B23 - Gastrointestinal Pharmacology

(a) To describe the pharmacology of the non-particulate & particulate antacids.

- weak bases that react with HCl to form salt & H2O
- principle effect = reduction of gastic acidiy
- secondary effect = promotion of mucosal defense by stimulation of prostaglandin production.

Agents:

- NaHCO3
- Calcium Carbonate
- MgOH
- Aluminium hydroxide

Particulate antacids

- aluminium hydroxide + magnesium hydroxide + Na+
- calcium carbonate + Na+
- pneumonitis may reflect a foreign body reaction to inhaled particulate antacid particles (? may aggravate aspiration pneumonitis)

Nonparticulate antacids

- Na+ citrate
- less likely to cause a foreign body reaction if aspirated
- onset more rapid
- administer 15 to 30mL of 0,3mol solution, 15 to 30min before induction of anaesthesia
- has unpleasant taste -> add flavoring material

- other agents: bicitra (Na+ citrate & citric acid), polycitra (Na+ citrate, K+ citrate & citric acid)

Mylanta

Chemical

- aluminium hydroxide (200mg/5mL)
- magnesium hydroxide (200mg/5mL)
- simethicone

Uses

(1) antacid

(2) anti-flatulent

Preparation

Route - PO

Dose

- 2-4 tablets tds
- 10-20mL tds

PK

Absorption - mostly passes through unabsorbed (renal patients are susceptible to Al intoxification)

PD

Main action - antacid

Mechanism

- neutralisation of gastric acid via algeinic acid reacting with gastric acid -> colloidal gel.
- this floats on the surface of the gastric contents and prevents reflux

GI

- slow gastric emptying
- constipation
- osmotic diarrhoea

GU

- nephrolithiasis

Metabolic

- binds phosphate in GI tract -> hypophosphataemia

Na+ citrate

Chemicals

- Na+ citrate
- surcose
- methyl hydroxbenzoate

Uses - antacid

Presentation - non-particulate, clear

Route - PO

Dose - 15-30mL 30 min pre GA

PK

Absorption
Distribution
Metabolism
Elimination

PD

Main action - antacid

Mechanism

- increased gastric pH by buffering H+

GI

- unpleasant taste (pH 8.4)

(b) To describe the pharmacology of the histamine 2 antagonists.

- ranitidine, cimetidine, famotidine & nizatidine
- produce selective & reversible inhibition of H2-receptor mediated secretion of acidic gastric fluid.

Mechanism

- histamine-H2 receptor complex -> increase intracellular cAMP -> activation of proton pump of gastric parietal cells -> secretion H+ against a large concentration gradient in exchange for K+ (H+/K+ ATPase)
- H2 antagonists competitively & selectively inhibit the binding of histamine to H2 receptor...

Uses

(1) DU
(2) antacid
(3) attenuation of allergic response

Onset - 1 to 3 hrs

Duration

- cimetidine - 6hrs
- ranitidine - 10hrs

PK

Absorption

- rapid via PO route
- bioavailability = 50% (except nizatidine = 100%)

Distribution

- Vd = 1-2 L/kg
- cross BBB, placenta & appear in breast milk

Elimination

- t1/2 = 2-4 hrs
- combination of hepatic metabolism, glomerular filtration & renal secretion.
- decrease dose in renal dysfunction

PD

CVS

- hypotension & arrhythmia (rare)

CNS

- headache
- fatigue
- confusion (rare)
- dizziness (rare)
- somnolence (rare)

GI

- diarrhoea
- increase LFTs (rare)

Metabolic

- gynacomastia (rare)
- galactorrhoea (rare)

Other adverse effects

- sk muscle pain
- thrombocytopenia (rare)
- drug fever (rare)

Drug interactions

- diazepam, lignocaine & propanolol -> increases plasma concentration
- ethanol -> increased absorption
- Mg2+ & NaOH -> decrease bioavailability

Ranitidine

Chemical - a furan derivative

Uses

(1) peptic ulder disease
(2) GORD
(3) Zollinger-Ellison syndrome
(4) preventionf of stress ulceration in ICU
(5) prior to GA in aspiration risk

Presentation

- injection: 25mg/mL
- tablets: 150, 300mg
- syrup: 15mg/mL

Routes - IV, PO, IM

Dose

- IV: 50mg QID
- PO: 150mg bd

PK

Absorption - bio = 50%
Distribution - protein bound = 15%, Vd = 1.5 L/kg
Metabolism - oxidation & methylation

Elimination - Cl = 10ml/min/kg, t1/2 = 2hrs, reduce dose in renal failure

PD

Main action - inhibtion of gastric acid secretion

Mechanism

- competitive blockade of H2 receptors -> decrease in secretion
- also decreases action of gastrin & Ach

CVS - none

RESP - none

GI

- gastric acid inhibtion
- increase in LES tone

Metabolic

- anti-adrongenic, antidopaminergic
- crosses placenta (no adverse effects on bubs)

Other adverse effects

- LFTs derangement
- rash
- anaphylactoid reaction
- confusion
- thrombocytopenia
- leukopenia

(c) To describe the pharmacology of the proton pump inhibitors

- omeprazole
- lansoprazole
- rabeprazole
- pantoprazole
- esoemprazole

- all substitued benzimidazoles that resemble H2 antagonists in structure but a completely different mechanism of action.

Uses

(1) GORD
(2) Peptic ulcer disease
(3) Non-ulcer dyspepsia
(4) Prevention of stress gastritis
(5) Gastrinomas

PK

Absorption

- administered as prodrugs
- formulated to protect from acid-labile prodrug from rapid destruction within gastric lumen
- after travelling through stomach into alkaline intestinal lumen -> enteric coated formulation dissolve -> absorption.
- weak bases (pKa 4-5)
- bioavailability 50-90% (decreased by food)

- dose: should be administered 1 hr before food
- duration: 24hr c/o irreversible inactivation of proton pump

Elimination

- t1/2 = 1.5hrs

PD

Mechanism

-> diffuse readily across lipid membrane into acidified compartments such as the parietal cell canaliculus -> rapid protonation & concentration within canaliculus -> rapid conversion to thiophilic sulfonamide cation. -> reacts with the H+/K+ ATPase -> irreversibly inactivates the enzyme.

CNS

- headache

GI

- diarrhoea
- abdominal pain
- subnormal levels of B12
- small risk of increased enteric infections

Drug interactions

- ketoconazole & digoxin -> decreased bioavailability

- coumadin, diazepam & phenytoin -> decreaed metabolism

Omeprazole

Chemical - a benzimidazole derivative

Uses

(1) GORD
(2) PUD
(3) Zollinger-Ellison syndrome (gastrinoma)

Presentation

- capsules: 10 to 40mg
- injection: 40mg vials as powder of Na+ salt of omeprazole

Route - IV, PO

Dose

- PO: 20 - 40mg/day
- IV: same

- no dose reduction needed in renal or hepatic impairment.

PK

Absorption - bioavailability = 70%

Distribution

- 96% protein bound
- predominately to albumin & alpha-1-acid glycoprotein
- Vd = 0.5L/kg

Metabolism

- rapidly & completely oxidised to sulphone
- reduced to sulphide
- by hydroxylation

Elimination

- 80% excreted in urine, 20% in faeces
- Cl = 600mL/min/kg

- t1/2 = 1hr

PD

Main action - inhibition of basal & stimulated gastric acid secretion

Mechanism - see above

Adverse effects - see above

(d) To outline the pharmacology of misprostol & sucralfate.

Misoprostol

Chemical - PGE 1 derivative

Uses

(1) - cytoprotective prostaglandin used in preventing peptic ulcer
(2) in combination with mifepristone for TOP
(3) anti-rejection therapy

Preparation

- PO: 100 to 200mcg

Dose

- 200mcg QID

PK

Absorption
Distribution
Metabolism - prompt
Elimination - minimal amount renal

PD

Mechanism

- prostaglandins also inhibit gastic acid secretion (thus why NSAIDs cause grief)
- maintains mucosal blood flow in response to gastic irritants

- increase mucus & HCO3- secretion

Adverse effects

- abdominal dyscomfort
- diarrhoea
- bone pain
- hyperostosis
- nephrolithiasis (Ca2+ oxalate stones)
- uterine contraction

Sucralfate

Chemical - aluminium salt of sulphated sucrose

Uses

(1) PUD
(2) prevention of stress ulceration

Presentation

- tablets: 1g
- suspesion: 200mg/mL

Route - PO

Dose -1g Q6hrly

PK

Absorption - 5% absorbed
Distribution -
Metabolism - NONE!
Elimination - unchanged in faeces

PD

Main action - cytoprotection of upper GI tract

Mechanism - acid pH sucralfate forms viscous paste -> adhere to ulcers via ionic binding -> acts as a barrier to the diffusion of acid, pepsin & bile salts.

GI

- weak antacid effect

- increases gastric blood flow & enhances gastric epithelial proliferation via stimulation of gastric mucosal epidermal growth factor & fibroblast growth factor
- constipation

Metabolic - hypophosphataemia