DRUGS ACTING ON THE CHOLINERGIC SYSTEM AND THE NEUROMUSCULAR BLOCKING DRUGS II
INDIRECT ACTING AGONISTS (ANTICHOLINESTERASES) (PP IX)

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Drugs acting on the cholinergic system
Indirect acting agonists (Anticholinesterases)

- Objectives and intended learning outcomes:
  - The student should be able to
    - Classify anticholinesterases
    - Describe their actions and uses
    - Know their adverse effects and toxicity
Indirect acting agonists (Anticholinesterases):

Drugs that inhibit the activity of cholinesterase indirectly provide a cholinergic action by prolonging the life time of Ach, produced endogenously at the cholinergic nerve terminal.

- These drugs therefore lead to the accumulation of Ach in the synaptic space and can produce a response at all cholinoreceptors in the body, including both muscarinic and nicotinic receptors of the ANS as well as the neuromuscular junction and the brain.

- Anticholinesterase can be subdivided into reversible AchE and irreversible AchE.

1- Reversible agents:
- Are carbonic acid esters "carbamates"
- Neostigmine is prototype.

2- Irreversible agents:
- Are phosphoric acid esters "organophosphates"
- Isoflurophate and echothiophate are prototypes.
- A third class which has only one number:
  Edrophonium: is an alcohol (not an ester) which is reversible with a very short duration of action.
1- **Reversible Anti ChE:**

The carbamate residue is released by ChE over a period of 2-8 hours.

**Physostigmine:** is an alkaloid, it’s a tertiary amine (can enter and simulate the CNS)

**Uses:**

1- Because it increases intestinal and bladder motility thus it is used in case of atony of bladder and paralytic ileus.

2- It is also used to treat over dose of drugs with anticholinergic action. Such as **Atropine, Phenothiazine,** and **TCA** (tricyclic antidepressants)

3- **Intraocular pressure (IOP)** thus it is useful in glaucoma but **pilocarpine** is more effective.

**Adv. Effects:**

**CNS:** may lead to convulsions. **In over dose,** bradychardia and neuromuscular (N-M) paralysis may also occur.
Neostigmine: is a synthetic compound (doesn’t enter the CNS), its effect on the skeletal muscles is more than physostigmine because it also has direct action on skeletal m. cholinergic receptors (nicotinic receptors of the N-M junction).

**Uses:**

1- Post operative and neurogenic ileus and urinary retention.
2- Antidote for tubocurarine and other competitive N-M blockers.
3- Symptomatic treatment of myasthenia gravis (weakness in the muscles).
**Pyridostigmine**: it’s duration of action is (3-6 hours) which is longer than Neostigmine (2-4 hours).

**Uses:**
Used in chronic management of myasthenia gravis.

**Edrophonium**: short duration of action (10-20 min).

**Uses:**
1- Used in diagnosis of myasthenia gravis and to differentiate myasthenic crisis from cholinergic crisis.
2- Used as antidote to curare like drugs.
Myasthenia gravis (MG) is a disease affecting skeletal muscle neuromuscular junctions. An autoimmune process causes production of antibodies that bind to the α subunits of the nicotinic receptor. This effect causes accelerated degradation of the receptor and blockade of ACh binding to receptors on muscle end plates. Frequent findings are ptosis, diplopia, difficulty in speaking and swallowing, and extremity weakness. Severe disease may affect all the muscles, including those necessary for respiration.
Indirect Acting Agents used to treat Alzheimer’s disease

- **Donepezil** delays progression of the disease by up to 55 weeks. Does not cause liver toxicity.
- **Galantamine** newest kid on the block
- **Rivastigmine** long acting.
- **Tacrine** hepatoxic. Elevated liver enzymes
In Alzheimer’s disease there is loss of cholinergic neurons.

Cholinacetyl transferase activity in the cortex and hippocampus is reduced from 30% to 70%.

Loss of cholinergic neurons contributes to much of the learning and memory deficit.

The number of M-cholinoceptors is not affected, but the number of N-receptors is reduced.
2- Irreversible Anti ChE:

A number of synthetic organophosphates have the capacity to bind covalently to ChE forming an extremely stable phosphate complex with the enzyme.

- The end result is increased Ach at all sites where it is released. Many of these drugs are extremely toxic and were developed by the military as nerve gas agents (sarìn, tabun, soman), related comp. such as parathion and malathion are employed as insecticides.

- Four organophosphates are used in medicine these are isoflurophate (DFP) and echothiophate (are used as antiglaucoma agents). Malathion as a *scabicide and metrifonate as *anti helimenthic agent.
Toxicity of Irreversible Anti ChE:

This usually occurs because of accidental exposure to toxic amount of pesticides, the most toxic of these drugs (e.g. parathion) are rapidly fatal if the exposure is not immediately recognized and treated.

- **Signs and symptoms of poisoning**: include
  - general cholinergic stimulation *muscarinic and nicotinic*
  - **paralysis of motor function** "causing breathing difficulty "
  - CNS stimulation leading to **convulsions** followed by respiratory and cardiovascular depression.

- The spectrum of toxicity can be remembered with the aid of the mnemonic "**DUMBELS**"
  - D: diarrhea
  - U: urination
  - M: miosis (contraction of pupil)
  - B: bronchoconstriction
  - E: excitation of skeletal muscles and CNS followed by depression
  - L: lacrimation
  - S: salivation and sweating
<table>
<thead>
<tr>
<th>Muscarinic</th>
<th>Nausea, vomiting, abdominal cramps, diarrhoea, faecal incontinence</th>
</tr>
</thead>
<tbody>
<tr>
<td>§Gastrointestinal</td>
<td>Pulmonary oedema, hypotension</td>
</tr>
<tr>
<td>§Respiratory</td>
<td>Bradycardia, hypotension</td>
</tr>
<tr>
<td>§Cardiovascular</td>
<td>Blurring of vision, miosis</td>
</tr>
<tr>
<td>§Pupils</td>
<td>Frequency, incontinence</td>
</tr>
<tr>
<td>§Urinary</td>
<td>Increased sweating, salivation and lacrimation</td>
</tr>
</tbody>
</table>

Note: The mnemonic DUMBELS describes most of the significant muscarinic features

<table>
<thead>
<tr>
<th>Nicotinic</th>
<th>Muscle twitching, fasciculation, cramps, weakness including respiratory muscles</th>
</tr>
</thead>
<tbody>
<tr>
<td>§Skeletal muscle</td>
<td>Pallor tachycardia, hypertension</td>
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<tr>
<td>§Sympathetic ganglion</td>
<td></td>
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</tbody>
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Nicotinic effects maybe sometimes overwhelming

<table>
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<tr>
<th>CNS</th>
<th>Giddiness, tension, anxiety, restlessness, difficulty in concentration, confusion, slurred speech, insomnia, headache, tremor, apathy, withdrawal and depression, drowsiness, nightmares, ataxia, generalized weakness, coma, cheyne-stokes respiration, convulsion, depression of respiratory and circulatory centres</th>
</tr>
</thead>
</table>
Treatment of toxicity:

1- Supportive care: Keep the vital signs,
Contaminated clothing should be removed and the skin washed.
Gastric lavage may be needed if many of the substances have been ingested.
Mechanical ventilation may be needed.

2- Atropine is the main stay of treatment; 2 mg is given IV or IM as soon as possible and repeated every 15-60 minutes. A 100 mg of Atropine may be required for a poisoned patient. Atropine antagonizes the muscarinic actions but has no effect on the nicotinic signs of toxicity.

3- Enzyme reactivation (enzyme regeneration) by using enzyme regenerators, compounds such as pralidoxime are used, which may also reverse the nicotinic signs if used early on "before aging occurs"
Aging: is a further chemical change in the enzyme which renders regenerator drugs unable to remove the inhibitor (organophosphates phosphorylate the active site of the enzyme cholinesterase, and following this covalent modification the phosphorylated enzyme undergoes a further chemical change (losses an alkyl group) which is called aging.
Pralidoxime (PAM):

Is an oxime compound. The oxime group has an extremely high affinity for the phosphate atom in the organophosphates insecticides because the affinity of the oxime group for the phosphorus exceeds that of the enzymes active site. This agent is therefore able to bind the inhibitor and displace (regenerate) the enzyme if aging has not occurred. Pralidoxime is given in a dose of 1 gm every 4 hours IM or by slow IV infusion.

- best results are obtained if it is given is within the first12 hours of poisoning.
- Muscle power may improve within 30 min.
SUMMARY

Indirectly acting cholinomimetics act by inhibiting the activity of cholinesterase enzyme and therefore indirectly provide a cholinergic action by prolonging the life time of Ach at all cholinoreceptors in the body, including both muscarinic and nicotinic receptors of the ANS as well as the neuromuscular junction and the brain.

Anticholinesterases are subdivided into reversible AchE and irreversible AchE.

The reversible are commonly used in medicine

The irreversible AchE are important because of their toxicity