DRUGS IN PEPTIC ULCER DISEASE

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LEARNING OUTCOMES
By the end of the lecture, students will be able to describe...

1. Pharmacological profile of:
   (i). Antacids
   (ii). H2 receptor antagonists
   (iii). proton-pump inhibitors
   (iv). cytoprotective agents

2. Interaction of drugs used for Helicobacter pylori eradication

OUTLINE....

A. What is Peptic Ulcer Disease (PUD) ?
B. Pathophysiology of PUD
C. Physiology of Gastric Acid Secretion
D. Pharmacological Treatment Options

PEPTIC ULCER DISEASE
A disease characterized by ulcers in gut mucosa exposed to gastric secretions.
E.g. Stomach, Duodenum

PHYSIOLOGY - GASTRIC ACID SECRETION

PHYSIOLOGY – MUCOSAL DEFENCE

Prostaglandins
Mucosal Cells
Vasodilation of mucosal blood vessels
Keep mucosa intact

Mucus and HCO3– Secretion
PATHOPHYSIOLOGY

Peptic ulceration develops...

a. When there's a breakdown in mucosal defense system of the stomach or duodenum.

b. When there is excessive and prolonged acid or pepsin secretion.
   E.g., Zollinger Ellison Syndrome

Role of Helicobacter pylori...

- A gram-negative rod found in the mucous gel coating the gastric mucosa or between the mucous layer and the gastric epithelium.
- Causes ~ 90% of duodenal ulcers and ~ 80% of gastric ulcers

Role of Helicobacter pylori...

- Cause ↑ resting and meal-stimulated gastrin levels
- ↓ gastric mucus production and duodenal mucosal bicarbonate secretion

NSAIDs and PUD...

- Cause ~ 24% of peptic ulcers in US
- Via ↑ acid secretion and ↓ mucosal protection by blocking prostaglandin synthesis
- Less common with COX-2 selective NSAIDs
  E.g., Celecoxib

DRUGS USED TO TREAT PUD

- Antisecretory Agents
  E.g., Proton pump inhibitors
  Histamine H₂ receptor antagonists
  Antimuscarinic agents
- Agents Enhancing Mucosal Defenses
  E.g., Misoprostol
  Sucralfate
- Antacids
- H. pylori eradication

PROTON PUMP INHIBITORS

- Diminish the daily production of acid by 80-95%
- ↓ both basal and stimulated gastric acid secretion
- Pro-drugs that require activation in an acid environment
- Several PPIs available- all equally efficacious
  E.g., Omeprazole, lansoprazole, esomeprazole, rabeprazole and pantoprazole
**MODE OF ACTION...**

- Irreversibly binds and blocks the proton pump.
- Acid secretion resumes only after new pump molecules are synthesized and inserted into the luminal membrane.
- Provides a prolonged (up to 24 to 48 hour) suppression of acid secretion.

**PHARMACOKINETICS**

- Degrades rapidly at low pH. Administered as capsules containing enteric-coated granules.
- From systemic circulation, the pro-drug diffuses into the parietal cells of the stomach and accumulates in the acidic secretory canaliculi.
- It is activated in this acidic milieu.

**ADVERSE EFFECTS...**

- Remarkably few ADRs.
- Most common: nausea, abdominal pain, constipation, flatulence, and diarrhoea.
- Other concerns with chronic use:
  - Increased incidence of *C. difficile* infections
  - ↓ absorption of vitamin B12
  - ↑ risk of fractures.
  - Hypergastrinemia and theoretical risk of gastric tumours.

**DRUG INTERACTIONS**

- With drugs metabolized through same CYP enzymes:
  - Warfarin
  - Diazepam
  - Clopidogrel
  - Phenytoin
- Via inhibition of CYP2C19:
  - Clopidogrel
- ↑ antiplatelet effect
  - Phenytoin
  - ↑ Serum concentration.
**DRUG INTERACTIONS**

OMEPRAZOLE (Active) → Clopidogrel (Inactive)

OMEPRAZOLE (Inactive) → Clopidogrel (Active)

**HISTAMINE(H₂) ANTAGONISTS**

- **e.g.** Cimetidine, Famotidine, Ranitidine

**Mode of action**
Competitively blocks the histamine H₂ receptor and ↓ acid secretion

- Predominantly inhibit basal acid secretion
- Suppress 24-hour gastric acid secretion by ~70%

**HISTAMINE(H₂) ANTAGONISTS**

**Mode of action…** Histamine

**Adverse Effects**
- Minimal
- Diarrhoea and constipation
- Headache, drowsiness, and muscular pain

Cimetidine,
1. ↓ testosteron binding to the androgen receptor
2. inhibit CYP metabolism of oestradiol

Galactorrhea in women
Gynaecomastia, Impotence in men

**HISTAMINE(H₂) ANTAGONISTS**

- **Drug Interactions…**
  - Cimetidine
  - Inhibit hepatic cytochrome P450
  - ↑ warfarin, phenytoin, theophyllin concentrations

- **Tolerance** (diminished therapeutic effect with continued drug administration)
  - can develop within 3 days
  - due to secondary hypergastrinaemia

**PIRENZEPINE**

**Mode of action…**

Acetylcholine

K⁺ → H⁺
MUCOSAL PROTECTORS

- Prostaglandin analogues – MISOPROSTOL
  - Acid secretion, ↑ mucus and HCO₃⁻

- SUCRALFATE
  - Forms a physical barrier

- COLLOIDAL BISMUTH
  - Forms a physical barrier, inhibit H. pylori

MISOPROSTOL

Prostaglandins

\[ \downarrow \text{Vasodilatation of mucosal blood vessels} \]

Mucosal Cells

\[ \downarrow \text{Keep mucosa intact} \]

Mucus and HCO₃⁻ Secretion

ANTACIDS

[Al(OH)₃], Mg(OH)₂, Sodium bicarbonate

- Mode of action…
  - Neutralizes gastric acid.
  - Decreases pepsin activity secondary to ↑ gastric pH

- Adverse Effects…
  - Aluminium Salts → Constipation
  - Magnesium Salts → Diarrhoea

SUCRALFATE

- In an acid environment (pH <4), sucralfate produces a viscous, sticky polymer
  - the polymer adheres to epithelial cells and ulcer craters
  - prevents pepsin-mediated hydrolysis of mucosal proteins

ANTACIDS

- Caution….
  1. High sodium antacids – In Hypertension and CCF
  2. Aluminium containing antacids – in renal impairment

- Interactions….
  - Bind other drugs and prevent absorption
e.g. Tetracycline, digoxin, iron
H. PYLORI ERADICATION

Antibiotics (Amoxycillin / Clarithromycin / Metronidazole)

+ Antisecretory Agent (Ranitidine / Proton pump Inhibitor)

± Colloidal Bismuth

DURATION OF TREATMENT 10-14 DAYS

BISMUTH COMPOUNDS

- As effective as cimetidine in patients with peptic ulcers

- Modes of action:
  - Bind to the base of the ulcer and prevent mucosal injury
  - Promote mucin and bicarbonate production
  - Antibacterial effect against H. pylori