarinic excess within 15–30 minutes.

Treatment is with **atropine**, 1–2 mg parenterally.

-These mushrooms cause muscarinic poisoning

-Atropine is classical muscurinic blocker (blocks all muscurine receptors)

Direct-Acting Nicotinic Stimulants

Acute Toxicity

- The **fatal dose** of nicotine is 40 mg, or 1 drop of the pure liquid.

  This is the amount of nicotine in two regular cigarettes. Fortunately, most of the nicotine in cigarettes is destroyed by burning or escapes via the "side stream" smoke.

- Ingestion of nicotine insecticides or of tobacco by infants and children is usually followed by vomiting, limiting the amount of the alkaloid absorbed.

- Nicotine is a very poisonous or toxic material. In fact ; it is used as rat poison .

Toxic effects of a large dose of nicotine are:

(1) central stimulant actions, which cause convulsions and may progress to coma and respiratory arrest;

(2) skeletal muscle end plate depolarization, which may lead to depolarization blockade and respiratory paralysis.

(3) hypertension and cardiac arrhythmias.

Treatment of acute poisoning is symptom-directed.

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- Nicotine is a drug of abuse and cause addiction because nicotine can stimulate release of dopamine in the pleasure centers
- Treatment of acute poisoning is symptom directed : we see the symptoms and treat each one
  e.g. if we have convulsions we give diazepam anticonvulsant

- Muscarinic excess resulting from parasympathetic ganglion stimulation can be controlled with **atropine.**

- Central stimulation is treated with anticonvulsants such as **diazepam**. Neuromuscular blockade is not responsive to treatment and requires mechanical respiration.

- Fortunately, nicotine is metabolized and excreted relatively rapidly. Patients who survive the first 4 hours usually recover completely if hypoxia and brain damage have not occurred.

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(Note that there is no pharmacological treatment for depolarizing neuromuscular blockade , but there is treatment for the NON-depolarizing ones .)

Chronic Nicotine Toxicity

- Nicotine contributes to the increased risk of **vascular disease and sudden coronary death associated with smoking**.
- Also, the high incidence of **ulcer recurrences** in smokers.
- **Replacement therapy with nicotine** in the form of gum, transdermal patch, nasal spray, or inhaler are used to help patients stop smoking.

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For smokers , It's well-known now that tobacco smoking is a cause of sudden coronary death and heart-attack .
- Also , high incidences of ulcer recurrences in smokers with peptic ulcer .
-there are two elements that causes addiction for smokers :
1- the body's craving or desire for nicotine (can be solved by partial effect nicotine such as gum …)
2- the habit of liking a cigarette

Varenicline

- Has **partial agonist action at central nicotinic receptors.**
- **It also has antagonist properties** that persist because of its long half-life; this prevents the stimulant effect of nicotine at presynaptic nicotinic receptors that cause release of dopamine.
- its use is limited by nausea and insomnia and also by exacerbation of psychiatric illnesses, including anxiety and depression.

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The main idea ; is that it blocks the central nicotinic receptors whom (the receptors) cause the release of dopamine .Dopamine gives the smoker the feeling of pleasure ; so by blocking dopamine release , we cut that pleasure!

•Insomnia ; which is habitual sleeplessness or inability to sleep .

Cholinesterase Inhibitors

- The major source of intoxications is **pesticide**.
- **pesticides** can cause symptoms which persist for days.
- chemical warfare agents (**soman, sarin, VX**) induce effects rapidly.

. **Miosis, salivation, sweating, bronchial constriction, vomiting, and diarrhea**.

CNS involvement (**cognitive disturbances, convulsions, and coma**) usually follows rapidly, accompanied by peripheral nicotinic effects, especially depolarizing neuromuscular blockade.

Pesticide : is taken in by inhalation

Anything that is taken by (inhalation) is absorbed instantly . e.g. when you inhale nicotine it will reach brain faster than if it was taken intravenously (IV) because by inhalation it goes (lungs→heart→brain)

Therapy always includes:

(**1**) maintenance of vital signs—respiration in particular may be impaired.

(**2**) decontamination to prevent further absorption.

(**3**) atropine parenterally in large doses, given as often as required to control muscarinic excess.

Therapy often also includes treatment with pralidoxime, and benzodiazepines for seizures.

- **Preventive therapy for cholinesterase inhibitors warfare agents**
- Personnel are given **autoinjection syringes containing pyridostigmine and atropine**.

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-contamination #2 : by gastric lavage(غسيل المعدة) for example

-As an example of #3 : sometimes we inject the patient every 15 minutes until we see that the patient is about to have toxicity due to atropine ; like until the pupil is very wide .

- **Chronic exposure** to certain organophosphate compounds causes **delayed neuropathy associated with demyelination of axons**.
- The effects are not caused by cholinesterase inhibition but rather by neuropathy target esterase (NTE) inhibition whose symptoms (weakness of upper and lower extremities, unsteady gait) appear 1–2 weeks after exposure.

- **Another nerve toxicity called intermediate syndrome** occurs 1–4 days after exposure to organophosphate insecticides. This syndrome is also characterized by muscle weakness; its origin is not known but it appears to be related to cholinesterase inhibition.

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Un-steady gait ; which is an abnormality in walking

now ,We will start with a new subject ; with Slide number 3 !

Cholinoceptor -Blocking Drugs

Drugs that block muscarinic cholinoceptors.

Five subtypes of muscarinic receptor :

- **M1** on CNS neurons, sympathetic postganglionic cell bodies, and many **presynaptic** sites.
- **M2** in the **myocardium**, smooth muscle organs, and some neuronal sites.
- **M3** on effector cell membranes, especially **glandular** and **smooth muscle** cells.
- **M4** and **M5** play a greater role in the CNS than in the periphery.

Note that all of the 5 types are found in the CNS (exactly in the brain) ; yet only M1 , M2 & M3 are found in the peripheral nervous system .

Absorption

- Natural alkaloids (Solanaceae species, e.g. atropa belladona) & most tertiary antimuscarinic drugs are well absorbed
- **Scopolamine** is absorbed across the skin (transdermal).
- Quaternary antimuscarinic drugs 10–30% of a dose is absorbed after oral administration

Distribution

- Atropine and the other tertiary agents are widely distributed, reach CNS within 30 minutes to 1 hour.
- Scopolamine is rapidly and fully distributed into the CNS where it has greater effects than most other antimuscarinic drugs.
- In contrast, the quaternary derivatives are poorly taken up by the brain.

atropabelladonna (**atopa** : a Greek God that is thought to strangle people+ **belladonna** : is a beautiful lady ; as this drug was as a cosmetic used to plush cheeks and pupil the eyes)

- We also have quaternary antimuscarinic drugs which are synthetic . They don't cross the Brain-Blood-Barrier (BBB) ; so it's doesn't have a central effects . And only about 10-30% of the drug dose is absorbed after oral administration

Distribution: depends whether we are talking about natural or synthetic antimuscarinic drugs.
- Natural alkaloids like atropine and other tertiary agents are widely distributed; they can reach the CNS within 30 minutes to 1 hour.
- Scopolamine is rapidly and fully distributed into the CNS where there; it has the greater effects than most other antimuscarinic drugs (at low dose it causes amnesia but at high dose it can cause hallucinations, convulsions and excitation).

Metabolism and Excretion

Elimination of **atropine** occurs in two phases:

the *t*1/2 of the rapid phase is 2 hours and that of the slow phase is 13 hours.

About 50% of the dose is excreted unchanged in the urine (***the dextro form***, *levo isomer is* ***hyoscyamine***).

Most of the rest appears in the urine as hydrolysis and conjugation products.

The drug's effect on parasympathetic function declines rapidly in all organs **except the eye.**

Effects on the iris & ciliary muscle persist for 72 hours

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t1/2) = half-life

Why we have here 2 half-life for atropine ?

because Atropine exists as *levo*-hyoscyamine in plants ; and when you extract the *levo*- ; half of it becomes *dextro*- ; and that mixture is atropine! -What happens is that the *levo*- metabolized in the fast phase and the other half which is *dextro*- is excreted in the urine.

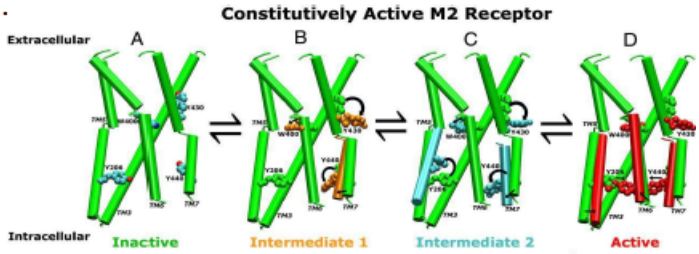
Mechanism of Action

Atropine causes reversible blockade of all M receptors.

Muscarinic receptors are **constitutively active**, and muscsrinic blockers are **inverse agonists** that shift the equilibrium to the inactive state of the receptor.

Inverse agonists include:

Atropine, pirenzepine, trihexyphenidyl & a methyl derivative of scopolamine



Tissues most sensitive to atropine are the salivary, bronchial, and sweat glands.

Secretion of acid by the gastric parietal cells is the least sensitive.

Antimuscarinic agents block exogenous cholinoceptor agonists more effectively than endogenously released

- Drugs go with competitive antagonism for muscarinic receptors. Atropine causes reversible blockade (can be overcame by increasing the concentration of the agonist).

- **constitutively active** receptors are receptors presented in many forms (active / inactive) and they tend to shift into the active form (here the doctor mentioned : inactive→intermediate1→ intermediate 2 →active) . in constitutively active receptors, the active form can produce its effect even the agonist isn't presented .

- Muscarinic receptors are **constitutively active**

- **inverse agonists:** an agent that binds to the same receptor as an agonist but induces a pharmacological response opposite to that agonist (acts as antagonist or blocker), so it shift the reaction towards the inactive form

Organ System Effects

Central Nervous System

Atropine has minimal stimulant effects on CNS.

Scopolamine has more marked central effects, producing drowsiness and amnesia.

In toxic doses, scopolamine, and to a lesser degree atropine, can cause excitement, agitation, hallucinations, and coma.

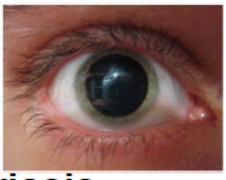
The tremor of Parkinson's disease is reduced by centrally acting antimuscarinic drugs, and atropine—in the form of belladonna extract—was one of the first drugs used in the therapy of this disease.

Parkinson disease: degeneration of dopamine neurons in the brain , leads to imbalance between : cholinergic transmition and dopaminergic transmition , which gives finally symptoms like muscles rigidity and tremor .

Vestibular disturbances

Scopolamine is effective in preventing or reversing these disturbances.

Eye

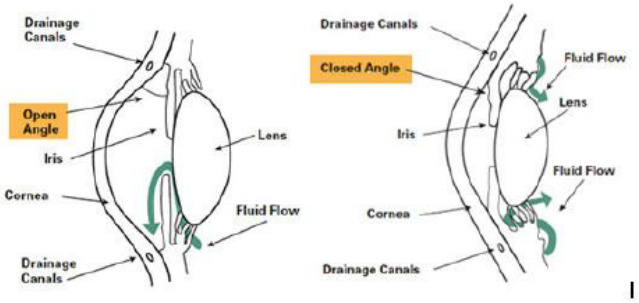


Atropine and other tertiary antimuscarinics cause an unopposed sympathetic dilator activity & **mydriasis**

Paralysis of the **ciliary muscle**, or **cycloplegia** resulting in **loss of accommodation** the fully atropinized eye cannot focus for near vision.

cause acute **glaucoma** in patients with a narrow anterior chamber angle.

Antimuscarinic drugs



reduce lacrimal secretion causing dry or "sandy" eyes.

-mydriasis is the dilation of the eye pupil .

-what determine pupil size is the amount of light presented (low light = dilated pupil) and vice versa .