Drugs used in the Management of PUD & GORD

Intended learning outcomes

- Appreciate the pathophysiology of PUD & GORD and how it determines the rationale of the therapeutic approach.
- List the histamine H2-receptor antagonists and PPIs that inhibit gastric acid production and describe their mechanisms of action, therapeutic uses, and adverse effects.
- List the drugs used therapeutically to promote the defense of the GI tract from the effects of acid, and describe their mechanisms of action, therapeutic uses, and adverse effects.
- Critique the H. Pylori eradication, List the antacid agents and describe their mechanisms of action, therapeutic uses, and adverse effects.

Definitions

Prodrugs: Inactive compounds that are metabolized in the body to therapeutically active agents.

Proton pump: An integral membrane protein that can move H + across a cell membrane, mitochondria, or other organelle. Responsible for acidification of the gastric lumen.

About peptic ulcer disease (PUD)

Relevant pathophysiology PUD

Peptic ulceration is traditionally considered a consequence of an imbalance between aggressive and protective factors in the upper gastrointestinal tract.

The principal aggressive factors:	
gastric acid and pepsin.	H. pylori infection, NSAIDs, smoking and alcohol increase the risk of ulceration.

H. pylori and PUD

- Stimulates gastrin release
- Increased acid secretion in genetically susceptible individuals.
- Causes direct damage to the mucosa.
- Eradication of H. pylori infection prolongs remission from peptic ulceration and usually with permanent cure.
- Smoking in combination with H. pylori increases the risk of ulcers but not their healing.

The aims of treatment of peptic ulceration

RELIEVE PAIN

HEAL THE ULCER

PREVENT ULCER RECURRENCE

PREVENT COMPLICATIONS E.G PERFORATION OR GI BLEEDING

Drugs used in the treatment of peptic ulcer

1. Antacids

2. Drugs that inhibit gastric acid secretion:

- H2-receptor Antagonists
  - Less effective than PPIs, used to heal DU and benign GU.
- PPIs

3. Drugs that do not directly inhibit gastric acid secretion:

- Sucralfate.

4. Drug combinations to eradicate H. pylori.

Pharmacology of Agents for Upper GI Disorders

Drugs used to treat acid-peptic diseases:

- Reduce gastric acidity (antacids, histamine H2-receptor antagonists, and PPIs)
- Or promote the defense of the GI mucosa (sucralfate, bismuth subsalicylate, and the prostaglandin analogue;misoprostol).

About gastroesophageal reflux disease (GORD)

Relevant pathophysiology GORD

Gastro-oesophageal reflux disease (GORD) is the reflux of stomach content into the oesophagus, causing symptoms.

Associated with obesity, alcohol intake and increasing age.

Most patients with GORD secrete a normal amount of gastric acid. Reflux occurs due to a dysfunctional lower esophageal sphincter. Allowing excessive reflux of gastric contents, containing acid and pepsin, into the oesophagus.

Damage to the mucosal surface provokes oesophageal dysmotiliy.

Complications and precipitants of GORD

- Complications of GORD include: Oesophagitis, peptic strictures, dysphagia, Barrett's oesophagus and oesophageal adenocarcinoma.
- Medications that worsen the symptoms of GORD:
- Calcium channel antagonists, nitrates, theophylline, bisphosphonates (alendronate in particular).
- Steroids and non-steroidal anti-inflammatory drugs (NSAIDs).
- Where possible these should be discontinued, and lifestyle changes considered.

The aims of treatment of GORD

Eliminate	Eliminate symptoms
Prevent	Prevent the relapse of esophagitis
Prevent	Prevent the development of complications
Heal	Heal esophagitis

Drugs used in the treatment of gastro-oesophageal reflux disease

1. Antacids and antacid/alginate combinations

2. Drugs that inhibit gastric acid secretion:

- H_2-receptor antagonists
- Proton pump inhibitors, e.g. omeprazole, lansoprazole, esomeprazole

3. Drugs that act on oesophageal and/or gastric motility:

- Metoclopramide, domperidone

Histamine H2-receptor antagonists

Histamine H2-receptor antagonists are used to treat:

- Dyspepsia
- GORD
- Peptic ulcer disease
- stress-induced gastritis

Mechanism of Action:

H2-receptor antagonists are highly specific and selective competitive antagonists of histamine, binding to gastric parietal cell, histamine H2 receptors.

They prevent activation of **adenylyl cyclase and accumulation of cAMP,** which mediate acid release into the gastric lumen.

Parietal cell acid secretion induced by the **secretagogues; gastrin and acetylcholine**, which act synergistically with histamine, is inhibited indirectly.

- Available OTC.
- Used to heal peptic ulcers but relapse off treatment is common
- Patients should have nothing by mouth after the dose
- May be used prophylactically in some critically ill patients to prevent stress-related gastric mucosal bleeding
- The two most commonly used are ranitidine and cimetidine
- Mechanism:
- Reduced acid secretion by the parietal cells, especially at night and in the fasting state.
- They are less effective in reducing food-stimulated acid secretion.

Prescribing points H2 antagonists

Pharmacokinetics Histamine H2-receptor antagonists

- All histamine H2-receptor antagonists can be given orally.
- They are absorbed rapidly; however, cimetidine, ranitidine, and famotidine only have 50% bioavailability.
- Relatively short half-lives
- They are excreted largely unchanged by the kidneys.
- ∴ Cimetidine, famotidine, and ranitidine are available for parenteral use.
- Clearance of Histamine H2-receptor antagonists, reduced in the elderly, renal and hepatic dysfunction.
- Cimetidine inhibits the activity of several hepatic cytochrome P450 enzymes that can prolong the duration of action of a number of other drugs.

H2-receptor antagonists Adverse effects

Cimetidine is weakly anti-androgenic in humans and may cause impotence or gynaecomastia.

Cimetidine and ranitidine may cause reversible mental confusion, particularly in frail, elderly patients.

Cardiac dysrhythmias following intravenous injections of H2-receptor antagonists.

Proton Pump Inhibitors (PPIs)

PPIs resemble histamine H2-receptor antagonists but have a different mechanism of action.

PPIs are considered the first-line drugs for treating acid peptic disease due superior efficacy and safety profile.

- More effective in reducing acid secretion than H2-receptor antagonists.

Relief of symptoms takes from 1 to 4 days.

PPIs are also used to treat:

- Dyspepsia, GORD, peptic ulcer disease. stress-induced gastritis, Gastrinomas

Pharmacokinetics of PPIs

Bioavailability is decreased by food

PPIs are best administered within an hour of meals, since maximal inhibition of H +, K +-ATPase occurs when proton pumps are actively secreting acid.

After dissolution of the enteric-coated PPI capsule in the intestine, the lipophilic prodrug diffuses into the acidic environment of the parietal cell, where it becomes protonated and highly concentrated.

It is then converted to a reactive sulfenamide cation that **irreversibly binds to and inactivates parietal cell H +, K +-ATPase**

Although their serum half-life is short (2–4 hours), PPI inhibition of the proton pump lasts up to 24 hours while synthesis of new H +, K +-ATPase occurs.

PPIs are metabolized by hepatic P450 microsomal enzymes; however, no clinically significant drug-drug interactions have been documented.

Promoters of GI mucosa defense: **Sucralfate**

1. **Sucralfate** use replaced by other agents for the treatment of upper GI disorders.
   - Still used clinically to treat stress-related gastritis.
- Sucralfate is a complex salt of sucrose sulfate and aluminum hydroxide.
- Mechanism of Action:
  - Sucralfate in its viscous form may bind to positively charged proteins to coat epithelial cells and form a physical barrier in the GI tract. That protects the luminal surface and any already formed ulcers from the effects of gastric acid and pepsin.
- Sucralfate can be given orally.
- Sucralfate is very insoluble; hence, it acts locally with little systemic absorption from the GI tract.

Promoters of GI mucosa defense: **Misoprostol**

Misoprostol is used to treat nonsteroidal anti-inflammatory drug (NSAID)-induced peptic ulcer disease.

- Misoprostol is a prostaglandin analog of prostaglandin E1 (PGE1).

Mechanism of Action:

Stimulates bicarbonate, mucus secretion and mucosal blood flow, resulting in **enhanced neutralization and protection from secreted acid.**

Binds to parietal cell prostaglandin receptors to modestly **inhibit secretagogue-induced** acid secretion.

Misoprostol is absorbed rapidly and metabolized to an active agent that has a very short serum half-life and short duration of action. Therefore, it is administered three to four times daily.

Promoters of GI mucosa defense: Bismuth subsalicylate

3. **Bismuth subsalicylate (Pepto-Bismol)** is used to treat:
   I. Dyspepsia
   II. Acute diarrhea
   III. Second-line agent in a multidrug combination, H. pylori infection (quadruple therapy).
      - **It is thought to inhibit growth of the organism.**
   - Mechanism of Action:
   I. Bismuth subsalicylate, coats epithelial cells to form a physical barrier in the GI tract and protect it from the deleterious effects of gastric acid and pepsin.
   II. May also stimulate bicarbonate and PGE2 secretion.
   - Bismuth subsalicylate is rapidly dissociated in the stomach into bismuth, which is eliminated in the stool, and salicylate; which is absorbed systemically.

PPIs in triple therapy against H. Pylori

PPIs are used in a multidrug regimen in treatment of peptic ulcer disease caused by H. pylori.

- Includes antibiotics clarithromycin or amoxicillin and metronidazole. **(Triple therapy)**
- **Bismuth subsalicylate plus thrapple therapy = quadruple therapy**
- Omeprazole available orally

PPIs pantoprazole and esomeprazole (pediatrics) are available for parenteral use.

Antacids

Antacid preparations are used to treat heartburn and dyspepsia.

- They may reduce absorption of other (concomitent) drugs through:
  - Direct binding
  - Increase in gastric pH: altering their dissolution or solubility.

Mechanism of Action:

- Antacids are weak bases that directly neutralize gastric hydrochloric acid to form a salt and water
- Reduce pepsin activity
- They may stimulate production of prostaglandins, increasing the defense of the GI mucosa.

All antacids can be given orally

Pharmacokinetics of antiacids

The acid-neutralizing capacity of available antacid preparations varies considerably. Being highly influenced by their:

- rate of dissolution
- their solubility in water
- the rate of gastric emptying, etc.

Sodium bicarbonate and **calcium carbonate** react more rapidly with HCl to produce CO2 and water, than magnesium or aluminum hydroxide. Therefore, the former may cause bloating and belching.

Magnesium hydroxide, can cause diarrhea, and **aluminum hydroxide**, can cause constipation, so they are usually administered in combination to balance their effects on the GI tract.

Drugs acting on oesophageal and/ or gastric motility

Metoclopramide and domperidone

They may have some efficacy in patients with mild grades of GORD because of their actions on the motility of the upper gut: they have a weak tonic effect on the lower esophageal sphincter;

They improve esophageal clearance and gastric emptying.

They are seldom effective alone and are used as an adjunct to acid suppressant treatment.

Metoclopramide is not recommended for long-term use because of its adverse effects on the central nervous system (CNS).

PRESCRIBED READINGS

- James M. Ritter et al. (2019) Rang & Dale's Pharmacology E-Book 9th Edition. Elsevier.
- Katzung B.G, Trevor A.J, Masters S.B. (2017) Basic and Clinical Pharmacology 14th Edition. Los Altos. Lange Medical Publications.
- Morris J. Brown, Pankaj Sharma, Fraz A. Mir, Peter N. Bennett (2018). Clinical Pharmacology 12th Edition. ELSEVIER
- Woodrow R, Colbert D. J, Smith D.M (2018). Essential Pharmacology for Health Professionals, 8th Edition; New York: Delmar
- Laura Rosenthal, Jacqueline Burchum (2017) Lehne's Pharmacotherapeutics for Advanced Practice Providers 1st Edition. Saunders

RECOMMENDED READINGS

- Laurence Brunton), Bjorn Knollman, Randa Hilal-Dandan (2017), Goodman and Gilman's Pharmacological Basis of Therapeutics, 13th Edition, McGraw – Hill
- Boarder M, Navti P, Newby D (2017) Pharmacology for Pharmacy and the Health Sciences: A Patient-centred Approach 2nd Edition, Oxford University Press, USA
- Wells B, DiPiro J, Schwinghammer T, DiPiro C (2017) Pharmacotherapy Handbook, 10th Edition, McGraw – Hill
- Judith A. Rees, Ian Smith, Jennie Watson, (2015) Introduction to Pharmaceutical Calculations, 4th Edition, Amazon.com Services LLC
- Jane Rice (2016), Principles of Pharmacology for Medical Assisting 6th Edition, Cengage Learning.
- British National Formulary. Regular updates
- Zambia National Formulary (2013)
- Ministry of Health Standard Treatment Guidelines (2013)