PEPTIC ULCER DISEASE

From pH to Hp

by

Dr G Muntingh

Gastric Physiology
Gastric Acid Secretion

- Histamine
  - Most important stimulant of gastric acid secretion
  - released from ECL cells by gastrin and cholinergic activity
- Acetylcholine
- PG and somatostatin
  - inhibit acid secretion

Gastric Acid Secretion

- Histamine
  - increases parietal cell cAMP
  - activates cAMP dependent protein kinase
- Gastrin
  - direct stimulation of parietal cells
    - stimulation of histamine release from ECL cells
- Acetylcholine
  - increases parietal cell cytosolic calcium
- PG and somatostatin
  - inhibits G proteins
  - decreased generation of cAMP

Phases of Gastric Acid Secretion

- Cephalic
- Gastric
- Intestinal
- Basal or interdigestive
  - unrelated to feeding
  - peaks at about midnight and ebbs at about 7 AM
  - mediated by neural pathways

Gastric acid secretion

- Inhibitors
  - Acid
    - induces feedback inhibition of gastrin release
    - somatostatin reduces acid secretion by
      - inhibiting gastrin release
      - inhibiting parietal cell secretion
      - inhibiting release of histamine
    - stimulates release of secretin
  - hyperglycemia
  - Hypertonic fluids
  - Fats
    - gastric inhibitory peptide

CLASSIFICATION OF PEPTIC LESIONS

- Erosions
  - superficial, does not penetrate the mucosa
- Ulcers
  - deeper lesions, penetrates beyond the muscularis mucosa
    - Acute - less than 2 weeks, not associated with any fibrotic reaction in the submucosa
    - Chronic- more than 2 weeks and associated with fibrosis and formation of granulation tissue
- Inflammation

PEPTIC ULCER

- ulcerative disorders of the upper gastrointestinal tract involving principally the most proximal portion of the duodenum and the stomach
- **Major Forms**
  - **Duodenal Ulcer**
  - **Gastric Ulcer**

Pathogenesis of Peptic Ulcer Disease

- Aggressive Factors
  - Acid
  - Pepsin
  - Bile
  - Helicobacter pylori
  - Aspirin and NSAIDs
- Defensive Factors
  - Gastric mucus
  - Mucus Gel layer
  - Bicarbonate
  - Mucosal barrier
  - mucosal blood flow
  - endogenous PGs
  - cell restitution

Aggressive Factors

- Acid
  - secreted by parietal (oxyntic) cells
  - principal aggressive factor
    - pepsin is active only in a low pH
    - acid by itself can damage the mucosa
- Pepsin
  - secreted by peptic or chief cells
- Bile
- Helicobacter pylori
- Aspirin and NSAIDs

Pathogenesis of PUD Aggressive Factors

- Aspirin and NSAIDs
  - direct toxicity to gastric mucosa
  - depletes protective endogenous PG
    - inhibits PG synthesis
  - interrupts gastric mucosal barrier
    - permit H+ ion back diffusion
  - decrease gastric mucus and bicarbonate secretion
  - increased gastric acid secretion
  - impaired epithelial cell replacement

Pathogenesis of PUD Defensive

- Gastric mucus gel layer
  - stimulated by
    - mechanical & chemical irritation
    - cholinergic stimulation
  - slows down ionic diffusion
  - impermeable to macromolecule
  - continuously secreted and solubilized by pepsin
  - increased by prostaglandin
  - decreased by aspirin and NSAIDs

Pathogenesis of PUD Defensive Factors

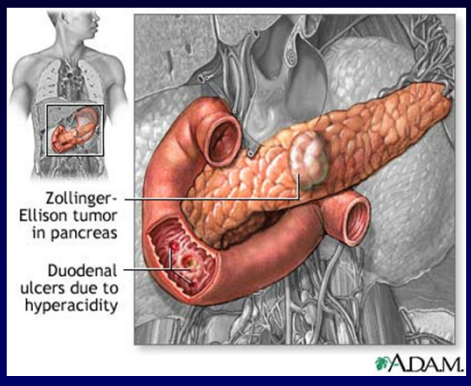
- Gastric mucosal barrier
  - luminal surface
  - intercellular tight junctions
  - almost impermeable to H ion back diffusion from the lumen
  - interrupted by
    - bile acids, salicylates, alcohol, weak organic acids

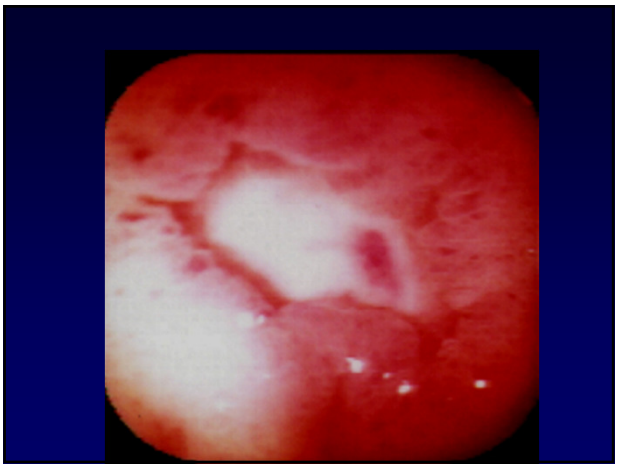
Pathogenesis of PUD Defensive Factors

- Gastric mucosal blood flow
- Cell restitution
- Endogenous Prostaglandins
  - stimulates
    - gastric mucus secretion
    - gastric/duodenal HCO_3 secretion
    - maintains good mucosal blood flow
    - maintains integrity of mucosal barrier
    - promotes epithelial cell renewal

Duodenal Ulcer

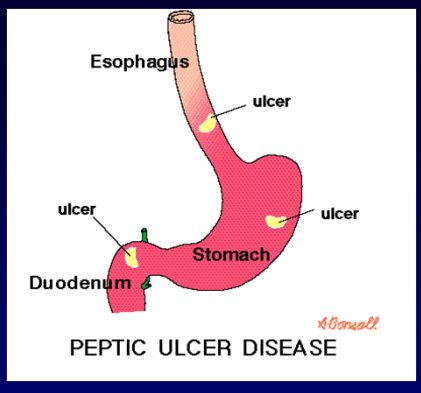
- Chronic and recurrent disease
- Deep and sharply demarcated
- > 95% in the duodenal bulb
- 6-15% of western populations
- Natural history
  - Spontaneous healing and recurrence
  - Recurrence may be asymptomatic

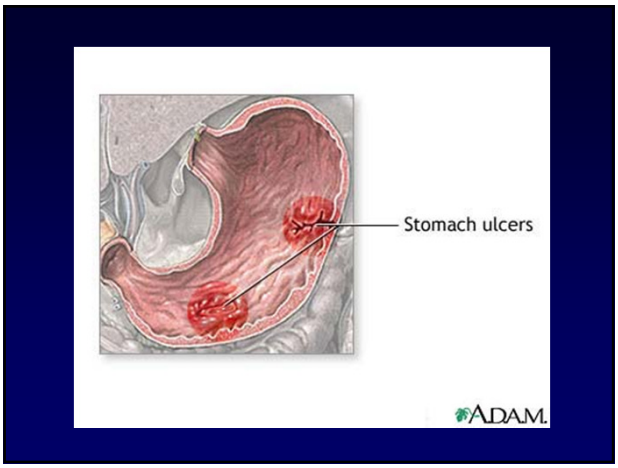


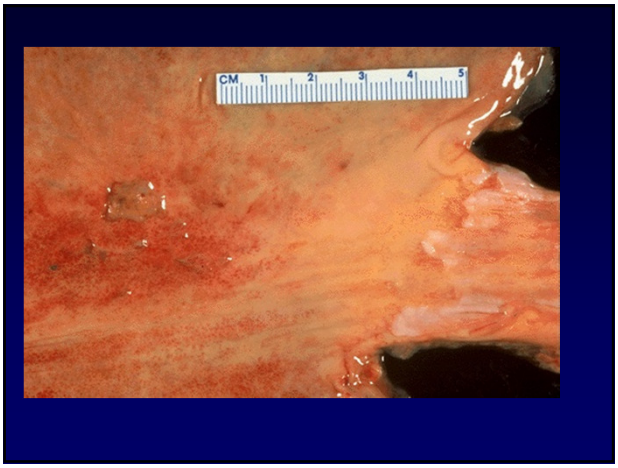


GASTRIC ULCER

- 60% of GU are located within 6 cm. of the pylorus, at or near the right-hand region of the stomach and most frequently on the posterior wall.
- Appears as an eroded or "punched out" area of mucosa surrounded by inflamed and swollen tissue.
- Malignant- lesser curve, larger ulcers
- 1 - 8% that are radiographically benign are maligant




Stomach ulcers
A.D.A.M.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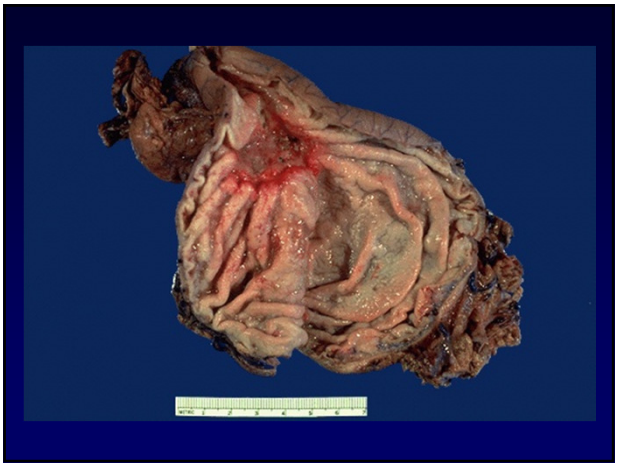
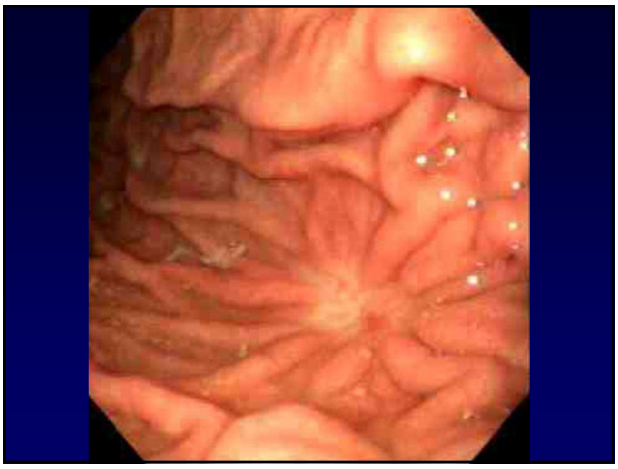
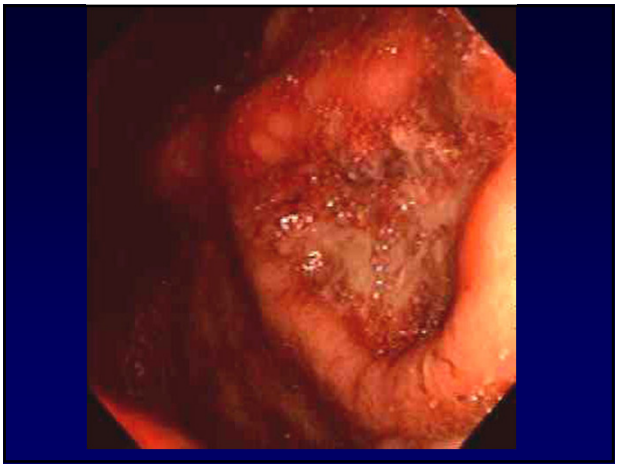
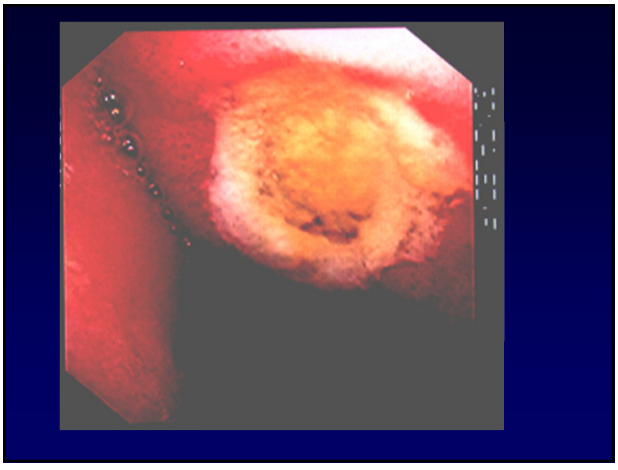








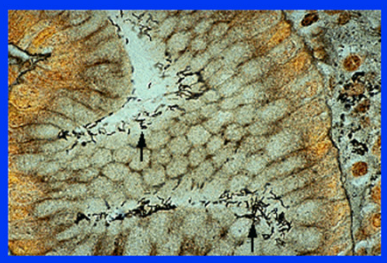
HELICOBACTER PYLORI

- A bacteria, Gm-, microoerophilic, spiral bacillus, secretes toxins that cause chronic inflammation and contribute to the formation of ulcers
- Also secretes proteins that attract cells that cause inflammation
- Cause almost all cases of ulcer disease that are not medication related

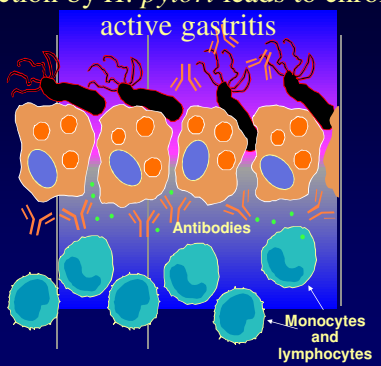
Pathogenesis of PUD Aggressive Factors

- Helicobacter pylori
  - Urease
  - Surface proteins
  - Proteases and phospholipases
  - Adhesins
  - Cytoxin associated gene A
  - Vacuolating cytotoxin A

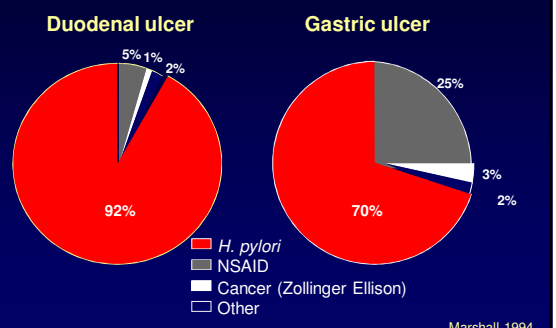
HELICOBACTER PYLORI
(SILVER STAIN)



Evasion of the host chronic inflammatory reaction by *H. pylori* leads to chronic active gastritis

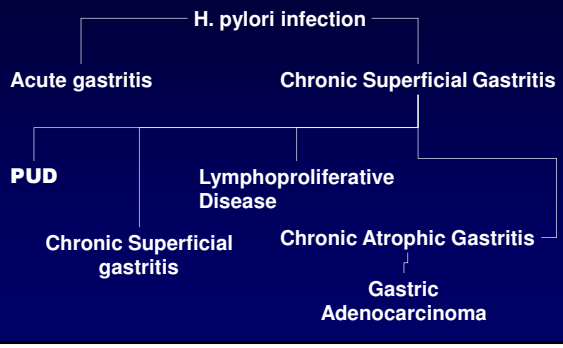


H. pylori is a causal factor in most cases of peptic ulcer disease



Marshall 1994

Consequences of Hp Infection



What can you do for your patients?

- Drugs that neutralize existing acid

  Antacids
- Drugs that suppress acid formation

  H2 receptor antagonists

  PPI

  Antimuscarinic agents
- Drugs for Mucosal protection

  Prostaglandins Sucralfate Carbenoxolone colloidal bismuth
- Miscellaneous

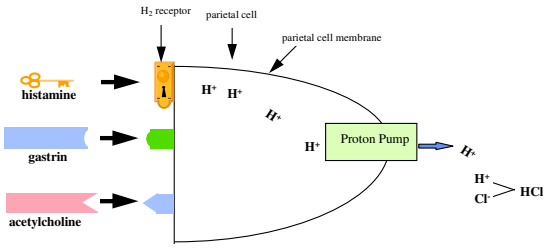
Antacids

- Calcium bicarbonate
- Sodium bicarbonate
- Aluminum hydroxide
- Magnesium hydroxide

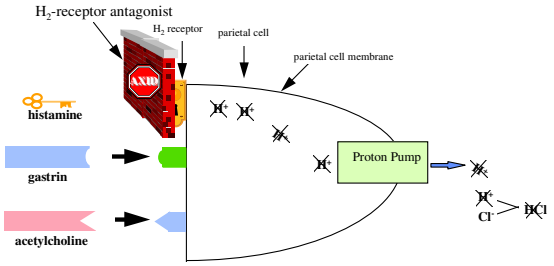
❖ Rarely used as a primary therapeutic agent but for symptomatic relief only

❖ Mostly used in combination

PHYSIOLOGY OF HCl SECRETION



HOW H2-RECEPTOR ANTAGONISTS WORK



H2 Receptor Antagonists

Cimetidine Famotidine

Ranitidine

- Structures share homology with histamine
- Different potency but all significantly inhibit basal and stimulated acid secretion
- Similar ulcer healing rates
- Often used for active ulcers (4 - 6 wks) in combination with antibitiotics for H.Pylori

Cimetidine- Competitive Inhibition

- 60 - 70% bioavailability (oral)
- not affected by food
- oral = parenteral
- metabolized in liver
- excreted in urine (48% -oral dose; 75% IV or IM dose); faeces and bile (10%)
- caution with warfarin, phenytoin, theophylline (inhibition of P450)

Cimetidine

- Dose: 300 mg QID
  800 mg for active ulcer- healing
  Rate of 80% in 4 weeks
- AE: gynecomastia (high doses, prolonged)
  Loss of libido; Impotence; Decrease in Sperm count, confusion, elev. Of aminotransferases, creatinine, prolactin

* Rare toxicities: neutropenia, pancytopenia, anemia, thrombocytopenia

Ranitidine

- 5 X more potent
- Less adverse effects
- No significant drug interaction
- No antiandrogenic activity

❖ Cimetidine and ranitidine can bind to hepatic cytochrome P450, famotidine does not

HOW PROTON PUMP INHIBITORS WORK

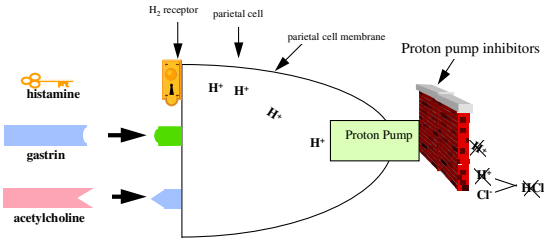


Figure 1-5 Proton Pump Inhibitor Mechanism of Action

Proton Pump Inhibitors

Omeprazole Lanzoprazole

Pantoprazole

- Substituted benzimidazole derivatives that covalently bind and IRREVERSIBLY inhibit H^+,K^+, ATPase
- Most potent acid inhibitors

PPI - Omeprazole, Lanzoprazole

- Potently inhibit all phases of gastric secretion
- Rapid onset of action, max acid inhibitory effect between 2 and 6 hrs and duration lasts for 72 to 96 hrs.
- T1/2: 18 hrs, can take 2 and 5 d for gastric acid secretion to normalize after discontinuance

PPI - Omeprazole, Lanzoprazole

- Given before meals- pumps need to be activated
- SE: 1.Mild to mod hypergastrinemia
  2.Carcinoid tumors in animals, none in Humans
  3.Interfere with absorption of ketoconazole, ampicillin, iron, digoxin

Mucosal Protectors

Sucralfate
Colloidal Bismuth
Prostaglandins
Carbenoxolone

SUCRALFATE

- Complex sucrose salt in which hydroxyl group substituted by AlOH and sulfate
- Insoluble in water, becomes viscous paste that bind to site of active ulceration in ↓ pH
- Toxicity- rare, constipation most reported, also hypophosphatemia

Sucralfate

Moa:

- AlOH- binds to damaged tissues within ulcer bed and provides physicochemical barrier impeding further tissue damage
- Induce trophic effect- enhance prostaglandin synthesis, stimulate mucus and bicarbonate secretion, enhance mucosal defense and repair

Colloidal Bismuth

Potential mechanisms

- Ulcer coating
- Prevention of further pepsin/HCl induced damage
- Binding of pepsin
- Stimulation of prostaglandins, bicarbonate, and mucous secretion
- chelates with protein and granulation tissue

Colloidal Bismuth

- Healing rate comparable with H2 receptor antagonist
- Produce darkening of stools

Prostaglandin Analogues- Misoprostol

- Clinical use- prevention of NSAID-induced mucosal injury(only drug approved by FDA)
- Rapidly absorbed after oral dose
- Therapeutic effect is by enhancement of mucosal defense and repair

❖Enhance mucous bicarbonate secretion

❖Stimulate mucosal blood flow

❖Decrease mucosal cell turnover

Prostaglandin Analogues- Misoprostol

- AE: diarrhea (10 - 30%)

  Uterine bleeding and contraction

  (Contraindicated in pregnancy)

Dose: 200ug four times a day

Carbenoxolone

- Enhances synthesis of gastric mucus
- Decrease pepsin secretion
- Increase life of mucosal cells and diminishes mucosal exfoliation
- AE: sodium retention

  Hypertension

  hypokalemia

Miscellaneous

1. Anticholinergic- designed to inhibit activation of muscarinic receptors in parietal cells

- PIRENZEPINE - selective M1 receptor antagonist

  > Synergistic with cimetidine

  Cimetidine alone-- 60-70%

  Pirenzepine alone - 58%

  C + P --- 89%

  > Prolongs action of antacids

Miscellaneous

2.Tricyclic antidepressants

> Toxicity precludes utility

H. Pylori Eradication Therapy

Treatment	Efficacy
H2-blockers alone	No effect
Omeprazole alone	No effect
Bismuth+amoxycillin	44%
Bismuth+metronidazole	55%
Omeprazole+amoxycillin	58%
Bismuth+metronidazole+amoxycillin	73%
Bismuth+metronidazole+tetracycline	94%

Regimen-1 for H. Pylori Triple Therapy

Bismuth subsalicylate – 30ml QID

+

Metronidazole – 250mg QID

+

Tetracycline 500mg QID

Or

Amoxycillin 500mg QID

Regimen-2 for H. Pylori Triple Therapy

- Lansoprazole – 30mg BD

Or

- Omeprazole 20 BD

+

- Clarithromycin 500mg BD

+

- Amoxycillin 1g BD

Or

- Metronidazole 400mg BD

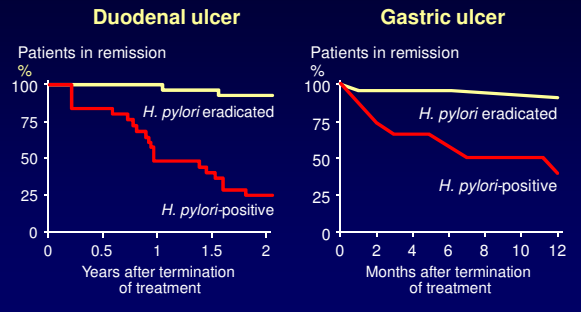
Regimen-3 for H. Pylori Triple Therapy

- Ranitidine - 300mg BD
- +
- Tetracycline - 500mg QID
- +
- Clarithromycin - 500mg BD
- Or
- Metronidazole - 400mg BD

Regimen-4 for H. Pylori Quadruple Therapy

- Omeprazole/Lansoprazole
- +
- Metronidazole
- +
- Tetracycline
- +
- Bismuth subsalicylate

Eradication of *H. pylori* results in long-term remission of peptic ulcer disease



Miehlke et al 1995, © by Karger, Basel 1995; Axon et al 1997

Eradicating *H. pylori* effectively reduces complications

Complication	*H.pylori* Present (% patients)	Absent (% patients)
Recurrent ulcer	62.5	2.4 (p<0.001)
Recurrent bleeding	37.5	0 (p<0.001)

Labenz & Börsch 1994

Gastroesophageal Reflux Disease (GERD)

- Non-pharmacological interventions:
- Elimination of agents that acid production:
  - coffee
  - NSAID's (causes ulceration)
  - Delayed gastric emptying (narcotics, fatty foods)
  - ⇦lower oesophageal sphincter pressure (cigarettes, alcohol & certain drugs)

Drugs that decrease lower oesophageal sphincter pressure

- Anticholinergic drugs
- Antispasmodic drugs
- Anti-histamines & antiemetics
- TAD's
- Phenothiazine neuroleptics
- Nitrates and Ca-channel blockers

Useful drugs in treating GERD

Drug	MOA	Dose
Antacids	Neutralize acid	30ml qid
Alginic's	Protective barries	10ml qid
Metoclopramide	Prokinetic	10mg tid
H2-blockers	Reduces acid production	
Omeprazole	Proton pump inhibitor	20 daily