**Pharm-10B5 Describe the pharmacodynamic effects and clinical uses of anticholinesterase drugs.**

**Background**

Acetylcholinesterase (AChE) is an enzyme that hydrolyse acetylcholine (ACh) into choline and acetate. AChE is commonly found in synaptic clefts and is responsible for the termination of synaptic transmission.

3 main types of anticholinesterase:
1. reversible antagonist via electrostatic binding – e.g. edrophonium
2. reversible antagonist via covalent bonding – e.g. neostigmine
3. irreversible antagonist via covalent bonding – e.g. organophosphates

**Pharmacodynamic effects**

Anticholinesterase drugs inhibit AChE, thereby increase the concentration of ACh at both nicotinic and muscarinic ACh receptors.

Muscarinic effects occur at lower doses than nicotinic effects.

**Muscarinic effects**

CVS – bradycardia ± hypotension

RESP – bronchoconstriction ± bronchospasm

CNS – miosis, cholinergic syndrome – confusion, agitation, nausea/vomiting

GIT – hypersalivation, ↑GIT motility, nausea/vomiting, diarrhoea

GUT – urination, incontinence

OTHER – lacrimation, diaphoresis

**Nicotinic effects**

Reversal of non-depolarising neuromuscular blockers

Prolongs effect of suxamethonium (depolarising NMB)

Anticholinesterase overdose → excess synaptic ACh → depolarisation block ± fasciculation

**Mnemonic = SLUDGE**

Salivation, Lacrimation, Urination, Defecation, GI diarrhoea, Emesis
Clinical uses

(1) Reversal of non-depolarising neuromuscular blocker
Mechanism – anticholinesterase drugs ↑ synaptic ACh → competes with ND-NMB in synapse for nAChR → reversal of neuromuscular block

Drugs – usu. neostigmine, administered together with glycopyrrolate or atropine

(2) Diagnosis and treatment of myasthenia gravis
Mechanism – anticholinesterase drugs ↑ synaptic ACh → competes with myasthenia auto-antibodies for post-synaptic nAChR → ↑ muscle strength

Drugs – e.g. edrophonium for diagnosis, pyridostigmine for maintenance

(3) Treatment of cognitive impairment in neurodegenerative diseases (e.g. Alzheimer’s disease, Lewy body dementia, etc)
Mechanism – ↑ synaptic ACh in CNS → ↑ cholinergic transmission

Drugs – e.g. rivastigmine, galantamine, donepezil

(4) Treatment of glaucoma
Mechanism – constriction of sphincter pupillae and ciliary muscles → miosis → facilitate outflow of aqueous humor → IOP decreases

Drugs – e.g. echothiophate eye drops, physostigmine

(5) Treatment of anticholinergic syndrome
Mechanism – increase synaptic ACh

Drugs – e.g. physostigmine (tertiary amine + lipophilic → readily crosses BBB)

Examiner’s comments – 65% of candidates passed this question.

A brief definition of an anti-cholinesterase and its effect on acetylcholine concentrations at cholinergic receptors was expected.

Subsequently the marks were divided evenly between pharmacodynamics and clinical applications. Briefly an increase in acetylcholine levels at muscarinic receptors results in bradycardia, hypotension, salivation, bronchospasm, increased gut and urinary motility, miosis and central effects if the drug crosses the blood brain barrier.

Only a few candidates mentioned that muscarinic effects occurred at lower concentrations than nicotinic effects.

However the single largest error in answering this question was candidates discussed structure activity relationships and pharmacokinetics of individual agents at length and failed to mention any pharmacodynamics.

Clinical uses of these agents are legion and were very well discussed. No value would be gained in repeating these here. Some candidates spent an inappropriate amount of time discussing organophosphates but by elaborating the adverse effects of these
agents ("SLUDGE' acronym) they gained marks en passant for the pharmcodynamic effects.