GASTROINTESTINAL PHARMACOLOGY

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

	Particulate antacids	**Non-particulate antacids**
Examples	$Al(OH)_3$, $Mg(OH)_2$ and $CaCO_3$	$NaHCO_3$ and Na citrate
Characteristics	- Insoluble powder → does not form a clear solution - Low H_2O solubility → slow onset and less potent (due to poor mixing with gastric fluid), but prolonged effect (due to poor absorption from gut) - Commonly combined (esp Mg and Al salts) to ↓ side-effects and ↑ potency	- Form a clear solution - High H_2O solubility → rapid onset and more potent (due to better mixing with gastric fluid), but very brief effect (due to ↑ systemic absorption from gut)
Mechanism of action	- Neutralise gastric acid by reacting with HCl to form a neutral, less acidic or poorly soluble salt (Eg. NaCl, $MgCl_2$, Etc.) → also provides a base (-OH, $-CO_3$, $-HCO_3$, -citrate) that buffers H^+ ions - ↑ in gastric pH causes → (i) inactivation of pepsin (if pH > 5), (ii) ↑ gastric motility, and (iii) ↑ LOS tone	
Clinical uses	- (1) PUD → symptomatic relief and ulcer healing (1°ly duodenal ulcer) - (2) GORD → symptomatic relief - (3) Aspiration prophylaxis prior to GA o Immediate ↑ gastric pH BUT ↑ gastric fluid volume (cf. other agents) o Usually → 15-30 mL Na citrate (0.3 M) given 15-30 mins pre-operatively	
Use as aspiration prophylaxis prior to GA	(i) ↓ gastric pH BUT ↑ gastric fluid volume (ii) Longer onset time and failure to ↑ gastric fluid pH (↓ potent) (iii) Prolonged duration of effect (iv) ↑ lung damage with aspiration → due to ↑ risk of pneumonitis	(i) ↓ gastric pH BUT ↑ gastric fluid volume (ii) Rapid onset and ↑ potent at ↑ gastric fluid pH (iii) Short duration of effect (30-60 mins) (iv) ↓ lung damage with aspiration
Issues	- (1) Osmotic diarrhoea (Mg salt) - (2) Constipation (Al and Ca salts) - (3) Acid rebound → due to hypersecretion of H^+ (Ca salt) - (4) ↑ Mg^{2+}, Al^{3+} and Ca^{2+} load (esp with renal failure) - (5) Milk-alkali syndrome (Ca salt) - (6) ↓ PO_4^{3-} (Al and Ca salt) - (7) Belching/flatulence → CO_2 release from stomach (Ca salt) - (8) Unpleasant taste - (9) ↑ UTI/bacterial colonisation of gastric mucosa → due to chronic alkalinsation of urine and gastric fluid - (10) Altered absorption/elimination of drugs → due to chronic alkalinsation of urine and gastric fluid	- (1) ↑ Na^+ load - (2) Metabolic alkalosis (with $NaHCO_3$) - (3) Belching/flatulence → CO_2 release from stomach (with $NaHCO_3$) - (4) Unpleasant taste - (5) ↑ UTI/bacterial colonisation of gastric mucosa - (6) Altered absorption/elimination of drugs

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

Overview of histamine 2 antagonists (H2RBs):

- H2RBs inhibit gastric acid secretion (both basal and stimulated secretions) → a/w ↓ gastric acidity AND gastric fluid volume. However, it has no effect on LOS tone or gastric emptying
- Includes – Famotidine (most potent) > Ranitidine = Nizatidine > Cimetidine (least potent)

Mechanism of action of H2RBs:

- Competitive inhibition of histamine activity at H2R (acts via Gi – ↓ IC cAMP) → selectively inhibits H2R at parietal cell (despite H2R being distributed widely in body)

Clinical uses of H2RBs:

- (1) Treatment of PUD (duodenal and gastric ulcers)
- (2) Treatment of GORD
- (3) Treatment of Zollinger-Ellison syndrome
- (4) Prevention of stress ulceration in critically ill patients
- (5) Some protection against drug-induced allergic reactions → when used with H1RBs, it can ↓ hypotension (but NOT histamine release)
- (6) Aspiration prophylaxis prior to GA
    - More reliable than PPI in ↓ gastric fluid volume and ↑ gastric fluid pH
    - H2RB given 1.5-2 hrs preoperative and night before
    - No immediate influence on current gastric pH (cf. antacids)

Pharmacokinetics of H2RBs:

Absorption	PO: - Well-absorbed but 50% bioavailability (due to extensive 1st pass metabolism) → EXCEPT nizatidine (100% bioavailability) - Cimetidine 300-800 mg, Ranitidine 150-300 mg, Nizatidine 150-500 mg, Famotidine 20-40 mg IV → Cimetidine 300 mg, Ranitidine 50 mg, Famotidine 20 mg
Distribution	- Protein binding 15-30%; V_D 1-1.5 L/kg - Can cross BBB and placenta - Time to peak [ ] (and onset of action) ~ 1-3 hrs after oral administration - Duration of single dose 6 hrs (cimetidine); 10 hrs for other H2RBs
Metabolism and elimination	- Hepatic metabolism (CYP450) into renal clearance (filtration and secretion): o Oral intake → mainly hepatic clearance (EXCEPT nizatidine) o IV intake → mainly renal clearance o Nb. Nizatidine is metabolised to an active metabolite (60% activity) - Elimination t ½ ~ 1.5-4 hrs - Dose reduction required with renal failure only (and NOT hepatic failure)

Issues with H2RBs:

- Side-effects are rare:
    - Mainly diarrhoea, dizziness, myalgia and rash
    - Cardiac effects occur 2° rapid IVI (esp in critically unwell or elderly patient) → hypotension, bradycardia, arrhythmia, cardiac arrest
    - Gastric achlorhydria → alter gastric flora due to change of pH → potential for systemic and/or pulmonary infections (esp in critically unwell patients)
    - Hypergastrinaemia and rebound hypersecretion of gastric acid → with cessation of chronic therapy
- Side-effects specific to cimetidine (>> ranitidine):
    - Inhibition of hepatic CYP450 → ↓ drug metabolism of warfarin, phenytoin, TCAs, propanolol, amide LAs, quinidine, Bz's, ketoconazole
    - Hepatotoxicity (elevated serum transaminase)
    - Cimetidine crosses BBB → cerebral effects (headaches, fatigue, confusion, hallucinations, seizures) → esp with renal failure

- Interstitial nephritis
- Granulocytopaenia and thrombocytopaenia
- Impotency/↓ sperm count → due to binding of androgen receptors
- Galactorrhoea (females) and gynaecomastia (males) → due to ↑ PRL

Note:
- Ranitidine weakly inhibits CYP450, while famotidine and nizatidine do NOT affect it
- Other H2RBs do not cross BBB readily nor affect androgen receptors

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

Overview of proton pump inhibitors (PPIs):

- PPIs are the MOST effective drug that inhibits gastric acid secretion (both basal and stimulated secretions) → a/w ↓ gastric acidity AND gastric fluid volume. However, it has no effect on LOS tone or gastric emptying
- Types of PPIs – Omeprazole (substituted benzimidazole → exists as a racemic mixture), Esomeprazole (L-isomer of omeprazole), Pantoprazole, Rabeprazole, Lansomeprazole

Mechanism of action of PPIs:

- Acts on terminal step in gastric HCl secretory pathway → irreversibly inhibits H^+/K^+ ATPase on canalicular membrane of parietal cell → ↓ H^+ secretion into gastric lumen
- PPIs are weak bases → unionised (inactive) "prodrug" at neutral pH → they diffuse into parietal cells and accumulates specifically at canalicular membrane → ↓ pH environment causes drug to be ionised (active) and trapped there
- Single dose of PPI inhibits only proton pumps that are currently present → inhibition of newly generated pumps require continued dosing

> Note – Daily PPI administration for 5 days produces maximal antisecretory effect → so cessation of therapy with repeated use is a/w delayed return of gastric acid secretion

Clinical uses of PPIs:

- PPIs are the agents of choice (Ie. better than H2RBs) for the treatment of:
  - (1) PUD (duodenal and gastric ulcers)
  - (2) GORD
  - (3) Zollinger-Ellison syndrome
- Aspiration prophylaxis prior to GA:
  - PPIs are not as reliable as H2RB in ↓ gastric fluid volume and ↑ gastric fluid pH
    - Single PPI dose → needs to be given > 3 hrs prior (as onset is within 2-6 hrs) → but prolonged effect (> 24 hrs) due to accumulation in canaliculi
    - 2x PPI dose (night before, and morning of surgery) → more effective
  - No immediate influence on current gastric pH (cf. antacids)
- Can also be used in the prevention of stress ulceration in critically ill patients

Pharmacokinetics of PPIs:

Absorption	PO: - Prepared as enteric-coated granules (due to rapid degradation at ↓ pH of stomach) → absorbed in small intestines - Oral bioavailability 60-85% - Omeprazole 20 mg, pantoprazole 40 mg, lansomeprazole 15 mg, rabeprazole 20 mg IV → only pantoprazole (40 mg)
Distribution	- Redistributes specifically to parietal cell canaliculi (due to ion-trapping) - Time to peak [ ] ~ 2-4 hrs → duration of single dose > 24 hrs (due to ion-trapping)
Metabolism and elimination	- Hepatic metabolism (CYP450) into inactive metabolites → renal/bile excretion - Elimination t ½ ~ 0.5-1.5 hrs

Issues with PPIs:

- Generally well-tolerated with minimal side-effects:
  - (i) GI upset – N/V, diarrhoea, abdominal pain
  - (ii) CNS effects (omeprazole crosses BBB) – headache, confusion, agitation
  - (iii) Gastric ECL cell hyperplasia and hypergastrinaemia
  - (iv) Small bowel bacterial overgrowth (due to acid suppression)
- Drug interactions due to hepatic CYP450 metabolism (EXCEPT for pantoprazole and rabeprazole) → ↓ clearance of warfarin, phenytoin, Bz's

(d) ***To outline the pharmacology of misoprostol and sucralfate.***

Misoprostol:

- Synthetic analogue of PGE-1 → used to prevent and treat gastric ulceration a/w chronic NSAID use
- Mechanism of action:
  - (i) Inhibits gastric acid secretion (both basal AND stimulated secretions) → by direct inhibitory effect (Gi-mechanism) on parietal (oxyntic) cell
  - (ii) Augments gastric and duodenal mucous/HCO_3^- secretion → by direct effect on mucous-secreting cells and ↑ mucosal blood flow
- Pharmacokinetics:
  - Given PO → rapidly absorbed from GI tract
  - Metabolised by FA-oxidising systems throughout body → thus, no dose adjustments required with renal/hepatic dysfunction
- Issues:
  - (i) Diarrhoea and abdominal cramps
  - (ii) Uterine contractions → issues with miscarriage, PV bleeding, menorrhagia
  - (iii) Hypotension is rare at normal doses

Sucralfate:

- Complex of salt of AlOH and sulphated sucrose → used to (i) treat PUD, and (ii) prevent stress ulceration in critically-ill patient
- Mechanism of action:
  - In the presence of acidic pH → forms a viscous paste that binds with high affinity to both normal and ulcerated mucosa → this paste:
    - (i) Forms a cytoprotective barrier over gastric and duodenal mucosa → prevents degradation of mucous by pepsin and limits diffusion of H^+
    - (ii) Releases Al → binds proteins, drugs, and mucins → inhibits pepsin activity, retards absorption of other drugs, and forms a gel with mucous
    - (iii) Stimulates mucous and HCO_3^- secretion and PG production
    - (iv) May have a bacteriostatic effect
  - It does NOT alter gastric pH, LOS tone or gastric emptying
- Pharmacokinetics:
  - Given PO (1 g) → 1 hr before meal and at bedtime
  - Virtually no GI absorption (< 5%) due to poor H_2O solubility → 30% remains in stomach 3 hrs post-administration → minimal systemic effects
- Issues:
  - (i) Few side-effects → mainly GI (esp constipation); minimal systemic side-effects
  - (ii) Al toxicity in patients with renal dysfunction → due to absorption of Al
  - (iii) Reduces absorption of other drugs → due to drug binding with Al
  - (iv) Reduced efficacy if other antacids are given previously → b/c it requires acidic environment for effect

Aside: Antimuscarinics (Eg. pirenzipine):

- Selective mAChR (M1R) antagonist → direct effect on parietal cell and indirect effect via ↓ histamine release (ECL cells)
- Selective effect on GI tract → ↓ gastric acid secretion, BUT less effectively (cf. other agents) and ↓ LOS tone and gastric emptying
- Formerly used to treat PUD (esp gastric ulcers)
- Minimal side-effects