Pharm-16B10 Describe the effects of giving an unopposed dose of neostigmine.

Background

Neostigmine is an acetylcholinesterase (AChE) inhibitor

Structure
- carbamoyl ester
- quaternary amine → cation at physiological pH → does not cross BBB

Mechanism
- inhibit AChE → prevent hydrolysis of ACh
- increase ACh at both muscarinic (mAChR) and nicotinic (nAChR) junctions
- inhibit butyrylcholinesterase (BChE)

Pharmacological actions
1) stimulation of mAChR at autonomic effector organs
2) stimulation of nAChR at autonomic ganglia (usu. negligible for neostigmine)
3) stimulation (and in excess, depression) of nAChR at skeletal muscles
4) reduce metabolism of sux, miv, ester LAs, etc

Clinical relevance
- usu. used for its nicotinic effects in the reversal of non-depolarising neuromuscular blockade
- as there are finite AChE at NMJ → ceiling effect → cannot be used to reverse deep neuromuscular blockade (usu. administer only when TOF number ≥ 2)
- usu. given together with an antimuscarinic (atropine or glycopyrrolate), which offsets the unwanted muscarinic effects of neostigmine during neuromuscular blockade reversal

Muscarinic effects

CVS
- increases vagal tone → increases dromotropy → bradycardia (± arrest)
- exact clinical effect depends on cardiovascular status, e.g. infant whose cardiac output is heart rate dependent → bradycardia may result in reduced cardiac output and hypotension

RESP
- increase bronchial secretions
- bronchoconstriction

Eye
- conjunctival hyperaemia
- miosis
- inhibit accommodation reflex
GIT
- enhance gastric motility
- increase gastric acid secretion
- increase peristalsis (both small and large bowel) – both amplitude and frequency
  → may lead to involuntary defecation
- increase ureteric peristalsis → may lead to increased urination
- increase secretions from salivary and pancreatic acinar glands
- increase PONV

Other
- increase sweating
- increase lacrimation

Nicotinic effects

NMJ
- increase residence time of ACh at nAChR → prolongation of EPP → disrupts
  synchrony between EPP and muscle action potential → involuntary twitching
  and fasciculations
- when there is sufficient AChE inhibition → ↑ACh at nAChR → depolarisation of
  endplate → neuromuscular blockade → paresis (fatigability and generalised
  weakness)

Pre-ganglionic nicotinic actions are usu. masked by the post-ganglionic muscarinic
effects

Examiner’s Comments

This was a question of two parts – requiring both muscarinic and nicotinic receptor
effects for a good mark.

Outside of bradycardia, the cardiac effects were generally poorly-covered. Non-specific
comments such as “urination” did not attract marks, whereas a point such as “increases
ureteric peristalsis may lead to urination” did.

Good candidates were able to explain how neostigmine works, why neostigmine is
given, when it is appropriate to give neostigmine, discuss the effects at both the
nicotinic and muscarinic receptors and apply clinical relevance to both. Extra marks
were awarded for applying clinical relevance to the question, particularly if candidates
explained why an antimuscarinic medication is usually co-administered when
neostigmine is used to reverse non-depolarising muscle blockade.