DRUGS USED IN PEPTIC ULCER DISEASE

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OVERVIEW

- Naturally, the gastro intestinal tract has its protective mechanism even as the secretions remain viable for normal digestion

- Acid secretion is under the nervous and hormonal control

- The body should therefore keep in check the balance between the protective and the injurious factors

- Any imbalance where the injurious factors thrive more than the protective factors may result into ulcer formation

Protective factors/mechanism

- Mucus
- Bicarbonate
- Prostaglandins

- Mucosal renewal
- Mucosal blood flow

Injurious factors

- Pepsin
- Bile reflux
- Gastric acid
- Helicobacter pylori
- Rapid gastric emptying

- Lifestyle - Stress, alcohol, smoking, obesity, fatty diet, chocolate, caffeine
- Drugs – NSAIDs, aspirin, clopidogrel, corticosteroids, SSRIs, calcium channel antagonists, nitrates, bisphosphonates, theophylline, potassium chloride

PEPTIC ULCER DISEASE (PUD)

- This is a discontinuity or bleach in the entire thickness of the gastric or duodenal mucosa of >5mm in diameter with associated inflammation

- This results from the damage of the mucus membrane that normally protects the esophagus, stomach and duodenum from

gastric acid and pepsin

- This damage is mostly precipitated by Helicobacter pylori infection and NSAIDs

- Other independent risk factors for bleeding and ulceration have also been responsible

Pathophysiology

- A physiologic imbalance between aggressive factors (gastric acid and pepsin) and protective factors (mucosal defense and repair)

- Over production of acid
  - Zollinger-Ellison: gastrin producing tumor

- Mucosal integrity compromise:
  - *H.pylori*, NSAID use

Common symptoms of PUD

Common presenting symptoms are;

- Epigastric pain
- Heartburn
- Belching

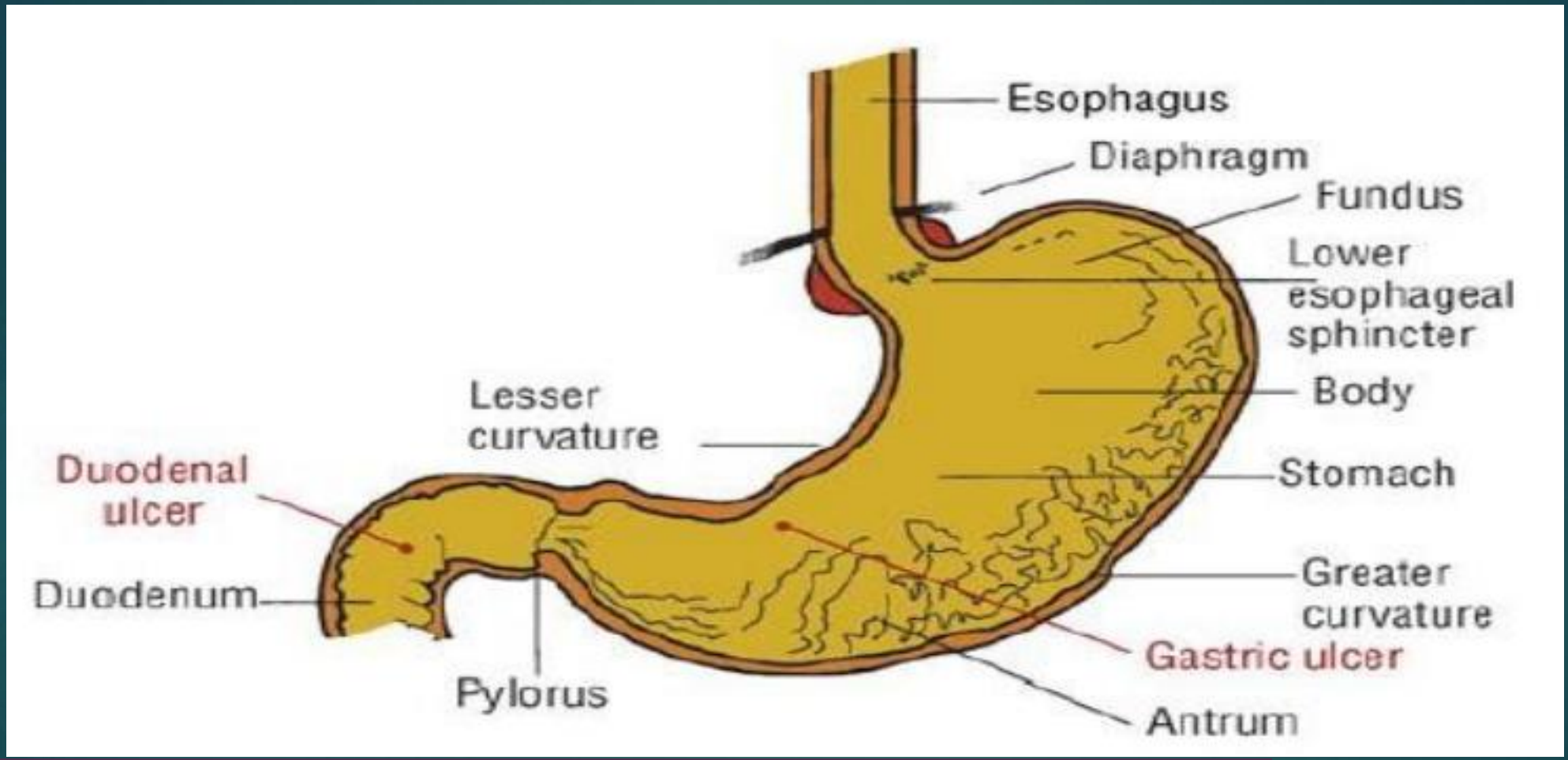
- Bloating
- Nausea
- Anorexia (loss of appetite) and weight loss caused by inflamed excavations of the mucosa and underlying tissue of the upper GIT

Classification of PUD

- **Duodenal ulcer (DU):**
- These affect the duodenum
- Symptoms of pain are usually nocturnal and before meals
- Weight gain is common
- These same symptoms are relieved by food or anti acids but usually come back 1-3 hours later

- **Gastric ulcer (GU):**
- These affect the stomach
- Symptoms usually presenting as upper abdominal pain
- Weight loss is common
- 5% of GU cases are usually malignant
- Epigastric pain is often made worse by food

Structural locations of the PUD



PUD Complications

- Bleeding
- Gastric outlet obstruction
- Perforation

DRUG TREATMENT OF PUD

Histamine 2 Receptor Antagonists or

blockers (H2As)

Examples

- Ranitidine, cimetidine, nizatidine, famotidine

Pharmacokinetics

- H2 receptor blockers are well absorbed from the gut and undergo varying degrees of hepatic inactivation before excretion through urine

- Although the half life of H2 receptor blockers is only 2 to 3 hours, their duration of action is longer

- These drugs are therefore mostly administered either once or twice daily

Mechanism of action

- Stimulation of histamine 2 receptors in the parietal cells triggers the secretion of gastric acids into the stomach
- H2 receptor blockers are structurally similar to that of histamine whose binding to the receptor they block and thus preventing the secretion of gastric acid
- Have shown potent inhibition of both meal stimulated and basal secretions of gastric acid

PIG

- Since gastric acid catalyses the conversion of inactive pepsinogen to pepsin, its reduction both in volume and concentration by H2 receptor blockers produces a proportionate reduction of pepsin

- The H2 receptor blockers also reduce the secretion of intrinsic factor but not enough to significantly reduce vitamin B12 absorption

- They have no effect on gastric emptying time oesophageal sphincter pressure or pancreatic enzyme secretion

Indications

Conditions associated with excessive secretion of gastric acid including;

PH GAD

- PUD
- Dyspepsia (Epigastric pain after meals associated with impaired digestion and excessive stomach acidity)
- Gastro esophageal reflux disease (GERD)

- Heartburn

NB:

- Occasionally an H2 blocker can be used in combination with an H1 blocker for the treatment of allergic reactions that do not respond when an H 1 blocker is used alone

Extended information on H2 blockers Indications

- For dyspepsia, it is recommended that drugs are taken 30 minutes before a dyspepsia provoking meal

- For treatment of PUD, H2 blockers are administered once or twice daily at doses that raise the PH above 4 for at least 13 hours a day

- Most authorities recommend a single daily dose to be taken at bed time to ensure that acid is suppressed the whole night

- PPIs are preferred in this case because they heal almost 90% of all ulcers in 4 weeks when used alone while H2 blockers require 6 to 8 weeks to achieve this level of efficacy

Side effects

- Headache
- Dizziness
- Tiredness
- Rash
- Diarrhoea and other GIT disturbances

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- Altered liver function tests (rarely liver damage)
- Rarely pancreatitis, bradycardia, AV block, confusion, depression, hallucinations, hypersensitivityreactions (Fever, arthralgia, myalgia, anaphylaxis
- Cimetidine has weak anti **androgenic activity** and so can cause gynecomastia in elderly men but this reaction is uncommon with other H2 blockers

Drug interactions

- changes gastric pH → may alter medication absorption

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- Absorption of Ketoconazole, itraconazole, iron, atazanavir, delavirdine, indinavir,

nelfinavir is reduced

- On the other hand absorption of Raltegravir and saquinavir may be increased

- Cimetidine also inhibits CYP450 enzymes 1A2, 2C9, 2D6, and 3A4 → may affect the reduce metabolism of the following;
  - Warfarin
  - Theophylline
  - Carbamazepine
  - Lovastatin
  - Saquinavir
  - Alprozolam and other agents metabolized by these enzymes

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- The doses of these drugs may need to be reduced when used with cimetidine but other H2 blockers do not significantly inhibit CYP 450 and will be preferred preferred for patients receiving concomitant drug therapy

- Cimetidine may compete with medications and creatinine for tubular secretion in the

kidney

Proton pump inhibitors (PPIs)

Examples

- Omeprazole, esomeprazole, rabeprazole, lansoprazole, dexlansoprazole, pantoprazole

- Suppress acid for longer duration than do H2RAs

- Most effective if taken before meals and if administered twice daily then the evening dose should go with the evening meal

Pharmacokinetics

- PPIs are acid labile (Higher affinity for acid environment) prodrugs administered orally as sustained release, enteric coated preparations
- After absorption from the gut, they are distributed to the secretory canaliculi in the gastric mucosa and converted to the active metabolites
- The metabolites then bind to the proton pump **(H+,K+ - ATPase)**
- These metabolized are eventually metabolized to inactive compounds in the liver by CYP 450 microsomal enzymes and excreted through urine

- Those with CYP 2C19 extensive metabolizer phenotypes may require higher doses of PPIs

Mechanism of action

- Within the luminal membrane of the gastric parietal cell is the proton pump **(H+,K+ - ATPase) which is very key for gastric acid secretion**

- The active metabolites of PPIs form a covalent disulfide link with a cysteinyl residue in the proton pump **(H+,K+ - ATPase)**

- The drugs irreversibly block the proton pump and cause almost total acid suppression for > 24hours (extended period)

- Different PPIs bind different sites on the proton pump and this accounts for variation in potency

Further information on action of PPIs

- PPIs can produce dose dependent inhibition of up to 95% of gastric acid secretion and a single dose can inhibit acid secretion for 1 to 2 days

- PPIs are therefore, more efficacious and have got higher healing rates than H2 blockers for most conditions

Indications

- PUD – typically heal 80% to 90% of peptic ulcers in 2 weeks
- Healing can even be in less than 2 weeks when combined with antibiotics
- Comparatively, combination with antibiotics only achieve ulcer healing of 70% to 80% in 4 weeks

- Zollinger Ellison syndrome (Severe ulcers due to gastrin secreting tumors) where higher doses are needed
- Gastro esophageal reflux disease (GERD)
- Dyspepsia and heartburn
- Prevention of peptic ulcers and bleeding in persons receiving high dose or long term therapy with NSAIDs such as elderly on long term diclofenac treatment

Side effects

PPIs are usually well tolerated with only a few side effects;

- Gastro intestinal effects – diarrhea, constipation, vomiting, abdominal pain, flatulence
- CNS effects – headache, dizziness
- Skin rush
- Elevated hepatic enzymes and caution should be taken in severe liver disease
- Hypomagnesemia in patients taking drug for over a year
- Increased risk of hip/spine fracture has been reported with long term PPI use
- Increased risk of C. *difficile* infection

Drug interactions

- Omeprazole is a CYP 2C19 inhibitor → reduced activity of clopidogrel by preventing its conversion to its metabolite hence increasing risk of MI, stroke etc
- Also reduces metabolism of diazepam
- This interaction is not there with H2 receptor blockers and pantoprazole which are not metabolized by the enzyme
- Drugs with pH-dependant absorption are affected (Refer to the same effect under H2As)

- Co-administration with anti-bacterials increases risk of C. *difficile* 2 -3 fold and so review of all PPIs should be done on admission where there is high risk of C. *difficile* associated diarrhea (CDAD)

Caution

- PPIs may mask the symptoms of gastric cancer and particular care should therefore, be taken in those with alarm features

- In such cases, gastric malignancy should be rule out or excluded before PPI treatment is commenced

- Treatment with PPIs should be reviewed regularly to ensure that patients are not continued unnecessarily

Anti acids

Examples

- Magnesium hydroxide Or magnesium trisilicate
- Aluminium hydroxide
- Calcium carbonate
- These are available in chewable tablets and liquid suspensions

Mechanism of action

- Chemically neutralize stomach acid thereby raising the intra-gastric pH
- Increased PH further decreased activation of pepsinogen and increased Lower Esophageal Sphincter (LES) pressure
- All eventually leads to relief of dyspepsia pain and acid indigestion which also helps in the healing of peptic ulcers
- Alginate as an added ingredient forms a raft (artificial cover) over the stomach content and is very helpful in GERD

- Simethicone as another additional ingredient acts as anti-foaming agent which is significant in relieving of flatulence

Indications

Symptomatic relief of PUD especially in;

- Dyspepsia
- GERD
- Intermittent symptoms or as breakthrough symptom relief with H2RA/PPI therapy

NB

- Anti-acids were previously used for PUD but require larger frequent doses to achieve this effect
- Furthermore, the control of nocturnal acid secretion has also been difficult and hence it is seldomly used in PUD

Side effects

- Aluminium alone causes constipation while magnesium causes diarrhea

- For this reason most formulations contain combinations of aluminium and magnesium which has a relatively neutral effect on the GI motility

- Calcium carbonate can also cause constipation while large doses can lead to a rebound acid secretion

- Accumulation of aluminum/magnesium in renal disease

Drug interactions

- Chelation (fluoroquinolones, tetracylcines)

- Reduced absorption of the listed drugs below because of increased pH
  - Ketoconazole
  - Itraconazole
  - Iron
  - Atazanavir
  - Delavirdine
  - Indinavir
  - Nelfinavir)
- Absoption of raltegravir and saquinavir is increased

Cytoprotective drugs

Examples

- Sucralfate
- Misoprostol

- They both protect the GIT mucosa though with different mechanisms

Sucralfate

- A viscous polymer of sucrose octasulfate and aluminium hydroxide

- This sulfated polymer adheres to ulcer craters and epithelial cells therefore preventing pepsin catalyzed hydrolysis of mucosal proteins
- Sucralfate also stimulates prostaglandin synthesis in mucosal cells
- These actions contribute to the formation of a barrier to gastric acid and pepsin thereby, facilitating the healing of ulcers

Pharmacokinetics of sucralfate

- Administered orally as a tablet or suspension
- Not absorbed significantly and is primarily excreted in feces
- Patients absorb small quantities of aluminium and so should be used cautiously in patients with renal impairment

Indications

- Peptic ulcer disease

- Active ulcers
- Suppression of ulcer Recurrence

- Primarily used in patients who cannot tolerate H2 blockers or PPIs

Side effects

- Constipation
- Laryngospasm

Interactions

- Sucralfate can affect absorption of other drugs like digoxin, fluoroquinolones, ketoconazole and phenytoin

- If these drugs are to used together then they should be administered 2 hours apart

Misoprostal

- A prostaglandin E1 analogue
- Exerts a cytoprotective effect by inhibiting gastric acid secretion while promoting the secretion of mucus and

bicarbonate

Indication

- Primarily indicated for prevention of PUD in patients taking NSAIDs on the long term basis for conditions like arthritis and other conditions

- NSAID induced ulcers in the elderly or those with history of peptic ulcer disease

Pharmacokinetics

- Administered orally with food for the duration of NSAID therapy

Side effects

- Diarrhea
- Intestinal cramps

- Misoprostal can stimulate uterine contractions and induce labor in pregnant women and so its use is contraindicated during pregnancy

Treatment of Helicobacter pylori infection

- Studies show that 80% to 90% of patients who undergo monotherapy with gastric acid inhibitor have an ulcer recurrence within 1year after discontinuing

therapy

- In contrast , less than 10% of patients who undergo therapy with both gastric acid inhibitor and antimicrobial agents to eliminate H. pylori present with an ulcer recurrence
- Therefore, the combination therapy also know as **triple therapy** is now the standard of care which has a 90% to 95% cure rate
- The recommended combination consists of a PPI and two antimicrobial agents
- The common antimicrobial agents used are clarithromycin, Amoxyl, Tetracycline, tinidazole and metronidazole
- Sometimes more than two antimicrobials can be used in the H.pylori treatment together with other agents like bismuth subsalicylates

H. pylori treatment combination

Regimen	Duration (days)	Efficacy (%)[c]
Lansoprazole 30 mg bid + amoxicillin 1000 mg bid + clarithromycin 500 mg bid	10–14	81–86
Esomeprazole 40 mg once daily + amoxicillin 1000 mg bid + clarithromycin 500 mg bid	10–14	70–85
Omeprazole 20 mg bid + amoxicillin 1000 mg bid + clarithromycin 500 mg bid	10–14	70–85
Rabeprazole 20 mg po bid + amoxicillin 1000 mg bid + clarithromycin 500 mg bid	7	70–85
Bismuth subsalicylate 525 mg qid + metronidazole 500 mg tid + tetracycline 500 mg qid + PPI bid	14	75–90
Bismuth subcitrate 420 mg + tetracycline 375 mg + metronidazole 375 mg[d] 3 capsules qid + PPI bid	10	85–92
Sequential therapy PPI + amoxicillin 1 g bid for 5 days; then PPI, clarithromycin 500 mg bid + tinidazole 500 mg bid for 5 days	10 (5 each treatment)	> 90

Most common combination is that of;

Lansoprazole 30mg + Clarithromycin 250mg + tinidazole 500mg (Pylokit)

Other Combinations of *H.pylori* treatment

- Use of a PPI, bismuth subsalicylate, tetracycline and metronidazole for 14 days is suitable for those allergic to amoxicillin
- Formally used triple therapy of a PPI, amoxicillin and Clarithromycin should no longer be used because of increasing resistance
- Regardless of the combination used, therapy should be continued until eradication of *H. pylori is confirmed by a laboratory*
- H2 blockers and sucralfate plus antimicrobial agents may

also be used but often require 4 or more weeks and are reserved for those who cannot take PPIs

- Some gastric ulcers may longer treatment than is usually required for duodenal ulcers

END