Pharmacotherapy of Peptic Ulcer disease

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Pathogenesis and drug targets

Mucosal erosions or ulceration arise when the caustic effects of aggressive factors overwhelm the defensive factors of the gastrointestinal mucosa

Aggressive Factors

- Acid, pepsin
- Bile salts
- Drugs (NSAIDs)
- *H. pylori*

Defensive Factors

- Mucus, bicarbonate layer
- Blood flow, cell renewal
- Prostaglandins
- Phospholipids.

Therapy is directed at enhancing host defense or eliminating aggressive factors.

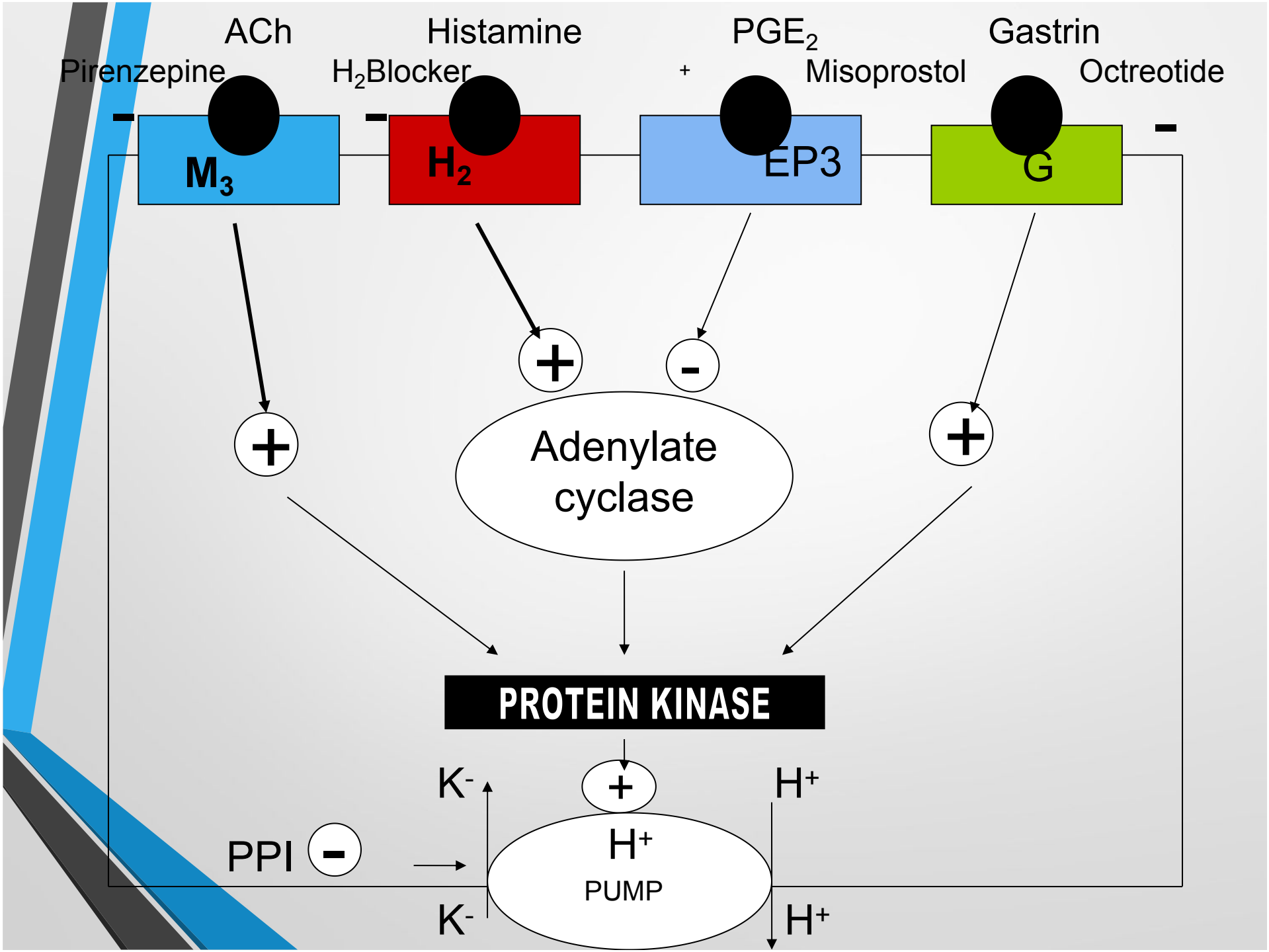
Drug Therapy

1. Antisecretory drugs
2. Mucosal protective agents
3. Drugs which neutralise gastric acid (Antacids)
4. Ulcer healing drugs
5. Antibiotics for *H. pylori* eradication

Antisecretory agents

These drugs reduce gastric acid secretion

- H_2-Receptor antagonists
- Proton pump inhibitors
- Anticholinergics
- Prostaglandin agonists


ACh
Pirenzepine
Histamine
H_2Blocker
PGE_2
Misoprostol
Gastrin
Octreotide
M_3
H_2
EP3
G
Adenylate cyclase
PROTEIN KINASE
PPI
K^-
H^+
H^+
PUMP
K^-
H^+

H_2-Receptor Antagonists

- Exhibit competitive inhibition at the parietal cell H_2 receptor:
  - suppress basal and meal-stimulated acid secretion in a linear, dose-dependent manner.
  - ↓ acid secretion stimulated by histamine, gastrin and cholinomimetic agents.
  - ↓ volume of gastric secretion and concentration of pepsin.

Clinical Comparisons of H2 Receptor Blockers.

Drug	Potency	Dose to Achieve >50% Acid Inhibition for 10 hrs	Dose for Acute Duodenal or Gastric Ulcer	Dose for Gastroeosophageal Reflux Disease	Dose for Prevention of Stress-Related Bleeding
Cimetidine	1	400–800 mg	800 mg HS or 400mg bid	800 mg bid	50 mg/h Continuous inf
Ranitidine	4-10	150 mg	300 mg HS or 150 mg bid	150 mg bid	6.25 mg/h continuous inf or 50mg IV every 6–8 h
Nizatidine	4-10	150mg	300 mg HS or	150 mg bid	Not available

H2-Receptor Antagonists

Side Effects

- Usually minor; include headache, dizziness, diarrhea, & muscular pain
- Cimetidine
  - elevates serum prolactin & alters estrogen metabolism in men
  - High doses Cimetidine for long periods causes Gynecomastia or impotence in men and Galactorrhea in women

H_2-Receptors Antagonists -Efficacy

- Inhibit 60–70% of total 24-hour acid secretion in usual prescription doses.
- Block > 90% of nocturnal acid, only 60–80% of daytime acid secretion.

Proton pump inhibitors

- Most potent suppressors of gastric acid secretion
- Pro-drugs activated to sulfenamide
- irreversibly inactivate the H+,K+-ATPase pump molecule.
- Acid secretion resumes only after new pump molecules are synthesized and inserted into the luminal membrane.

Proton pump inhibitors

- *Omeprazole* and its s-isomer *esomeprazole* ,
- *Lansoprazole*,
- *Rabeprazole*, and
- *Pantoprazole*.

Proton pump inhibitors

Pharmacokinetics.

- Ideally should be given about 30 minutes before meals so that the peak serum concentration coincides with the maximal activity of proton pump secretion.
- Rapidly absorbed in the small bowel .
- Highly protein bound, and extensively metabolized by hepatic CYPs, particularly CYP2C19 and CYP3A4.

Proton pump inhibitors

- Maximal suppression of acid secretion requires several doses of the proton pump inhibitors as not all pumps or all parietal cells are active simultaneously.
- It may take 2 to 5 days of therapy with once-daily dosing to achieve the 70% inhibition of proton pumps that is seen at steady state

Proton pump inhibitors

- Chronic renal failure does not lead to drug accumulation with once-a-day dosing of the proton pump inhibitors.
- Hepatic disease substantially reduces the clearance of esomeprazole and lansoprazole.
- Dose reduction is recommended for esomeprazole and should be considered for lansoprazole in patients with severe hepatic disease

Individual drugs

- Lansoprazole :
  - Partly reversible, little more potent, slightly more against *H. pylori*, ↑ bioavailability, rapid onset.
- Pantoprazole:
  - More acid stable
- Rabeprazole: Most rapid action.
- Es-omeprazole
  - Better intragastric pH , higher healing rates.

Adverse Effects

- Side effects are nausea, flatulence, and diarrhea (Commonest)
- Long term administration may lead to
  - Rise in Gastrin levels two- to four-fold .
  - Accelerated osteoporosis due to reduced calcium absorption
  - Few reports of gynecomastia and erectile dysfunction

PPIs in H. pylori

- promote eradication of *H pylori through* several mechanisms:
  - direct antimicrobial properties (minor)
  - by raising intragastric pH, lowers the MIC of antibiotics against *H. pylori*

Anticholinergic Drugs

- Selective M1– Pirenzepine, Telenzepine
- Block muscarinic M_1 receptors in stomach inhibiting acid secretion.
- Slight excess doses cause atropine like side effects on CVS,GIT or urinary bladder.
- Less popular, not used

Mucosal protective agents - Prostaglandin Agonists

Misoprostol (PGE1)

- It is a methyl analog of PGE1
- Stimulate secretion of mucus & bicarbonate
- reduces histamine-stimulated cAMP production and cause modest acid inhibition
- Stimulates intestinal electrolyte and fluid secretion, intestinal motility and uterine contractions.

Misoprostol

Administration

- Should be given 4 times/ day

Side effects

- Up to 20% develop diarrhea & cramps
- Should not be used during pregnancy.

Misoprostol

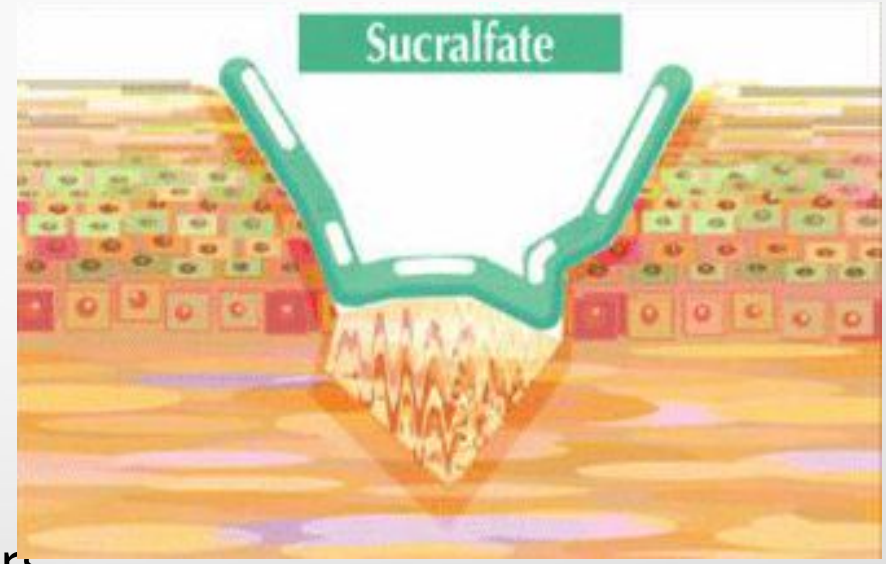
Indications

- prevention of NSAID-induced ulcers in high-risk patients.

Mucosal Protective Agents

1. Sucralfate
2. Bismuth salts

Sucralfate



Therapeutic action

- Ulcer protective

Indications

- Peptic ulcer,
- Prophylaxis of stress ulcers,
- Bile reflux.

Sucralfate

- Presentation
  - Tablets (1 g) and oral suspension (1 g/5ml)

Dosage

- Children: safety & efficacy not established but topically used in stomatitis
- Adults: 1 g taken one hour before the 3 major meals and at bed time for 4-8 weeks

Sucralfate

Adverse effects

- Constipation, diarrhoea, flatulence, dizziness, headache, bezoar formation,dry mouth and rash

Special precautions

- Renal impairment, pregnancy and breast-feeding.
- Sucralfate and enteral feeds should be separated by 1 hour

Colloidal bismuth subcitrate

- Water soluble, precipitate at pH < 5
- ↑ mucus & bicarbonate secretion
- With mucus it forms glycoprotein Bi complex that coats ulcer
- Detaches *H. pylori* from mucosa, kills directly
- Dose = 120 mg QID.

Colloidal bismuth subcitrate

Adverse Effects

- blackening of the tongue, dentures and stool.
- Prolonged usage may rarely lead to bismuth toxicity resulting in encephalopathy (ataxia, headaches, confusion, seizures) and osteodystrophy.

Ulcer healing drugs

- Carbenoxolone sodium:
  - Steroid like derivative of glycyretenic acid found in liquorice root
  - Augments viscid mucus production
  - Prolongs life span of gastric epithelial cells, prevents bile reflux
  - Major problem = mineralocorticoid action so not used now a days

Antacids

- Weak bases that react with gastric acid to form water & salt (Neutralize acid)
- Also promote mucosal defense mechanisms through stimulation of mucosal prostaglandin production.
- A single dose of 156 meq antacid given 1 hr after meal effectively neutralize gastric acid for 2 hr.

Antacids

- Carbonate salts of sodium and calcium are less popular
  - Formation of carbon dioxide results in gastric distention and belching.
  - NaCl absorption may exacerbate fluid retention in heart failure, hypertension, and renal insufficiency.
  - Unreacted alkali is readily absorbed, potentially causing metabolic alkalosis when given in high doses or to patients with renal insufficiency.

Calcium carbonate

- less soluble and reacts more slowly than sodium bicarbonate with HCl to form carbon dioxide and $CaCl_2$
- Excessive doses of either sodium bicarbonate or calcium carbonate with calcium-containing dairy products can lead to hypercalcemia, renal insufficiency, and metabolic alkalosis (milk-alkali syndrome).
- Rebound acidity when daily dose > 4 gm

Antacids

- **Magnesium hydroxide** or **Aluminum hydroxide** react slowly with HCl to form magnesium chloride or aluminum chloride and water.
- No gas is generated, belching does not occur.
- Unabsorbed magnesium salts may cause an osmotic diarrhea and aluminum salts may cause constipation, these agents are commonly administered together.

Antibiotics for *H. pylori* eradication

- Many regimens for *H. pylori* eradication have been proposed.
- Ideal regimen in this setting should achieve a cure rate of at least 80%.
- Five important considerations influence the selection of an eradication regimen

Antibiotics for *H. pylori* eradication

1. Combination therapy with two or three antibiotics (plus acid-suppressive therapy) is associated with the highest rate of *H. pylori* eradication.
2. A PPI or H_2-receptor antagonist significantly enhances the effectiveness of *H. pylori* antibiotic regimens containing amoxicillin or clarithromycin.
3. A regimen of 10 to 14 days of treatment appears to be better than shorter treatment regimens

Antibiotics for *H. pylori* eradication

4. Packaging that combines the daily doses into one convenient unit is available and may improve patient compliance .
5. The emergence of resistance to clarithromycin and *metronidazole* increasingly is recognized as an important factor in the failure to eradicate *H. pylori.*

Anti- H. Pylori regimens

- *Triple therapy* × *14 days:*

1. Proton pump inhibitor
2. clarithromycin 500 mg
3. metronidazole 500 mg or amoxicillin 1 g)] twice a day.

(Tetracycline 500 mg can be substituted for amoxicillin or metronidazole.)

- US-FDA approved regimen

1. Lansoprazole 30mg
2. amoxycillin 1000mg
3. Clarithromycin 500mg all given twice daily for 2 weeks.)

Therapy of *Helicobacter pylori*

- *Quadruple therapy* × *14 days:*
  1. Omeprazole 20mg BD
  2. Metronidazole 400 mg TID
  3. Tetracycline 500 mg QID
  4. Bismuth subsalicylate 120 mg QID

Adverse Effects

- The most commonly reported adverse events were nausea, vomiting, & diarrhea
- A bitter or metallic taste in the mouth is associated with eradication regimens containing clarithromycin
- Bismuth subsalicylate may cause a temporary grayish-black discoloration of the stool

Zollinger-Ellison Syndrome

- Therapeutic goal of reducing acid secretion to 1 to 10 mmol/h.
- Proton pump inhibitors are the drugs of choice.
- Dosage: twice the routine dosage for peptic ulcers.

Conclusion

- PPIs are superior for acid suppression in most clinically significant acid-peptic diseases.
- The delay in maximal inhibition of acid secretion with the PPIs (3 to 5 days) makes them less suited for use on an as-needed basis for symptom relief.
- H_2-receptor antagonists, while less effective than PPIs in suppressing acid secretion, have a more rapid onset of action that makes them useful mild or infrequent symptoms.


Thank you