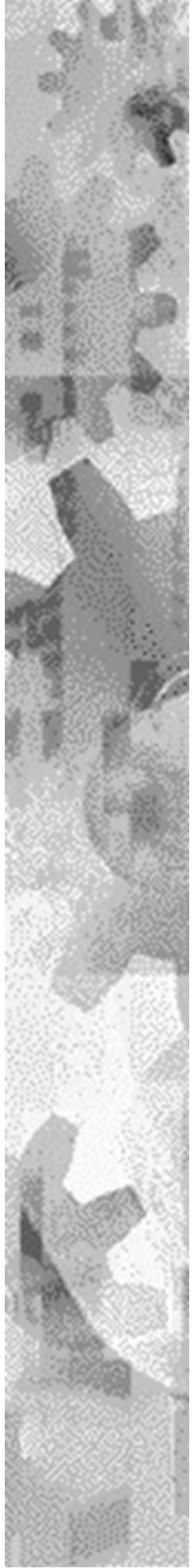


PEPTIC ULCER DISEASE

Ethiopathogenesis of Peptic Ulcers

Helicobacter pylori
NSAIDs

Gastrinoma
Crohn disease
Drugs

H.PYLORI-RELATED ULCERS:

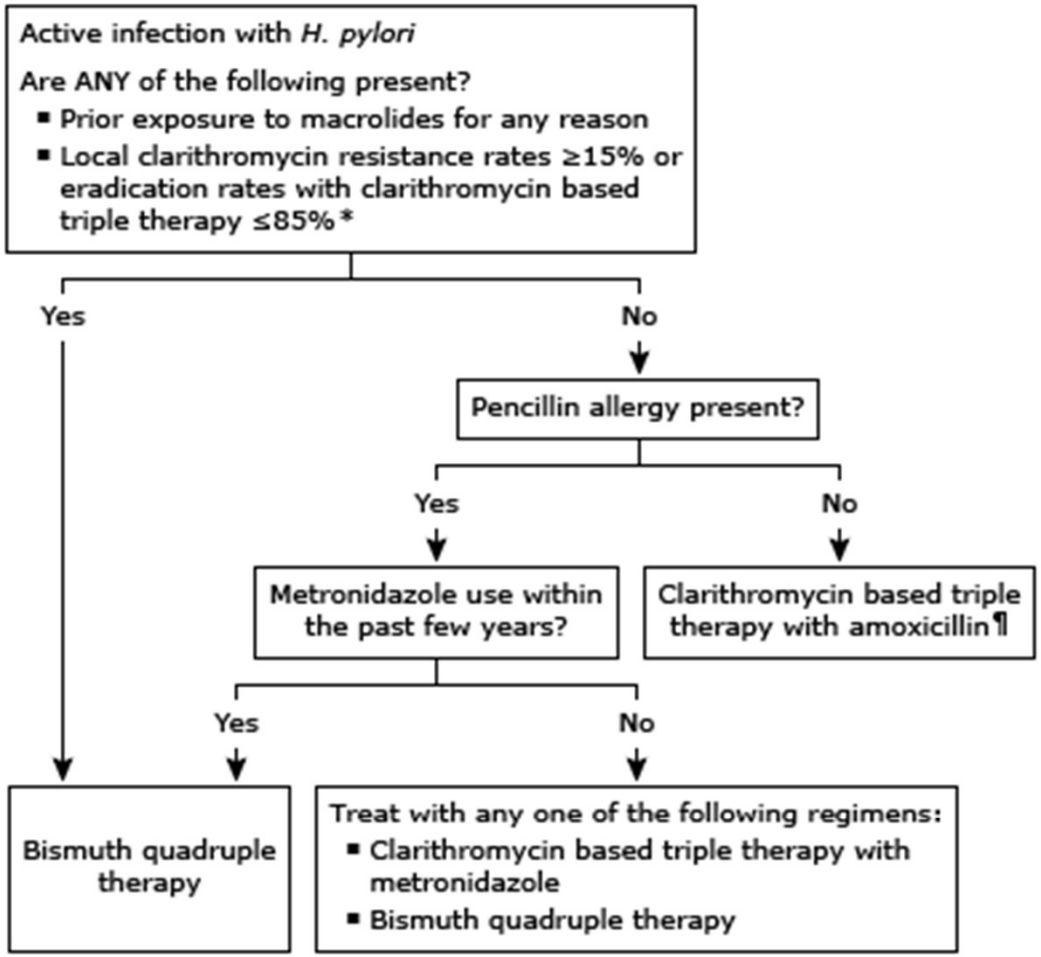
PPI + antimicrobial agent

Single agent?/combined therapy?

2 (3) ANTIBIOTICS – 10-14 DAYS

ANTIBIOTICS ???

Initial approach to antibiotic treatment for *Helicobacter pylori* infection



- Bismuth quadruple therapy consists of bismuth, metronidazole, tetracycline, and a PPI.
- Clarithromycin based triple therapy with amoxicillin consists of clarithromycin, amoxicillin, and a PPI.
- Clarithromycin based triple therapy with metronidazole consists of clarithromycin, metronidazole, and a PPI.

Helicobacter pylori Eradication Regimens

Standard therapy (if recommended)

Duration of therapy: 14 days

ERADICATION REGIMEN (I-CHOICE):

PPIAM

PPI + Amoxicillin (1.0g) + Metronidazole (0.5g) /2x

PPIAC

PPI + Amoxicillin (1.0g) + Clarithromycin (0.5g) /2x

Helicobacter pylori Eradication Regimens

Refractory infection?

Options?

Resistance of *H.pylori* to antibiotics:

PPIAM = PPI + Amoxicillin (1.0g) + Metronidazole (0.5g) /2x

QUADRUPLE THERAPY

PPI + Tetracycline (0.5g) **+** Metronidazole(0.5g) **+** bismuth(0.262) 4x/24h

PPI + Amoxicillin (1.0g) 2x **+** Metronidazole(0.5g) **+** Tetracycline (0.5g) 4x/24h

PPI + Amoxicillin (1.0g) 2x **+** Metronidazole(0.5g) **+** bismuth(0.262) 4x/24h

Helicobacter pylori Eradication Regimens

Sequential treatment

Duration – 10 days

Days 1- 5 – PPI (BID)+ Amoxicillin (1.0g)/2x

Days 6-10 - PPI (BID)+ Clarithromycin(0.5g) + Tinidazole (0.5g)/2x

First-line therapies for *H. pylori* infection

Regimen	Drugs (doses)	Dosing frequency	Duration (days)
Clarithromycin triple‡	PPI (standard* or double dose)	Twice daily	14
	Clarithromycin (500 mg)	Twice daily	
	Amoxicillin (1 gram) **or** Metronidazole (500 mg)	Twice daily (amoxicillin) Three times daily (metronidazole)	
Bismuth quadruple	PPI (standard dose*)	Twice daily	10 to 14Δ
	Bismuth subcitrate (120 to 300 mg [not available in US] or 420 mg [available in North America and elsewhere as part of Pylera combination pill])[1] **or** Bismuth subsalicylate (300 or 524 mg)[1]	Four times daily	
	Tetracycline (500 mg)	Four times daily	
	Metronidazole (250 to 500 mg)	Four times daily (250 mg)	
		Three to four times daily (500 mg)	
Clarithromycin-based concomitant‡	PPI (standard dose*)	Twice daily	10 to 14
	Clarithromycin (500 mg)	Twice daily	
	Amoxicillin (1 gram)	Twice daily	
	Metronidazole or tinidazole (500 mg)	Twice daily	
Clarithromycin-based sequential§‡	PPI (standard dose*) plus amoxicillin (1 gram) for 5 days followed by:	Twice daily	10 (total)
	PPI, clarithromycin (500 mg) plus either metronidazole or tinidazole (500 mg) for an additional 5 days	Twice daily	
Clarithromycin-based hybrid¥‡	PPI (standard dose*) plus amoxicillin (1 gram) for 7 days followed by:	Twice daily	14 (total)
	PPI, amoxicillin, clarithromycin (500 mg), plus either metronidazole or tinidazole (500 mg) for an additional 7 days	Twice daily	

Salvage therapies for *H. pylori* infection

Regimen	Drugs (doses)*	Dosing frequency	Duration (days)
Bismuth quadruple	PPI (standard dose¶)	Twice daily	14
	Bismuth subcitrate (120 to 300 mg [not available in US] or 420 mg [available in North America and elsewhere as part of Pylera combination pill])[1] **or** Bismuth subsalicylate (300 or 524 mg)[1]	Four times daily	
	Tetracycline (500 mg)	Four times daily	
	Metronidazole (250 to 500 mg)	Three to four times daily	
Levofloxacin triple	PPI (standard dose¶)	Twice daily	14
	Levofloxacin (500 mg)	Once daily	
	Amoxicillin (1 gram)	Twice daily	
Concomitant	PPI (standard dose¶)	Twice daily	10 to 14
	Clarithromycin (500 mg)	Twice daily	
	Amoxicillin (1 gram)	Twice daily	
	Metronidazole or tinidazole (500 mg)	Two or three times daily	
Rifabutin triple◇	PPI (standard dose¶)	Twice daily	10
	Rifabutin (300 mg)	Once daily	
	Amoxicillin (1 gram)	Twice daily	
High-dose dual	PPI (standard to double dose¶)	Three to four times daily	14
	Amoxicillin (1 gram three times daily or 750 mg four times daily)	Three to four times daily	

Choice of eradication regimen is influenced by:

*efficacy

*patient's tolerance - allergies (penicillin)

*the use of antibiotics in previous therapies

*existing antibiotic resistance

*cost of drugs

H.PYLORI-RELATED ULCERS:

2 (3) ANTIBIOTICS – 10-14 DAYS

+

ANTISECRETORY AGENT (PPI)

Complicated duodenal ulcers – 4-8 weeks

Complicated gastric ulcers – 8-12 weeks

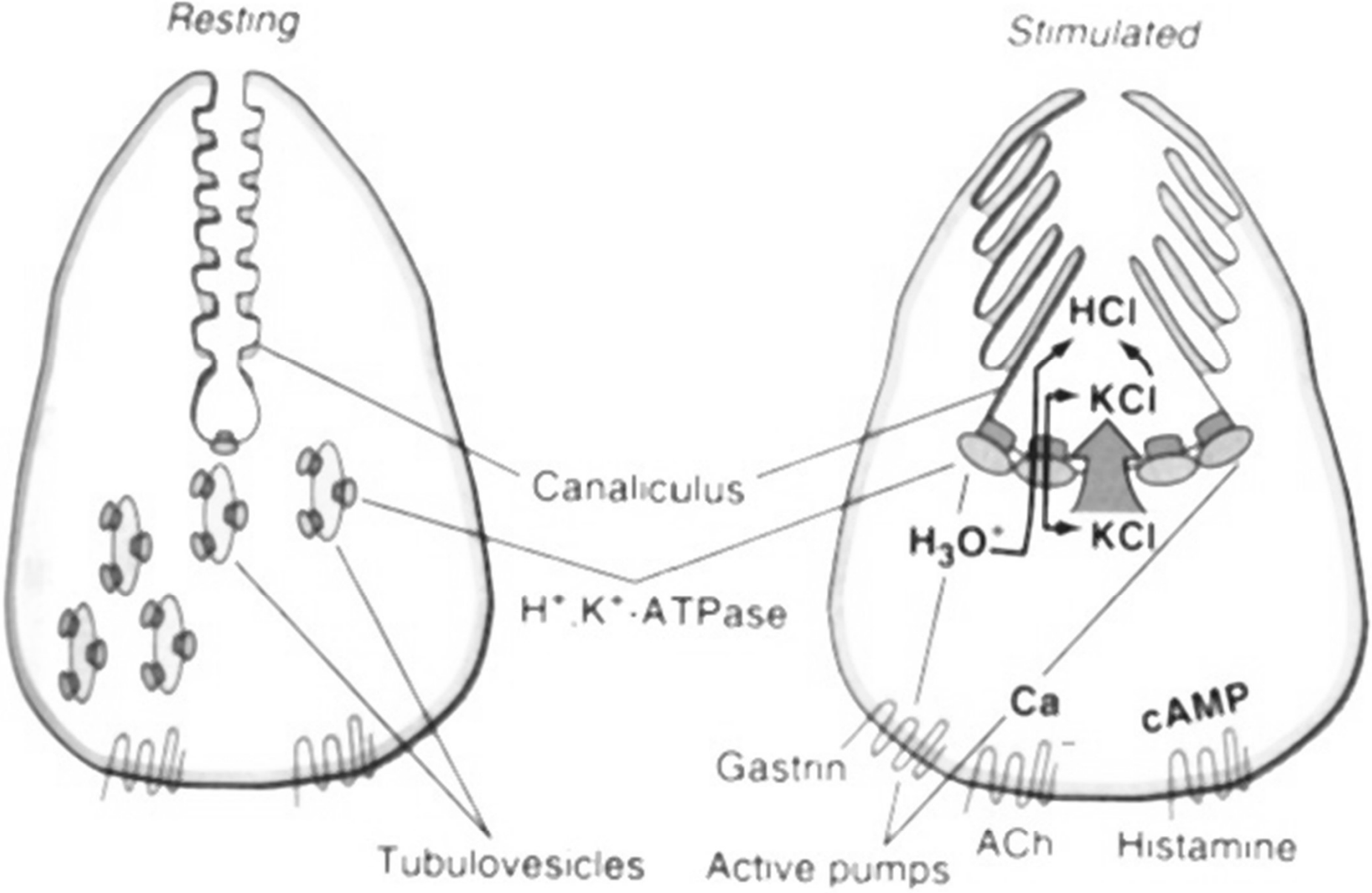
omeprazole
lansoprazole
rabeprazole
pantoprazole
esomeprazole

PPI

Mechanism of action?

Pharmacodynamic effects?

Inhibition of day-time or nocturnal acid secretion?


Resting
Stimulated
HCl
KCl
KCl
H_3O^+
Canaliculus
H^+,K^+-ATPase
Ca
cAMP
Gastrin
ACh
Histamine
Tubulovesicles
Active pumps

Proton Pump Inhibitors (PPI)

→should be taken **before a meal** (food stimulates proton pumps activation and acid production) – **in the morning before breakfast**

→ co-administration of other acid-suppressing agents may diminish the efficacy of PPI

→ **onset of action** – 60-120 min.,

→ **maximum acid inhibitory effect** – 2-6h,

→**duration of acid inhibitory effect** – 72-96h,

→**time required for new proton pumps synthesis – 18h**

→**after 3-4 days of therapy >95%** of acid production is inhibited

Proton Pump Inhibitors (PPI)

Therapeutic uses

1. peptic ulcers (gastric and duodenal)

2. reflux esophagitis (GERD) – more effective than H_2-antagonists

3. Zollinger-Ellison syndrome - more effective than H_2-antagonists

4. Prophylaxis and therapy of NSAIDs-related ulcers - more effective than H_2-antagonists

Proton Pump Inhibitors (PPI) adverse effects

- inhibition of cytochrome P_{450} – OMEPRAZOLE
- GI tract discomfort - nausea, vomiting, constipation or diarrhea, abdominal pain
- hypergastrinemia (5-10% of patients on long-term therapy) – not associated with hyperplasia of the enterochromaffin-like cells in humans
- inhibition of absorption of ketoconazole, ampicillin, iron, digoxin

LOW HCL PRODUCTION:

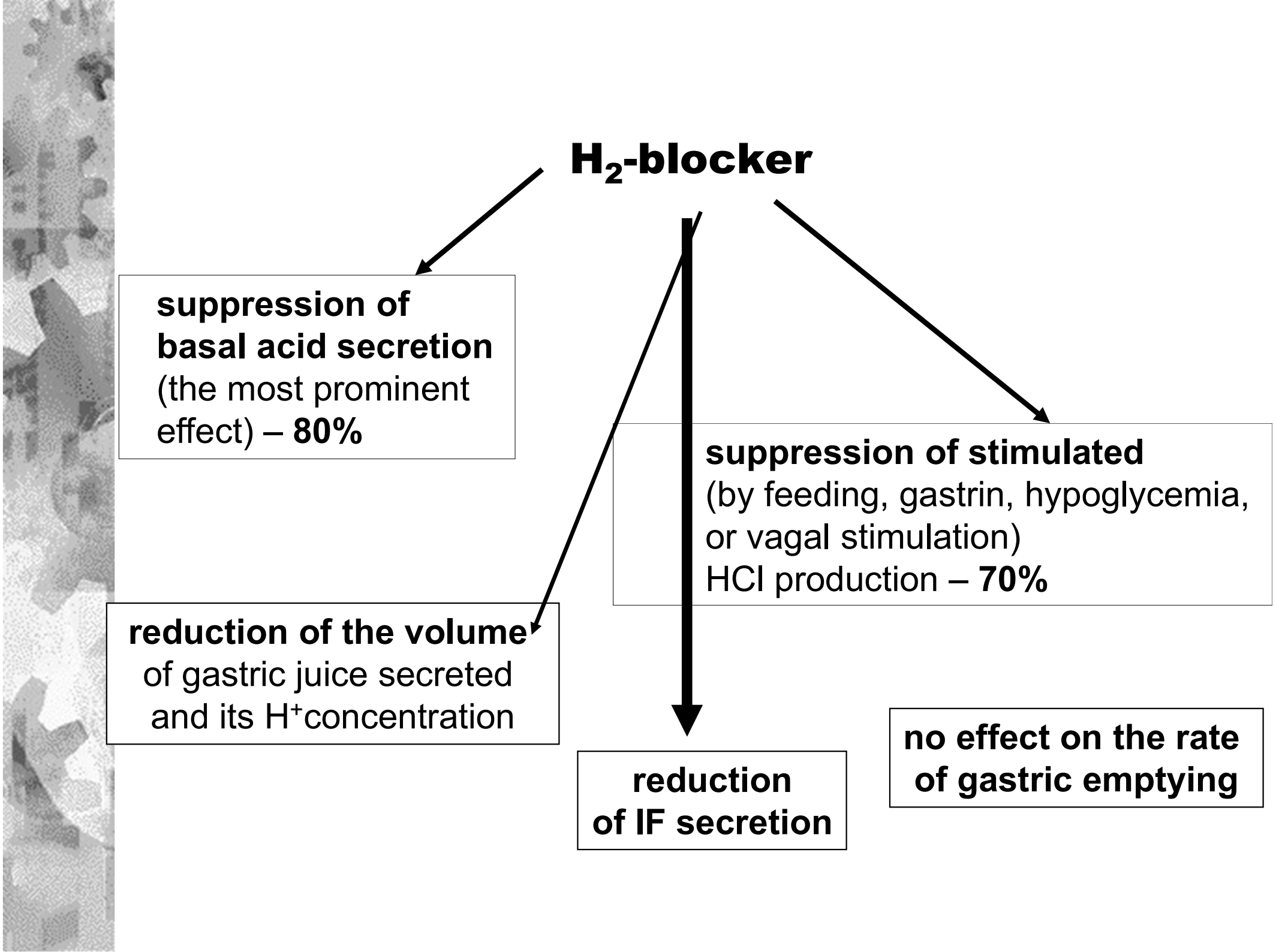
- decreased vitamin B12 absorption
- reduced Fe, Ca absorption – patients with risk factors for osteoporosis – bone density monitoring and Ca supplementation
- respiratory and enteric infections – uncertain clinical significance

Famotidine 40mg at bedtime was prescribed in the therapy of duodenal ulcer.

mechanism of action?

pharmacodynamics effects?

nocturnal or day-time acid secretion?


H2-blocker
suppression of basal acid secretion (the most prominent effect) – 80%
suppression of stimulated (by feeding, gastrin, hypoglycemia, or vagal stimulation) HCl production – 70%
reduction of the volume of gastric juice secreted and its H+concentration
reduction of IF secretion
no effect on the rate of gastric emptying

H_2-RECEPTOR ANTAGONISTS

Dose to achieve >50% Acid Inhibition for 10h

~~Ranitidine~~ 2020-04-01 FDA Requests Removal of All Ranitidine Products – contamination with known as N-Nitrosodimethylamine (NDMA); NDMA concentration increases over time and when stored at higher than room temperatures and may result in consumer exposure to unacceptable levels - ongoing research

Nizatidine – 150mg

Famotidine – 20mg

Cimetidine – 400 – 800mg

OTC formulation – less than 6h

Discontinuation of therapy with H_2-antagonists

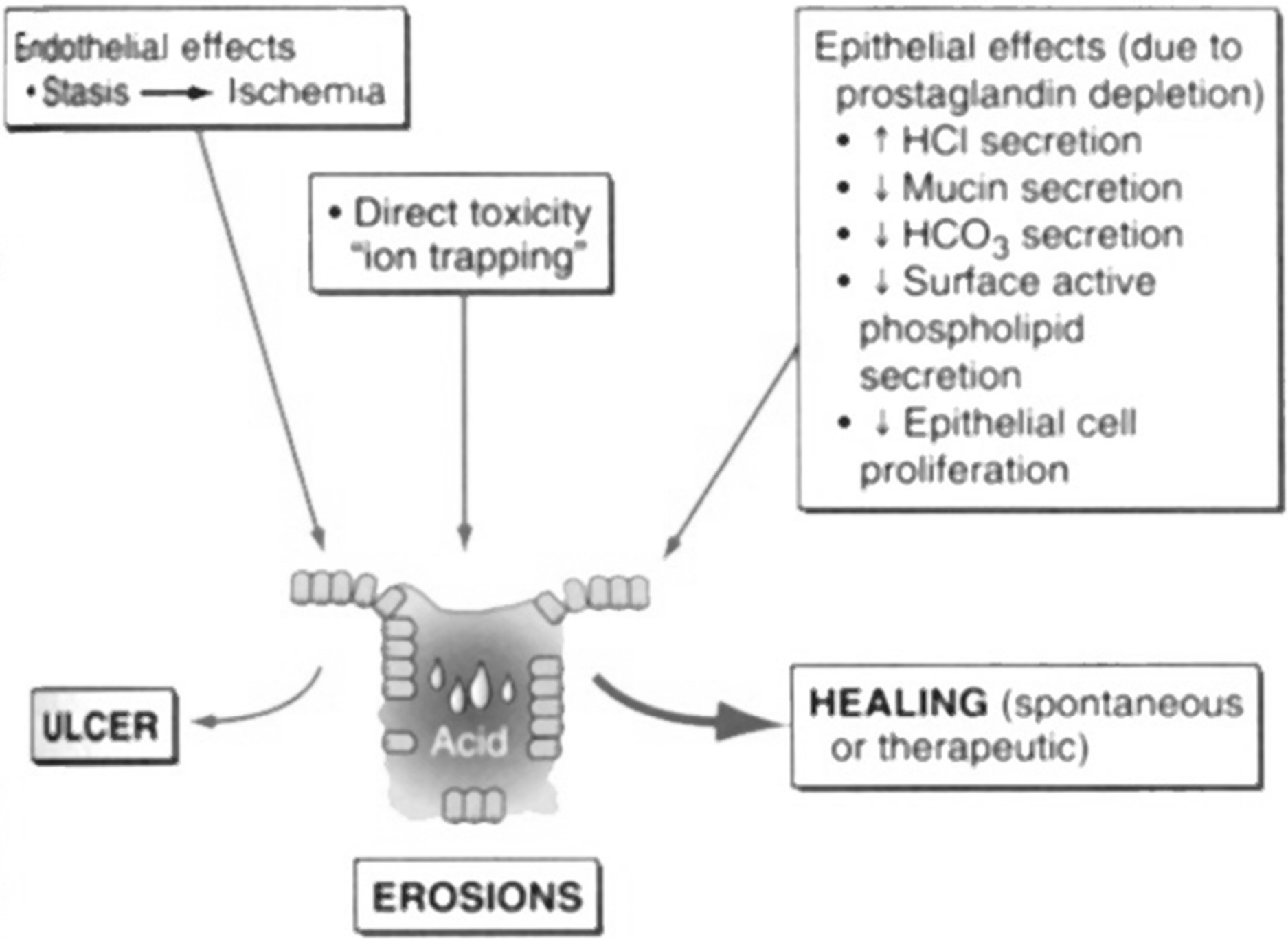
$\rightarrow$ rapid increase in HCl secretion for a few days – rebound syndrome (dangerous in the first few days of therapy)

Duration of therapy

symptomatic improvement does not correlate with healing (the pain relieve may precede healing of the ulcers)

H2-blockers = rebound HCl secretion!!!!

	duodenal ulcers	gastric ulcer
PPIs	2/4 weeks	4/6 weeks
H2-blockers	4/6 weeks	6/8 weeks


Endothelial effects
• Stasis → Ischemia
• Direct toxicity "ion trapping"
Epithelial effects (due to prostaglandin depletion)
• ↑ HCl secretion
• ↓ Mucin secretion
• ↓ HCO_3 secretion
• ↓ Surface active phospholipid secretion
• ↓ Epithelial cell proliferation
Acid
ULCER
EROSIONS
HEALING (spontaneous or therapeutic)

NSAID-related PUD prophylaxis

Risk factors for NSAID-induced ulcer

- confirmed prior ulcer
- age>65 years
- multiple or high-dose NSAID
- concomitant use of aspirin
- concomitant use of an anticoagulant, corticosteroid, bisphosphonate, clopidogrel, prasugrel, ticagrelol
- NSAID – COX-1 vs. COX-2

Primary prevention of NSAID-induced ulcers

- avoid unnecessary use of NSAIDs
- use acetaminophen when possible
- use the lowest effective dose of an NSAID
- use COX-2 selective NSAIDs in high-risk patients without cardiovascular disease

PROSTAGLANDIN ANALOGS – MISOPROSTOL

Misoprostol - analog of PGE_1:
inhibits adenylyl cyclase and decrease cAMP level – suppresses acid secretion

exerts cytoprotective effects by:
stimulation of mucin and bicarbonate secretion, and
improvement in mucosal blood flow

Disadvantages of misoprostol:
1. short time of activity - inhibition of acid secretion starts within 30 min, peaks at 60 to 90 min and lasts up to 3h – multiple daily doses
2. Adverse effects
→ diarrhea with or without abdominal pain and cramps (30% of patients)
→ clinical exacerbation in patients with inflammatory bowel disease
→ increase in uterine contractility (contraindicated during pregnancy)

Drugs that may cause gastroduodenal injury:

- NSAIDs
- Corticosteroids
- Iron salts
- Chemotherapeutic agents
- Ethanol
- Warfarin

ANTACIDS

Dose:

multiple-times-a-day regimens

↓

(1 and 3 hours after meals and at bedtime or on „as-needed” basis)

Start of work – 5-15 min.

(liquid formulations-more rapid acid-neutralizing action, tablet formulations should be chewed)

Duration of pain relief – 2h

(1) $Al(OH)_3 + 3HCl \rightleftharpoons Al\,Cl_3 + 3H_2O$

(2) $Mg(OH)_2 + 2HCl \rightleftharpoons Mg\,Cl_2 + 2H_2O$

(3) $Mg\,Cl_2 + Na_2\,CO_3 \rightleftharpoons MgCO_3\,(PPT) + 2NaCl$

(4) $MgCl_2 + 2R—COONa \rightleftharpoons Mg\,(R—COO)_2\,(PPT) + 2NaCl$

$NaHCO_3$ + heart failure =
Fluid retention
Antacids → constipation
Al, Ca
Antacids → diarrhea
Mg
Antacids and HCl secretion =
Rebound HCl secretion

ANTACIDS

Drug interactions

1. decreased bioavailability of: iron, tetracyclines, isoniazid, ethambuthol, benzodiazepines, ranitidine, nitrofurantoin, vitamin A,fluoride, and phosphate

2. alkalinization of the urine affects renal clearance of drugs:

- weak acids – increased elimination of salicylates and phenobarbital

- weak bases - decreased elimination of amphetamine, ephedrine and quinidine

Stress ulceration

Stress ulceration is associated with:

- Burns on over 35% of body surface area
- Neurological trauma
- Sepsis
- Hepatic failure
- Hypotensive states
- Respiratory failure
- Renal failure
- Major surgery

The underlying pathogenic event in the etiology of stress ulceration

is

gastric mucosal ischemia

Stress ulceration occurs in 100% of patients with significant physiological stress

- initial pathological lesions occur within hours
- they may progress over 48h to gastric or duodenal ulcers
- bleeding occurs in 16% of patients with mortality rate 68%
- in patients recovering from their stressful events GI mucosal abnormalities disappear within 4-14 days.

Prophylactic therapy

PPI (iv) –pantoprazole; *nasogastric tube* – omeprazole, lansoprazole

H_2-receptor antagonists *(iv)* +/- antacids (nasogastric tube every hour)

The most effective agent:

PPIs

H.pylori:

2/3 antibiotics + PPI,

Duodenal ulcers:

H2-blockers = PPIs

Gastric ulcers:

PPIs>H2-blockers

ZE-syndrome:

PPIs>H2-blockers

GERD:

PPIs>H2-blockers

NSAIDs-related ulcers:

prophylaxis- misoprostol or PPI,

active ulcer

(1) NSAIDs-discontinued PPIs or H2-blockers,

(2) NSAIDs-continued – PPIs

Stress-related ulcers:

H2-blokers iv, PPIs iv

Cytochrome P450 inhibition:

cimetidine, omeprazole, clarithromycin

DRUG INTERACTIONS:

PPI, H2-blockers, Antacids

↓

↑gastric pH - reduced absorpton digoxin, ketokonazol, iron salts