Q23 Classify antiemetic drugs and give an example from each group (60% of marks). Outline the gastrointestinal effects of metoclopramide (40% of marks) (March 2012)

Vomiting is a complex reflex, which results in the expulsion of gastric contents out of the mouth. The main receptors involved are the D2, 5HT3, muscarinic and histamine-1 receptors, hence the classification of anti emetics by the receptor upon which they act:

DOPAMINE ANTAGONISTS → block D2 receptors in the chemoreceptor trigger zone, thus reducing CTZ-mediated activation of the vomit centre in the lateral reticular formation. Also act peripherally on D2 receptors in the gut to increase GIT motility. Classes include:

- Phenothiazines (prochlorperazine, chlorpromazine)
- Butyrophenones (droperidol, domperidone, haloperidol)
- Benzamides (metoclopramide)

5-HT3 RECEPTOR ANTAGOINSTS → eg, ondansetron, granisetron. Block 5HT3 receptors both peripherally (in the stomach to reduce afferent signals to CTZ and VC) and centrally (in the CTZ) to reduce activation of the vomit centre.

ANTICHOLINERGICS → eg, atropine glycopyrrolate, hyoscine (most potent). Both peripheral (blocks vagal afferents and reduces GIT secretions) and central antimuscarinic effects (reduces activation of the vomit centre). Particularly good in motion sickness as blocks the muscarinic receptors in the labyrinths.

ANTIHISTAMINES → eg, cyclizine, promethazine. Inhibits H1- mediated activation of the vomit centre (particularly useful in blocking afferent signals from the labyrinths in motion sickness). Also display some anticholingeric effects, which enhances the anti-emetic action.

OTHER

- BENZODIAZEPINES → eg, lorazepam. Mode of action uncertain but may modify cortical inputs to the vomit centre
- CORTICOSTEROIDS → eg, dexamethasone. Mode of action uncertain but may act directly on the vomit centre to reduce activation.
- CANNABINOIDS → eg; cannabis. Blocks the cannabinoid receptors from the CTZ to the VC.
- PROPOFOL → mode of action unclear but GABA blockade may reduce activation of the VC
- NK1 ANTAGONISTS → eg; aprepitant. Blocks the NK1 receptors at the vomit centre to reduce activation.

METOCLOPRAMIDE →
Metoclopramide is a widely used antiemetic with actions at both the chemoreceptor trigger zone and on GIT motility. It is indicated for perioperative and chemotherapy induced nausea/vomiting.

Its effects on GI motility appear to be mediated by antagonism of peripheral D2 receptors, augmentation of peripheral cholinergic responses and direct action on smooth muscle tone. In doing so it reduces intestinal muscle fatigue, enhances the frequency and amplitude of longitudinal muscle contraction, and coordinates gastric, pyloric and duodenal activity to improve GI motility.

It also increases lower oesophageal sphincter pressure, relaxes the pyloric sphincter and antagonizes the inhibitory neurotransmitter, dopamine.

The central effects appear to be mediated by central D2 blockade, increasing the threshold at the CTZ, and a decrease in the sensitivity of visceral nerves supplying afferent information to the vomit centre.