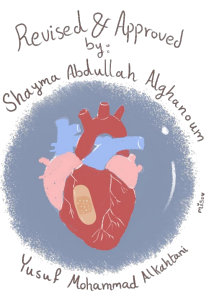
PHARMACOLOGY
TEAM 439



MED439
KING SAUD UNIVERSITY

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INDIRECT CHOLINOMIMETICS

Lecture 4

OBJECTIVES:

- Classification of indirect acting cholinomimetics
- Mechanism of action, kinetics, dynamics and uses and of anticholinesterases
- Adverse effects & contraindications of anticholinesterases
- Symptoms and treatment of organophosphates toxicity.

Important
In male and female slides
Only in male slides
Only in female slides
Extra information

Helpful video

Indirect cholinomimetics (Anticholinesterases)

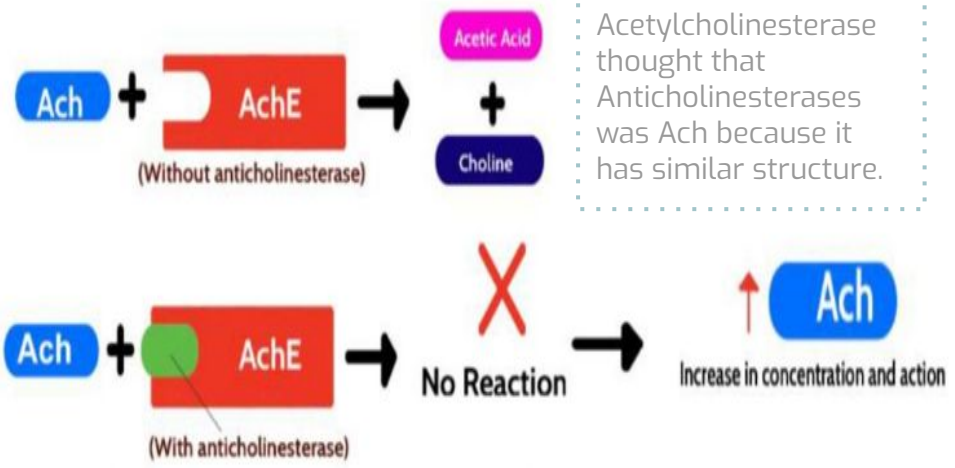
-Mechanism of action:

prevent the hydrolysis of acetylcholine by inhibiting Acetylcholinesterase; thus increasing acetylcholine concentration and action at the cholinergic receptors (both nicotinic and muscarinic) not like direct cholinomimetics

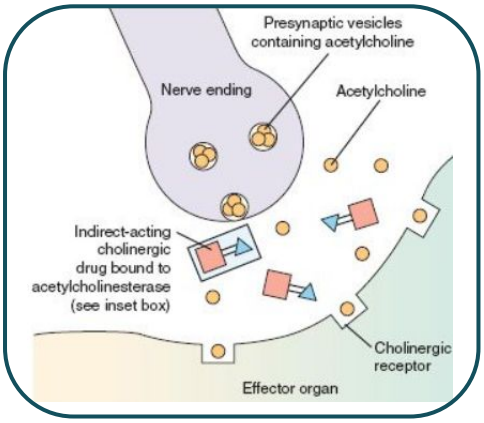
المحاضره هذي باختصار اني ابغى ازود تأثير ach عن طريق اني اسوي تثبيط للإنزيم اللي يكسر ach وهو esterase باستعمال أدوية محددة وتعتبر الطريقة هذه indirect.

-Anticholinesterases are similar in structure to Ach to combine with cholinesterase enzyme (2 sites: **Anionic polar** and **esteratic** sites) instead of Ach."

Ach esterase has 2 binding sites one that bind to the polar part of Ach (Anionic) and the other one bind to the ester part of Ach (Esteratic).



Acetylcholinesterase thought that Anticholinesterases was Ach because it has similar structure.



Classification of Anticholinesterases

(According to the duration of action)

- Reversible — 4-8 hours
- Irreversible — Weeks to days

Reversible Anticholinesterases (4-8 hours)

	Alcohols	Carbamate esters
Duration	Short acting because when it binds with esterase it binds to polar site only, while the Esteratic site remain empty.	Intermediate Acting
Binding with Ach esterase	Forms weak hydrogen **(electrostatic)bond** with acetylcholinesterase Enzyme (One site)	binds to two sites of Cholinesterase Enzyme **(covalent bond)**
Examples	Edrophonium	• Physostigmine • Neostigmine • Pyridostigmine
Further features	-----	• All polar and synthetic EXCEPT **physostigmine** (lipid soluble). • relatively stable in aqueous solution. but can be metabolized by esterases.

Irreversible Anticholinesterases (weeks to days)

	Phosphate esters
Duration	Long acting
Binding with Ach esterase	• Form very stable covalent bond with cholinesterase, resistance to hydrolysis. • Phosphorylate the enzyme.
Examples	e.g. insecticides, gas war, Echothio**phate** & Isoflurop**hate**. (Very toxic drugs but they are the only exception used medically (topical eye drops)).
Further features	-All phosphates are lipid soluble EXCEPT **Echothiophate** which is polar. -well absorbed from the skin, lung, gut & conjunctiva except ecothiopate. -less stable in aqueous solution.

Primary effect is to potentiate the action of endogenous Ach

Pharmacological effects of Anticholinesterases

- **-They act on both muscarinic and nicotinic receptors .**
- **-Some have CNS effects (only the lipid soluble drugs) e.g. physostigmine & phosphate ester(except ecothiophate that is polar).**
- **CNS actions:**
  -In low concentration:- The high lipid-soluble inhibitors cause diffuse activation of EEG leading to alerting response(ß wave).
  -In high Concentration:- generalized convulsions followed by coma & respiratory arrest.

	Site	Action
Nicotinic actions	Neuromuscular junction	-**Therapeutic dose:** muscle contraction. -**Toxic dose:** lead to fibrillation of muscle fibers, membrane depolarization becomes sustained.(depolarization block).
	Ganglia	stimulation of sympathetic and parasympathetic ganglia
	Adrenal medulla	release of catecholamines (adrenaline and noradrenaline)
Muscarinic actions	Eye	-Contraction of circular muscle of iris (also called constrictor pupillae or iris sphincter muscles) (miosis) **M3**. -Contraction of ciliary muscles for near vision **M3**. -Decrease in intraocular pressure.
	Heart endothelium	-bradycardia (decrease heart rate) **M2** -Release of NO (EDRF) (Vasodilation). -decrease conduction velocity through AV node, -decrease atrial contractility and modest change in Bp
	Lung	- Constriction of bronchial smooth muscles. - Increase bronchial secretion **M3**.
	GIT	-Increased motility (peristalsis). -Increased secretion. -Relaxation of sphincter **M3**.
	Urinary bladder	-Contraction of muscles.. -Relaxation of sphincter **M3**
	Exocrine glands	-Increase in secretion of sweat, saliva, lacrimal, bronchial, intestinal secretions **M3**.

Reversible indirect Cholinergic Drugs

drug	Edrophonium	Physostigmine	Pyridostigmine
action	muscarinic and nicotinic actions	muscarinic and nicotinic actions **has CNS effect**	muscarinic and nicotinic actions
P.K	Polar (alcohol) NOT absorbed orally must be given by **injection.** Distribution in the CNS is negligible Bind reversibly by electrostatic forces to the active site, preventing access of Ach enzyme-inhibitor complex is short lived'2-10min' *short duration of Action(5-15 mins)*	non polar **(lipid soluble).** Good oral absorption Form covalent bond. , more resistant to hydrolysis short duration of action(0.5-2 hr) Cross BBB (**has CNS effects**)	Polar short duration of action (3-6 hr) Distribution in the CNS is negligible.
Uses	★ **Used to diagnose myasthenia gravis** Very very Short duration of action so it is only use for diagnose المريض غالبا ماراح يكون يقدر يتحرك بعد ما نعطيه راح تتحسن الاعراض وتعرف ان التشخيص صحيح	-Acute angle closure Glaucoma (by eye drop). -Atropine toxicity (anticholinergic drug) (Atropine can cross BBB therefore we use Physostigmine which also can cross BBB to block the **muscarinic receptor** in the brain resulting in treating the toxicity)	Treatment of myasthenia gravis.
Binding with Ach esterases	Forms **weak hydrogen** (electrostatic) bond with acetylcholinesterase enzyme (binds to anionic site)	binds to two sites of cholinesterase enzyme(covalent bond)	binds to two sites of cholinesterase enzyme(covalent bond)
Chemical structure	Quaternary ammonium compound	Tertiary ammonium compound	Quaternary ammonium compound

Reversible indirect Cholinergic Drugs

drug	Neostigmine	Ambenonium	Donepezil (Cholinesterase reactivators (OXIMES))
action	muscarinic and nicotinic actions(similar uses to bethanechol,) ★ **(prominent on GIT& urinary tract)**	muscarinic and nicotinic actions	Is a centrally acting reversible acetylcholinesterase inhibitor **M4, M5**
P.K	polar compound more resistant to hydrolysis Can be used orally short duration of action(0.5-2 hr) **NO CNS effect.**	Polar. (4-8hr). Distribution in the CNS is negligible.	Lipid soluble Given orally .
Uses	Treatment of myasthenia gravis. -Paralytic ileus & Urinary retention. -Competitive neuromuscular blockers intoxication (curare toxicity). مثال: لو اعطينا دواء يقفل الreceptor مثل atracurium وحصل تسمم كيف نعالجه؟ بزيادة Ach عند الreceptor عبر استخدام antiAchesterase	Treatment of myasthenia gravis.	Treatment of **dementia** of Alzheimer's disease
Binding with Ach esterases	binds to two sites of cholinesterase enzyme(covalent bond)	----	---
Chemical structure	Quaternary ammonium compound	**Quaternary ammonium compound**	-----

Irreversible Indirect Drugs (Organophosphorous compounds)

Drug	Ecothiophate
Action	**Irreversible** anticholinestrases
P.K	Polar very **long** duration of action (100 hours). ★ **Aging** makes the bond extremely **stable** and makes the treatment difficult from toxicity. All the Organo -phosphorous compounds are **highly lipid** soluble **EXCEPT Ecothiophate** (polar).
Binding with Ach esteraseras	Bind to cholinesterase by **strong** covalent bond.(both sites)
Uses	Used for **Acute angle closure glaucoma.** Used as pesticides and veterinary vermifuge.

organo= lipid soluble

Symptoms of organophosphate toxicity

01 **Heart:** -Sever bradycardia, -hypotension.

02 **CNS:** convulsion, coma and respiratory failure.

03 **Lungs:** bronchospasm

04 **GIT:** Increased GIT motility cramps & diarrhea.

05 **Muscles:** initial twitching of skeletal muscles muscle weakness & paralysis

Treatment of organophosphate toxicity

Support respiration

Cholinesterase reactivators (Oximes)

تكون أفضل إذا جبنا المريض بدري

Atropine (to block muscarinic actions & CNS effects).

Pralidoxime is used as cholinesterase regenerator for organic phosphate poisoning

Cholinesterase reactivators

OXIMES

Pralidoxime (PAM)

Action	**-Cholinesterase reactivator** -Acts by **regeneration** of cholinesterase enzyme. **-Reactivates** recently **inhibited** enzymes before **aging.**
Uses	**I.V.over 15-30 min for organophosphate intoxication.**

Contraindications of cholinergic drugs

- **Bronchial asthma**
- **Peptic ulcer**
- **Angina pectoris**
- **Incontinence** lack of voluntary control over urination or defecation
- **Intestinal obstruction** Leads to ruptured intesti

Clinical uses of indirect cholinomimetics

1-Acute angle closure glaucoma

indirect stimulants e.g: **physostigmine**, **ecothiopate**.

2-GIT & Urinary tract

- **Postoperative ileus** "atony" and **Postoperative urinary retention** → **Neostigmine**
- **Xerostomia** → **Pilocarpine** (direct)

3-Neuromuscular junction

E.g: **Myasthenia gravis**
(discussed in the next slide)

4-To reverse pharmacological paralysis produced in case of anaesthetic adjunct (مساعدات التخدير)

(e.g: **neostigmine** versus **d-tubocurarine**).

5-Heart

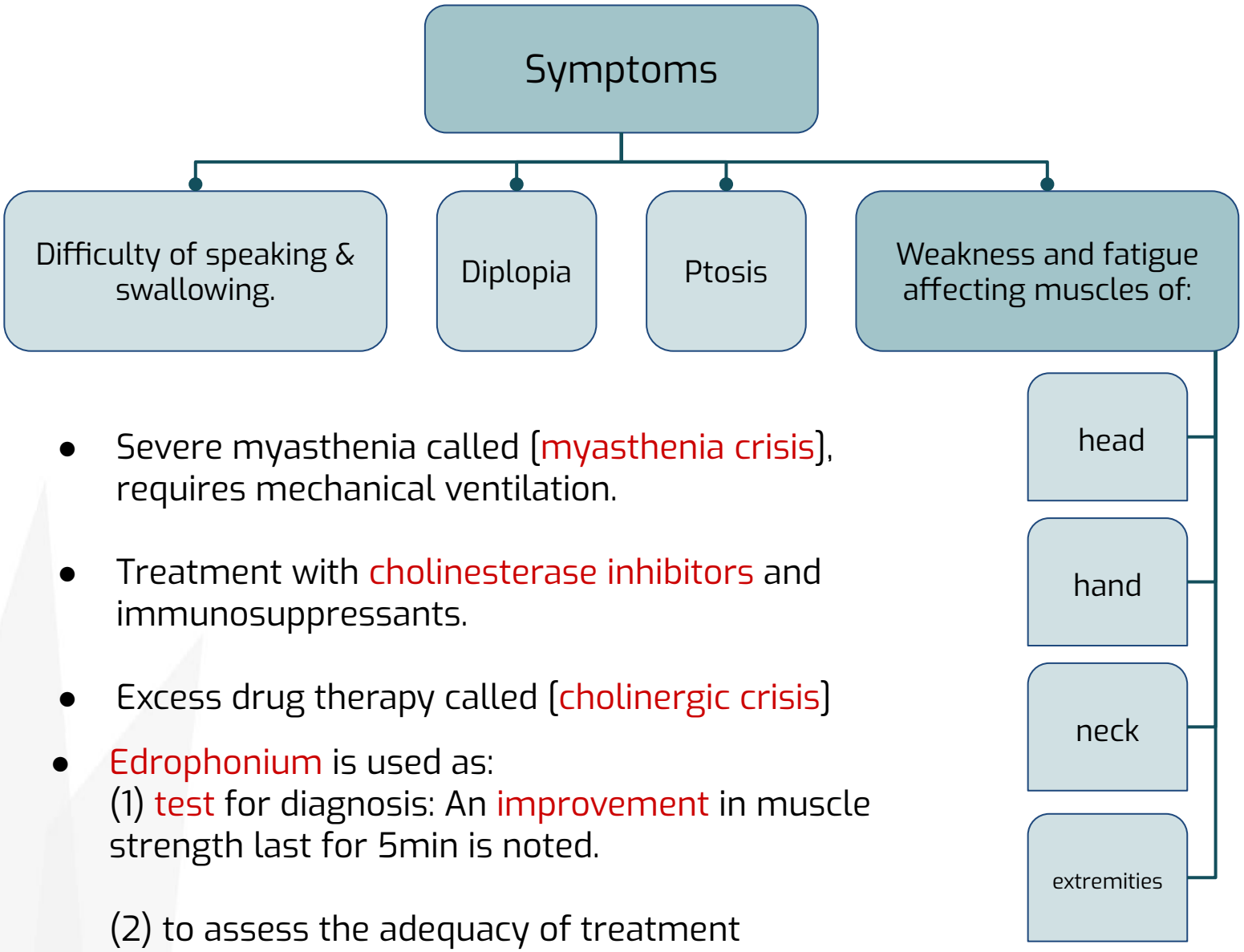
for treatment of supraventricular tachycardia, **edrophonium** potentates the effect of Ach at AV node causing slow AV conduction & ventricular rate.

6-Antimuscarinic drug intoxication

- Atropine overdose is toxic in children → severe muscarinic block
- Blockade is competitive, overdose can be overcome by increasing the amount of endogenous Ach
- **Physostigmine** is used because it can cross the BBB, Reverses central & peripheral signs

Myasthenia gravis

Definition: Autoimmune disease include Production of antibodies leading to decrease number of functioning nicotinic receptors at endplate.



- Severe myasthenia called [myasthenia crisis], requires mechanical ventilation.
- Treatment with cholinesterase inhibitors and immunosuppressants.
- Excess drug therapy called [cholinergic crisis]
- Edrophonium is used as:
  (1) test for diagnosis: An improvement in muscle strength last for 5min is noted.

  (2) to assess the adequacy of treatment with the longer –acting cholinesterase inhibitors.
- If a patient improves with a dose of edrophonium, an increase in cholinesterase inhibitor is indicated.(patient have myasthenia gravis)
- In case of excessive amount of cholinesterase inhibitor, a patient becomes weak because of depolarization block + symtoms of muscarinic stimulation.
- Chronic long term Therapy is done by neostigmine, pyridostigmine, ambenonium.
- Muscarinic side effects can be controlled by antimuscarinics.

Alzheimer's Disease

Characterized by:	loss of cholinergic neurons in the basal forebrain nuclei. Thus cholinesterase inhibitors are used to treat Alzheimer's Disease.
Treated by:	**Donepezil** (is not hepatotoxic), Used for treatment of dementia of AD, Taken orally.

cholinesterase toxicity

CNS involvement follows accompanied by peripheral nicotinic effects.

initial signs of muscarinic excess

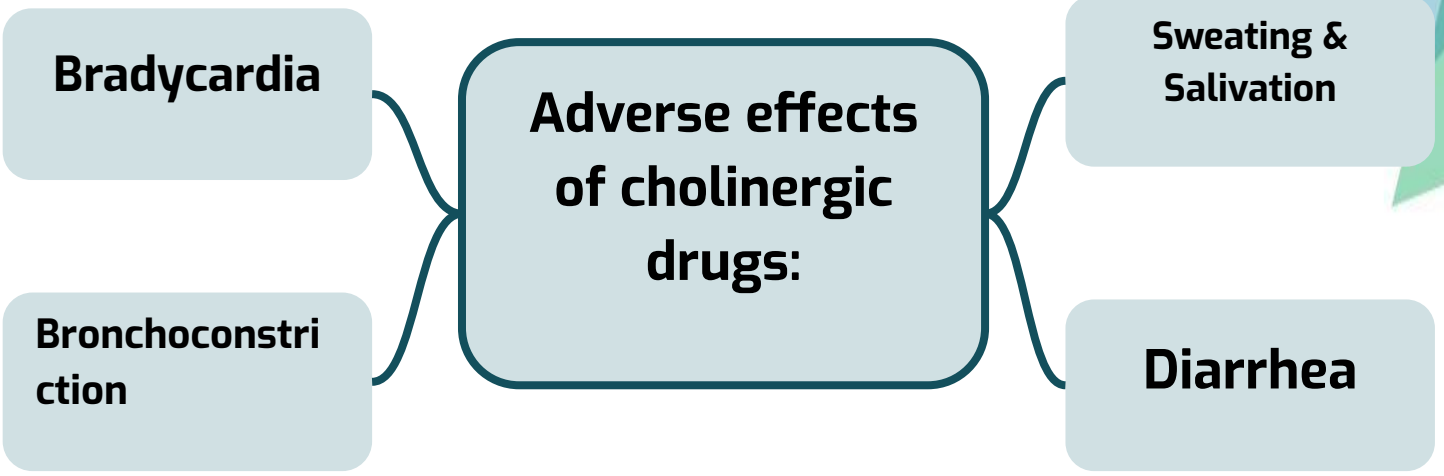
- vasodilation
- bronchial constriction
- salivation
- diarrhea
- sweating
- miosis

Therapy of cholinesterase toxicity:

1- Maintenance of vital signs , respiration may be impaired.

2-Decontamination to prevent further absorption, removal of cloth, washing of skin.

3-Parenteral atropine in large doses. Pralidoxime(PAM)(oxime) often.



Summary of cholinomimetics and their uses

Eye : treatment of glaucoma
-**pilocarpine,carbachol** (direct muscarinic agonist) -**physostigmine** - **ecothiophate** (indirect cholinomimetics)
Urinary retention and paralytic lieus
-**bethanechol** (direct) -**neostigmine** (indirect)
Myasthenia gravis (only indirect cholinomimetics)
-**neostigmine** , **Pyridostigmine, Ambenonium**
Xerostomia (Dry mouth)
-**pilocarpine** -**cevimeline** (sjogren's syndrome)
Alzheimer disease
-**donepezil**

MCQ

A quick quiz is waiting for you! Just click here

Q1: Anticholinesterases have similar structure to:			
A-Ach esterases	B-Ach	C-Both A & B	D-Non of them

Q2: Physostigmine is:			
A-Non polar	B-Polar	C-Lipid soluble	D-Both A & C

Q3: Ach acts on which receptor:			
A-B1	B-Muscarinic	C-Nicotinic	D-Both B & C

Q4: Which of these binds to the two binding sites of Cholinesterase:			
A-Alcohols	B-Carbamate esters	C-Phosphate esters	D-Both B & C

Q5: Which one of these drugs used as diagnosis of myasthenia gravis?			
A-Neostigmine	B-Edrophonium	C- isoflurophate	D- Donepezil

Q6 : Which drug has very long duration of action ?			
Ecothiophate	isoflurophate	Pyridostigmine	Neostigmine

Q7 : All of the following drugs used to treat myasthenia gravis except?			
Ambenonium	Neostigmine	Pyridostigmine	Physostigmine

ANSWERS

1	2	3	4	5	6	7
B	D	D	D	B	A	D

SAQ

1)Describe the bond between Ach esterase and Alcohol.

2)How many binding site does Ach esterase has? And there names?

3)Mention the drugs that has CNS effect.

4)What are the muscarinic action in the eye.

5)describe the mechanism of action of indirect acting Cholinergic drugs.

6)list to adverse effects of cholinergic drugs:

7)list 2 ways to treat organophosphate toxicity.

8)Treatment of dementia ?

ANSWERS

A1) ~~Forms weak hydrogen(electrostatic)bond with acetylcholinesterase enzyme.~~

A2) ~~2, anionic and esteratic.~~

A3) ~~physostigmine & phosphate ester.(except ecothiophate)~~

A4) ~~slide4.~~

~~A5)slde2~~

~~A6)slide10~~

~~A7)slide8~~

~~A8)~~Donepezil

GOOD LUCK!

Team leaders

- طرفة الشريدي
- حمود القاضب

Girls team members

منيرة السدحان
لينا المزيد
سديم الحازمي
نورة المسعد
وسام ال حويس
رانيا المطيري
الجوهرة البنيان
شادن العبيد
سديم آل زايد
روان باقادر
ميس العجمي
نورة السالم
نوف السبيعي
ندى بابللي
دانة نائب الحرم

Boys team members

عبداللطيف المشاط
بسام الاسمري
ماجد العسكر
باسل فقيها
عبدالرحمن الدويش
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