B. 8 Anticholinesterase drugs

a. Classify the anticholinesterase drugs in relation to mechanism of action.

- **anionic site of action**
  - competitive inhibitors of binding of quaternary nitrogen of ACh
  - edrophonium
  - tetraethylammonium

- **esteratic (and anionic) site of action**
  - transfer acidic group onto the esteratic site (carbamate or phosphate)
  - slow dissociation (minutes to weeks)
  - carbamates
    - neostigmine
    - pyridostigmine
    - physostigmine
  - organophosphates
    - ecdothiopate
    - parathion

b. Describe structure-activity relationships of these drugs.

- **quaternary ammonium group**
  - binds to anionic site by electrostatic force
  - reduces lipid solubility
  - poor oral bioavailability
  - don’t cross BBB

- **electrophilic group**
  - carbamate or phosphate
  - distance from N\(^+\) affects potency
  - reacts covalently with serine -OH at esteratic site
  - slow dissociation determines duration of action

- **thiophosphates**
  - require activation by substitution of oxygen for sulfur atom
  - very lipid soluble

\[ \text{Neostigmine:} \quad (\text{CH}_3)_2\text{N-C-O} \quad \text{Pyridostigmine:} \quad (\text{CH}_3)_3\text{N-C-O} \]

\[ \text{Edrophonium:} \quad \text{N'}\text{(CH}_3)\text{H}_3 \quad \text{Ecdothiopate:} \quad \text{C}_2\text{H}_5\text{O-S-CH}_2\text{CH}_2\text{N'}\text{(CH}_3)_2 \]

c. Compare and contrast the pharmacodynamics and pharmacokinetics of neostigmine, edrophonium, pyridostigmine, physostigmine and tacrine.

- **absorption**
  - quaternary amines have low bioavailability 10-20%
  - physostigmine and tacrine have higher bioavailability
  - lipophilic organophosphates have high bioavailability even transdermally

- **distribution**
  - quaternary amine reduces \( V_d \) and lipid solubility
prevents penetration into CNS
metabolism and elimination
esters are hydrolysed by cholinesterase and pseudocholinesterase
quaternary amines have high renal clearance
edrophonium is conjugated with glucuronide

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<thead>
<tr>
<th></th>
<th>$V_d$ (l/kg)</th>
<th>$t^{1/2}_\alpha$ (min)</th>
<th>$t^{1/2}_\beta$ (min)</th>
<th>duration (min)</th>
<th>reversing dose (mg/kg)</th>
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<tr>
<td>neostigmine</td>
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<td>edrophonium</td>
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<td>7.2</td>
<td>110</td>
<td>60</td>
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<tr>
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<td>120</td>
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<td>tacrine</td>
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Onset of action is determined by rate of diffusion and depth of NDB blockade.
Duration of action is determined by rate of dissociation from AChE of carbamates and phosphates or by conjugation and clearance for edrophonium.
For reversal, the duration of action of neostigmine and pyridostigmine is well-matched by glycopyrrolate (5 µg/kg) and that of edrophonium by atropine (7 µg/kg).

mechanism
esteratic site agents prevent hydrolysis of ACh
   ↑ ACh concentration in synaptic cleft
   competitive antagonism of NDB
edrophonium
   direct cholinomimetic activity
   some competitive inhibition of hydrolysis of ACh

d. Outline the effects and treatment of poisoning with organophosphate compounds.

organophosphates transfer phosphate to esteratic site of AChE
hydrolysis takes weeks
prolonged ↑ in ACh at muscarinic and nicotinic synapses

effects
muscarinic (apparent first)
   potent cholinomimetic effect
   salivation, lacrimation, ↑ gut motility, miosis
   bradycardia
   bronchoconstriction

nicotinic
   initial tetany, then depolarizing blockade
   weakness, paralysis
   minor preganglionic sympathetic actions
CNS (apparent last)
   excitation, convulsions

treatment
management of acute effects
   ventilation, sympathomimetics, pacing
   anticonvulsants
regeneration of AChE
   pralidoxime accelerates hydrolysis
blockade of autonomic effects
   atropine