B. 15 Antiemetic drugs

Definitions

nausea
unpleasant sensation referred to the pharynx and upper abdomen associated with the desire to vomit.

vomiting
forceful expulsion of gastric contents via the mouth (and nose).

retching
activation of the muscles involved in vomiting without expulsion of stomach contents.

regurgitation
return of gastric contents into the mouth without effort.

Mechanism of vomiting

detectors
peripheral
visceral afferents in the vagus (vagus is 80-90% afferent fibres)
mechanoreceptors responding to stretch
chemoreceptors in enterochromaffin cells
serotonergic transmission ($5\text{HT}_3$)
project to CTZ and nucleus tractus solitarius (muscarinic and H$_1$)

central
chemoreceptor trigger zone (CTZ)
in the area postrema, caudal part of the floor of the fourth ventricle
outside the blood-brain barrier
D$_2$ and $5\text{HT}_3$ transmission
vestibular system
in inner ear
detects movement and position of the head
cholinergic and H$_1$ transmission
integrated with visual and proprioceptive inputs in the cortex
project to CTZ
vision
can induce nausea alone if perception of motion does not match vestibular input
taste, smell
both directly and by association with memories
touch at the back of the pharynx
the gag reflex mediated by the glossopharyngeal nerve
cortex
memories, emotions and thought can induce or facilitate nausea
probable site of action of benzodiazepines

integration
medullary emetic centre (vomiting centre) in the brainstem
receives inputs from CTZ, cortex and nucleus tractus solitarius
predominantly muscarinic cholinergic and NK$_1$
operates a coordinated motor program acting on
dorsal motor vagal nucleus
nucleus ambiguus
dorsal and ventral respiratory groups
presympathetic neurones

effectors
sympathetic
cutaneous vasoconstriction, sweating, mydriasis, tachycardia
parasympathetic and enteric
  gastric relaxation, ↓ gastric secretion
  retrograde peristalsis from mid small bowel
  relaxation of oesophageal sphincters
somatic
  respiratory
diaphragm relaxed
  glottis closed, soft palate elevated
  abdominal
rectus contracts rhythmically
  flexed posture

a. Describe the pharmacokinetics and pharmacodynamics of dopamine antagonists, anticholinergic agents and serotonin antagonists.

metoclopramide
  substituted benzamide:
    methoxychloroprocainamide
pharmacokinetics
  75% oral bioavailability
  crosses BBB
  hepatic conjugation to glucuronide and sulfate
  renal excretion 25% unchanged
  excreted in breast milk
  crosses placenta
  t½,β 3-5 h, more rapid redistribution
pharmacodynamics
  D₂ antagonist and 5HT₄ agonist
  5HT₃ antagonist at high dose
sites of action
  central: CTZ
  gut: ↑ motility, LOS tone (centrally mediated)
adverse actions
  central D₁ effects: restlessness, drowsiness
  extrapyramidal effects: dystonia, akathisia
  ↑ prolactin, aldosterone secretion
  inhibits plasma cholinesterase
clinical use
  IV dose 0.15 mg/kg (up to 3 mg/kg in some centres)
  for prevention and treatment of PONV, chemotherapy nausea
  not effective for vestibular problems: vertigo, ENT surgery

prochlorperazine (similar to other phenothiazines)
  phenothiazine (7 times as potent as chlorpromazine)
pharmacokinetics
  high oral bioavailability
  lipid soluble
  crosses BBB
pharmacodynamics
  predominant D₂ antagonist
  also antagonist at α-adrenergic, muscarinic, histamine and serotonin receptors
adverse actions
  as for all phenothiazines
clinical use
  oily solution for IM injection
droperidol
butyrophenone
pharmacokinetics
used IV
90% protein bound
crosses BBB
t1/2 β 2-3 h
pharmacodynamics
potent D2 antagonist
some α-antagonist, histamine and serotonin antagonist activity
most potent in apomorphine-induced emesis
adverse actions
hypotension, sedation, dysphoria
eextrapyramidal effects
↑ prolactin
clinical use
10-20 µg/kg IV in adults, 50-75 µg/kg in children (e.g. squint surgery)

ondansetron
pharmacokinetics
oral bioavailability ≈50%
75% protein bound
hepatic metabolism
t1/2 β 4 h
pharmacodynamics
specific 5HT3 antagonist
acts at gut chemoreceptors and CTZ
potent antiemetic
adverse actions (rare)
headache, flushing
hypotension, bradycardia
involuntary movements
clinical use
4-8 mg IV or oral for adults
best agent for PONV and chemotherapy nausea
not good for opiate-induced nausea

other antiemetics in other sections
antihistamines
anticholinergics
benzodiazepines
steroids
cannabinoids
ephedrine
NK1 blockers in phase II trials may be better than 5HT3 antagonists

b. Critically appraise the clinical usage of these drugs.

decision to use preventively depends on patient's risk
increased by
school-age children, female sex, anxiety, pregnancy
history of PONV or motion sickness
full stomach, raised ICP
specific surgery (squints, gynae, ENT...)

choice of drug depends on likely cause
eliminate drugs from previous anaesthetics likely to have caused PONV
consider TIVA
spinal/epidural-induced nausea is often low CO, esp. in Caesars
treat with posture, fluid, ephedrine
ENT surgery: prochlorperazine, droperidol affect both dopamine and serotonin
opiate induced: droperidol probably best
other: high dose metoclopramide may be as effective as ondansetron
in susceptible patients, hypnosis or acupuncture are safest