Royal College of Anaesthetists

FRCA Final SOE 1 Example Question:
Clinical Anaesthesia with linked Applied Clinical Science

Pharmacology of antiemetics and clinical prevention strategies

Section
Science - **Pharmacology**

Opening question
Which receptors on activation lead to nausea and vomiting?

Scientific principles to be explored
Pharmacology of anti-emetics based on the physiological basis of vomiting

Clinical applications of the scientific principles
Understanding of the pharmacological principles underlying the treatment of PONV.

Guidance to examiners
All core knowledge should give accurate and complete account of neurophysiology and mechanism of action and precautions / side effects of 5 classes of drug to pass

Neurophysiology:
Afferent limbs of vomiting reflex include
• **GI tract -** mechano- and chemoreceptors via the vagus nerve to the nucleus tractus solitarius in the brain stem, involving cholinergic, 5-HT3, dopamine and neurokinin-1(NK1) receptors.
Ipecacuanha can be used in poisoning to directly stimulate these receptors
• **Chemoreceptor Trigger Zone**. Situated close to the area postrema in the floor of the fourth ventricle, outside the blood-brain barrier. Responsible for detecting toxins in blood and CSF (5HT3) also the nausea associated with sleep deprivation.
• **Vestibular system** - especially motion sickness (H1 and H2)
• **CVS** - afferents mainly from the baroreceptors
• **Higher centres** - sights, sounds, smells, unpleasant thoughts
• **Pharyngeal** afferents
• **Auricular** branch of the vagus nerve
• **Visceral** pain.

Vomiting centre
• Not an anatomical entity, several nuclei in the brain stem (e.g. nucleus tractus solitarius, dorsal vagal nuclei, reticular formation and respiratory neural networks) responsible for the co-ordination of the efferent limb of the vomiting reflex.
• Receives input from the afferent limbs of the reflex.

How does each class of anti-emetics act to reduce nausea and vomiting? What are their side-effects?
Drugs
• **Metoclopramide:** dopamine antagonist, also acts directly on GI tract so may be superior in gastroduodenal,hepatic and biliary disease to phenothiazines. Has some efficacy at 10 mg, at higher doses has an anti 5HT3 effect, but side effects generally unacceptable.
Side-effects- extrapyramidal reactions particularly oculogyric crisis,tardive dyskinesia especially in young females: agitation. Neuroleptic malignant syndrome. After iv injection, hypotension, sinus and supraventricular tachycardia.MHRA guidelines on use in view of serious neurological side effects
• **Phenothiazines** (antidopaminergic): promethazine, prochlorperazine (side-effects -extrapyramidal reactions (acute dystonia), sedation if large dose. Mainly in chronic use - jaundice, skin sensitization and haematological abnormalities). Cause of neuroleptic malignant syndrome. Many other effects through anticholinergic, anti-noradrenergic (a1 and a2) and antihistamine actions.

• **Butyrophenones** (dopamine antagonists). Droperidol and Haloperidol. Side effects - extrapyramidal reactions, apprehension, restlessness, nightmares. MHRA guidance on avoidance of cardiac toxicity (conductance disturbance) contraindicated with other drugs prolong QT interval or inhibit CYP 3A4. Domperidone useful inParkinsons disease to reduce nausea from dopinergic drugs
• **Anticholinergics:** hyoscine (scopolamine), atropine. Cyclizine is anticholinergic but also an antagonist at H1 receptor. No extrapyramidal side-effects but predominantly anticholinergics side effects- sedation, dry mouth, urinary retention, blurred vision, restlessness and hallucinations.
• **5-HT3 receptor antagonists:** ondansetron, granisetron, dolasetron. Side-effects- mild headache, sensation of warmth/flushing, visual disturbance, occasional cardiac arrhythmias and with chronic use- constipation.
• **Cannabinoids**. Nabilone useful with chemotherapy. Side effects dysphoria and hallucinations.
• **Dexamethasone:** Mechanism uncertain suggested mechanisms are reduced release of arachidonic acid reduced turnover of 5HT or decreased permeability of the BBB
Side effects - rectal / perineal warmth if given awake. Impaired glucose tolerance and risk of hyperglycaemia and associated wound healing and thrombotic issues, psychotic/ delusional reactions.
• **Neurokinin-**1 receptor antagonist – aprepitant, fosaprepitant specifically licensed for use with cisplatin chemotherapy.

Clinical Topic
General duties - Day surgery

Opening question
A young female presents for day case laparoscopic sterilisation. She has had a previous anaesthetic (breast augmentation) and was nauseous and sick repeatedly after the previous surgery. She asks you, will she be sick after this operation?
What would you say?

Guidance to examiners
A successful candidate will be aware that PONV remains a significant problem and will be able to describe how would manage this high risk patient and risk stratify to wider population.

Question
What would say?
• Sympathetic to problem.
• Explain real risk of happening again (high risk patient)
• Describe a range of things can do to try and stop it occurring.

Commonest cause of dissatisfaction in patients

Is PONV still a significant problem?
• Yes (30% all patients depending on surgery). Commonest cause conversion D/Cases to overnight stay)

What are the risks associated with PONV?
• Wound dehiscence
• Dehydration/electrolyte imbalance
• Psychological effects
• Aspiration
• Delayed nutrition

Which patients are particularly at risk?
• Patient factors
• (Apfel factors) – female, previous history of PONV or motion sickness, non smokers, anticipated use of post operative Opioids. Greater than 2 factors = high risk (60% incidence PONV). Less than 1 factor - 10-20%, more than 4 80%
• Surgery related factors
o Raised risks with ENT, squint surgery, laparoscopic gynae surgery, breast augmentation
o Increasing duration of surgery

Clinically, how would you try and stop PONV in this young lady?
• Represents high risk (greater than 2 pt risk factors)
• Prophylaxis more appropriate than treatment once PONV occurs

• 2 treatment approaches:
o Use of multiple anti-emetics (all equally effective (except metoclopramide),demonstrate additive effects)
o Avoidance of emetogenic factors (avoidance of nitrous oxide, propofol rather than inhalational agents, long acting opiates) +- hydration

Specifics?
• ?Pre-operative antacids/metoclopramide
• Give dexamethasone + 5HT3 antagonists and/or cyclizine intraoperatively
• TIVA with propofol based anaesthetic.

How effective are the various strategies?
• Anti-emetics
Single individual anti-emetics reduce risk by approx 20-40%
Risk reduction (cyclizine 0.6, Dex 0.55, Ondansetron 0.6, droperidol 0.65, metoclopramide 0.8, prochlorperazine 0.7)
Don't want to use anti-emetics which are too sedating as day case
Second anti-emetics are additive not synergistic. If pt low or high risk reduction still only 25%

Interventions reduce relative risk to a similar extent, so greatest absolute risk reduction in patients at highest risk of PONV. Single intervention in patient at 80% risk reduces risk to 59% (NNT 5 to prevent NV in one patient): patient baseline risk 10% reduces risk 3% (NNT 40)

• Anti-emetics similarly effective – logical to use safest ± least expensive first.
• Multiple antiemetics with different mechanisms of action (Triple therapy- Ondansetron, Dexamethasone and Cyclizine). Absolute risk reduction by second and third intervention less than first. A 70% reduction in relative risk is the best that can be expected. 'Rescue' treatments are ineffective when same drug has already been used prophylactically.
• Avoidance of all the factors in first section. Reasonable first line dexamethasone and total intravenous anaesthesia as these cannot be used once PONV has begun.
• Avoidance of factors
Avoidance of nitrous = variable results (? ? statistical but not clinically significant)
• Avoiding long acting opiates with good oral analgesia and local anaesthesia (infiltration/pouch of Douglas LA, tubal injection of LA
• Overall for this lady strategy probably reduces risk for pt population like this lady from 60%+ to about 30%

(Results for populations not individuals)
- TIVA based with propofol reduces by 50% in some studies

Filler
If asked to write one, what would be in your departmental policy for reducing rates of PONV?
- Risk stratification based on risk factors.
- Treatment based on risk / cost effectiveness
- Multimodal approach with use of multiple approaches in high risk groups

(Filler) How would you audit the effectiveness of policy?
- Multiple issues audit design
- ?How measure nausea (yes/no, Likert scales, interference with activity at home, more than 24 hrs?)