B16 - Anti-emetic Drugs

- nausea & vomiting = common problem encountered in anaesthesia
- vomiting center is in the lateral medullary reticular formation & co-ordinates vomiting through:

(1) CN VIII & X
(2) neural networks in the nucleus tractus solitarius - communicating with respiratory center, salivatory & vasomotor centers.

- high concentrations of H1 & 5-HT3 receptors have been identified in the vomiting center.

See diagram - Integration in control of vomiting

Five afferent inputs to the vomiting center:

(1) chemoreceptor trigger zone

- 4th ventricle
- outside BBB
- rich in D2 receptors, 5-HT receptors & opioid receptors.

(2) vestibular system

- important in motion sickness via CN VIII
- rich in muscarnic & H1 receptors

(3) irritation of the pharynx

- innervated by vagus
- provokes a GAG & retch reflex

(4) vagal & enteric afferents in the mucosa

- rich in 5-HT3 receptors
- irritation of gastrointestinal mucosa by:

- chemotherapy
- radiation therapy
- distension
- acute infections gastroenteritis

-> 5-HT3 release & receptor activation -> vagal afferent input to the vomiting center & chemoreceptor trigger zone.

(5) CNS

- psychiatric disorders

- stress
- anticipatory vomiting prior to chemotherapy

(a) To describe the pharmacodynamics & pharmacokinetics of

- dopamine antagonists
- anti-cholinergics agents
- serotonin antagonists
- anti-histamines
- corticosteroids.

Dopamine Antagonists

- droperidol (central)
- metoclopramide (peripheral & central effects)

Droperidol

Chemical - butyrophenone derivative

Uses

(1) premed
(2) neuroleptanalgesia
(3) PONV & chemo/radio therapy
(4) treatment of psychosis
(5) control of perioperative hiccuping

Preparation

- PO: tablets & syrup
- IV: clear, colourless solution of 5mg/mL

Route - PO, IM, IV

Dose

- PO or IM: 5-10mg for adult
- IV: for PONV 0.5mg

- onset 10min
- duration 12hrs

PK

Absorption - well absorbed IM

Distribution

- 90% protein bound
- Vd 2 L/kg

Metabolism

- hepatic
- oxidative N-dealkylation

Elimination

- 75% excreted in urine, 22% in faeces
- 1% unchanged
- Cl = 15mL/min/kg
- t1/2 = 2hrs

PD

Mode of action - antiemetic & neuroleptic

Mechanism of action

- antiemetic & neuroleptic effects mediated by D2 blockade in chemoreceptor trigger zone & post-synaptic GABA antagonism

CVS

- QT prolongation
- extrapyramdial side effects
- hypotension

RESP

- decreased in minute ventilation
- decrease in FRC
- decrease in airway resistance

CNS

- neurolepsis (diminished motor activity, anxiolysis & indifference to the external environment)
- seizure threshold increases with drug

GI

- central anti-emetic action (see above)

Metabolic

- hyperprolactinaemia
- reduces total body O2 consumption

Other adverse effects

- extrapyramdial side effects
- anomalies in LFTs
- malignant neuroleptic syndrome

Metoclopramide

Chemical - chorinated procainamide derivative

Uses

(1) digestive disorders (GORD, HH, gastritis)
(2) N & V
(3) migraine
(4) prokinetic

Presentatioin - tablets, syrup, clear & colourless solution for injection (5mg/mL)

Route - IV, PO, IM

Doses - all routes 10mg Q8hrs

PK

Absorption - bioavailability 80%
Distribution - 20% protein bound, Vd 3 L/kg
Metabolism - liver
Elimination - urine (20% unchanged), Cl = 10mL/min/kg, t1/2 = 4hrs

PD

Main action - increased GI motility & antiemetic

Mechanism of action:

Prokinetic:

(1) antagonism of D2 receptors in gut
(2) augmentation of peripheral cholinergic responses
(3) increase smooth muscle tone

Antiemetic:

(1) central D2 receptor blockade -> increased threshold for vomiting in chemoreceptor trigger zone
(2) decrease in sensitvity of visceral nerves supplying afferent information to vomiting centre.

CVS

- hypotension
- cardiac arrest
- dysrrhythmia

CNS

- increased threshold for vomiting at chemoreceptor trigger zone
- prevents apomorphine induced vomiting in man
- antipsychotic action

GI

- increased tone of the lower oesophageal sphincter.
- accelerated gastic contractions
- increased small bowel transit time

GU - increased ureteric peristaltic activity

Metabolic

- stimulates prolactin release
- transient increase in ALD secretion

Other adverse effects

- drowiness
- dizziness
- faintness
- extrapyramdial side effect (akathesia, oculogyric crises)
- neuroleptic malignant syndrome

Anti-cholinergics (muscarinic antagonsim)

- promethazine
- prochlorperazine
- thiethylperazine
- hyoscine (scopolamine)

Promethazine

Chemical - phenothiazine

Uses

(1) PONV
(2) motion sickness
(3) allergic reactions
(4) pruritis
(5) sedation in children

Preparation - tablets, elixir & injection

Routes - PO, IM, IV

Doses

- PO: 25-50mg in divided doses
- IV: 25-50mg

- acts in 15min
- duration 10-20hrs

PK

Absorption - well absorbed orally

Distubution

- 93% protein bound
- Vd 2.5 L/kg

Metabolism

- hepatically by sulphoxidation & N-dealkylation

Elimination

- urinary
- 2% unchanged

- Cl = 1.5mL/min/kg
- t1/2 = 10hrs

PD

Main action - anti-histaminergic, sedative & antiemetic

Mechanism of action

(1) revesible, competitive antagonism at H1 receptors
(2) anti-cholinergic
(4) anti-serotinergic
(5) anti-dopaminergic

CVS - no effects @ normal dosage

RESP

- bronchodilation
- reduced secretions
- anti-tussive

CNS

- potent sedative & anxiolysis
- reduced motion sickness by suppression of vestibular end-organ receptors & by inhibition at chemoreceptor trigger zone.

GI - decreases tone of oesophageal sphincter

Other adverse effects

- extrapyramdial side effects
- jaundice
- photosensitivity
- excitatory phenonmena

Hyosine - see anticholinergics

Serotonin antagonists (5-HT3 antagonists)

- act:
(1) peripherally by blockade of 5-HT3 receptor on intestinal afferents
(2) centrally by blockade of 5-HT3 in vomiting center & chemoreceptor trigger zone.

- agents: ondansetron, granisetron, dolasetron, tropesitron.

Ondansetron

Chemical - synthetic carbazole

Uses

(1) N & V induced by chemotherapy & radiation
(2) PONV

Preparation

- IV: clear, colourless solution in 2 or 4mg amp
- PO: tablets or waffers

Routes - PO, IV, IM

Dose

- PO: 8mg Q8hrly
- IV or I'M: 4mg Q8hrs

PK

Absorption - bioavailability = 50%

Distribution

- 75% protein bound
- Vd 2 L/kg

Metabolism

- hepatic
- hydrolylation or N-demethylation of the indole nucleus -> conjugation with glucuronic acid or sulphate.

Elimination

- <5% excreted unchanged in urine
- Cl = 6mL/min/kg
- t1/2 = 3hrs

PD

Main action - antiemetic

Mechanism of action

- highly selective antagonist @ 5-HT3 receptors peripherally & centrally
- emetogenic stimuli -> release of 5-HT in small intestine & initiation of vomiting reflex via vagal afferents & 5-HT3 receptors.
- ondansetron blocks the initation of this reflex

CVS - no effects

RESP - no effects

CNS - headache (rarely)

GI - increases large bowel transit time, constipation

Metabolic - no effect

Other adverse effects

- anaphylaxis has been reported.
- no alteration needed in renal failure
- adjust for hepatic failure (8mg/day max)

Anti-histamines

- promethazine (see above)
- cyclizine

Cyclizine

Chemical - a piperazine derivative

Uses

(1) PONV - opioid or GA
(2) motion sickness
(3) radiation sickness
(4) Meniere's disease

Presentation

- tablets: 50mg
- solution: clear, colourless, 50mg/mL

Route - PO, IV

PK

Absorption - bioavailability = 80%
Distribution -
Metabolism - N-demethylation to norcyclizine
Elimination - t1/2 = 10hrs

PD

Main action - antiemesis

Mechanism

- competitive antagonist at H1 receptor (? centrally)

CVS - slight tachycardia
RESP -
CNS - slight sedation, anti-emetic, blurred vision
GI - increase in tone of LOS, dry mouth

Corticosteroids

Dexamethasone

Chemical - fluorinated derivative of prednisolone

Uses

(1) deficiency states
(2) allergic therapy
(3) asthma
(4) anti-emetic
(5) post-op analgesia
(6) cerebral oedema
(7) aspiration pneumonitis
(8) lumbar disc disease
(9) immunosuppression
(10) antiinflammatory
(11) prem babies to prevent respiratory distess syndrome.

Presentation - clear, colourless soultion for injection

Routes - PO, IM, IV

Dose

- 0.1mg/kg
- duration of action = 2days

PK

Elimination - t1/2 = 4 hours

PD

Main action - see above

Mode of action

- inhibition of prostaglandin synthesis
- increase release of endorphins -> mood elevation & appetite stimulation
- attach to cytoplasmic receptors to stimulate transcription -> protein synthesis

CVS - no effects

RESP - decreased secretions

CNS

- increased neuroses & psychoses (mania & depression)
- cataracts

GI

- peptic ulcer disease

Metabolic

- suppression of the hypothalamic-pituitary-adrenal axis.
- electrolyte disturbances (hypokalaemic metabolic alkalosis -> absorption of Na+ & loss of K+
- oedema
- weight gain
- hyperglycaemia
- osteoporosis
- peripheral blood changes -> increase haematocrit & WCC
- inhibition of normal growth

Other adverse effects

- skeletal muscle myopathy

- increased susceptibility to bacterial infections.

Other methods of decreasing PONV

Benzodiazepines
Propofol - central D2 antagonism
Avoid N2O
FIO2 > 80%
Hydration
TIVA
Minimise opioid exposure

(b) To critically appraise the clinical usage of these drugs.

Reasons why I use Ondanestron

- far better side effect profile than the other medications (constipation & headache - rare)
- renal excreted but doesn't require adjustment in renal impairment
- reasonably cost effective = NZ$10 for 4mg -> good anti-emesis
- peripheral & central effects against the 5-HT3 receptor.