

DRUGS IN PEPTIC ULCER DISEASE

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(2013/04/24)

LEARNING OUTCOMES

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

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

- II. 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

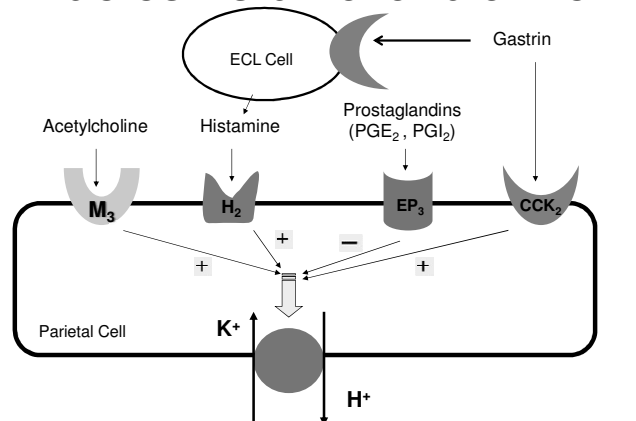
PEPTIC ULCER DISEASE

A disease characterized by ulcers in gut mucosa exposed to gastric secretions.

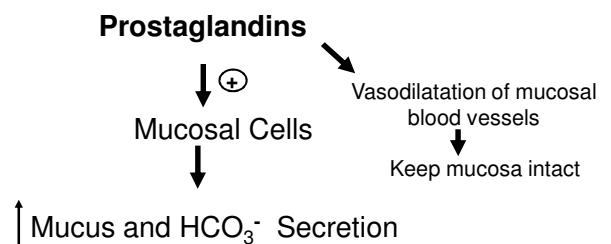
E.g. Stomach, Duodenum



PHYSIOLOGY - GASTRIC ACID SECRETION



PHYSIOLOGY – MUCOSAL DEFENCE



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

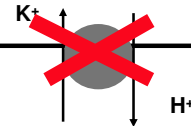
- Diminish the daily production of acid by 80-95%
- ↓ both basal and stimulated gastric acid secretion
- Pro-drugs that require activation in an acid environment
- Several PPIs available- all equally efficacious
 - e.g. Omeprazole , lansoprazole , esomeprazole
 - rabeprazole and pantoprazole

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

MODE OF ACTION...

Irreversibly binds and blocks the proton pump.



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

PHARMACOKINETICS

- Rapidly absorbed, highly protein bound, and extensively metabolized by hepatic CYP 450 system
- Elimination half life ~ 1 hour

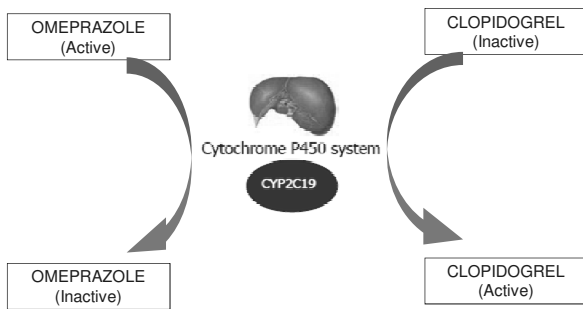
ADVERSE EFFECTS...

- 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↑ Effect
- Via inhibition of CYP2C19
 - Clopidogrel - ↓ antiplatelet effect
 - Phenytoin - ↑ Serum concentration

DRUG INTERACTIONS



HISTAMINE(H₂) ANTAGONISTS

e.g. Cimetidine, Famotidine, Ranitidine

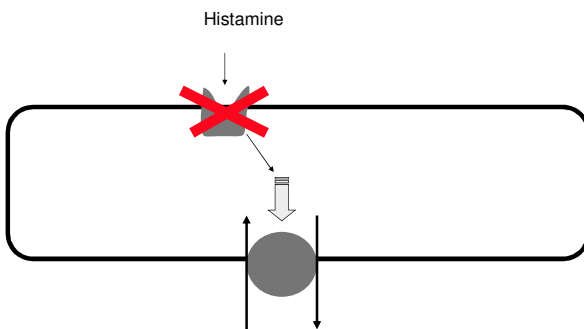
Mode of action

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(H₂) ANTAGONISTS

Adverse Effects

- Minimal
- Diarrhoea and constipation
- Headache, drowsiness, and muscular pain

Cimetidine,

1. ↓testosterone binding to the androgen receptor
2. inhibit CYP metabolism of oestradiol

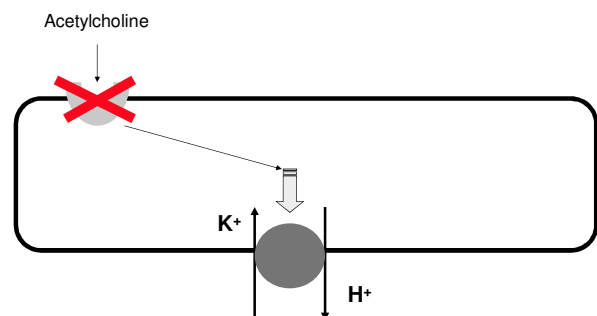
Galactorrhea in women
Gynaecomastia, Impotence in men

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

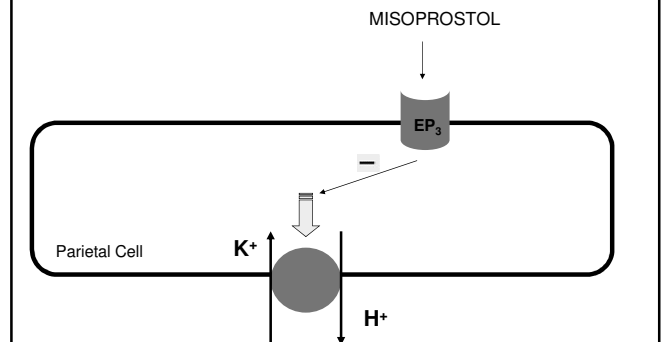
Mode of action...



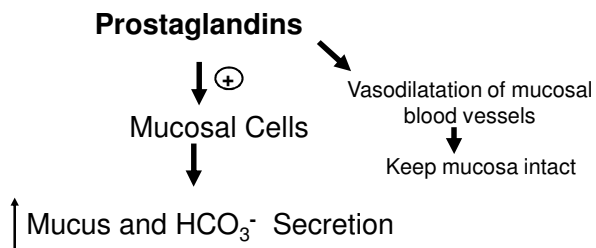
MUCOSAL PROTECTORS

- Prostaglandin analogues – **MISOPROSTOL**
 \downarrow Acid secretion, \uparrow mucus and HCO_3^-
- **SUCRALFATE**
 Forms a physical barrier
- **COLLOIDAL BISMUTH**
 Forms a physical barrier, inhibit *H. pylori*

MISOPROSTOL



MISOPROSTOL



SUCRALFATE

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

ANTACIDS

- $\text{Al}(\text{OH})_3$, $\text{Mg}(\text{OH})_2$, Sodium bicarbonate
- Mode of action...
 Neutralizes gastric acid.
 Decreases pepsin activity secondary to \uparrow gastric pH
 - Adverse Effects...
 Aluminium Salts \rightarrow Constipation
 Magnesium Salts \rightarrow Diarrhoea

ANTACIDS

- Caution....
 1. High sodium antacids – In Hypertension and CCF
 2. Aluminium containing antacids – in renal impairment
- Interactions....
 Bind other drugs and prevent absorption
 eg: Tetracycline, digoxin, iron

H.PYLORI ERADICATION

Antibiotics (Amoxicillin / 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:
 - a. Bind to the base of the ulcer and prevent mucosal injury
 - b. Promote mucin and bicarbonate production
 - c. Antibacterial effect against H.pylori