LEBANESE UNIVERSITY
Faculty of Pharmacy

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DIGIHEALTH

GASTROINTESTINAL PHARMACOLOGY : DRUGS USED TO DECREASE GASTRIC ACIDITY

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DIGIHEALTH project – Blended module

Chapter design

- Please go to the following page to visualize the designed activities of this chapter
  - https://view.genial.ly/62c44e604f372600111f4b8d/interactive-content-antiacid-drugs

- Click each  to read more about each activity

Activities before the class

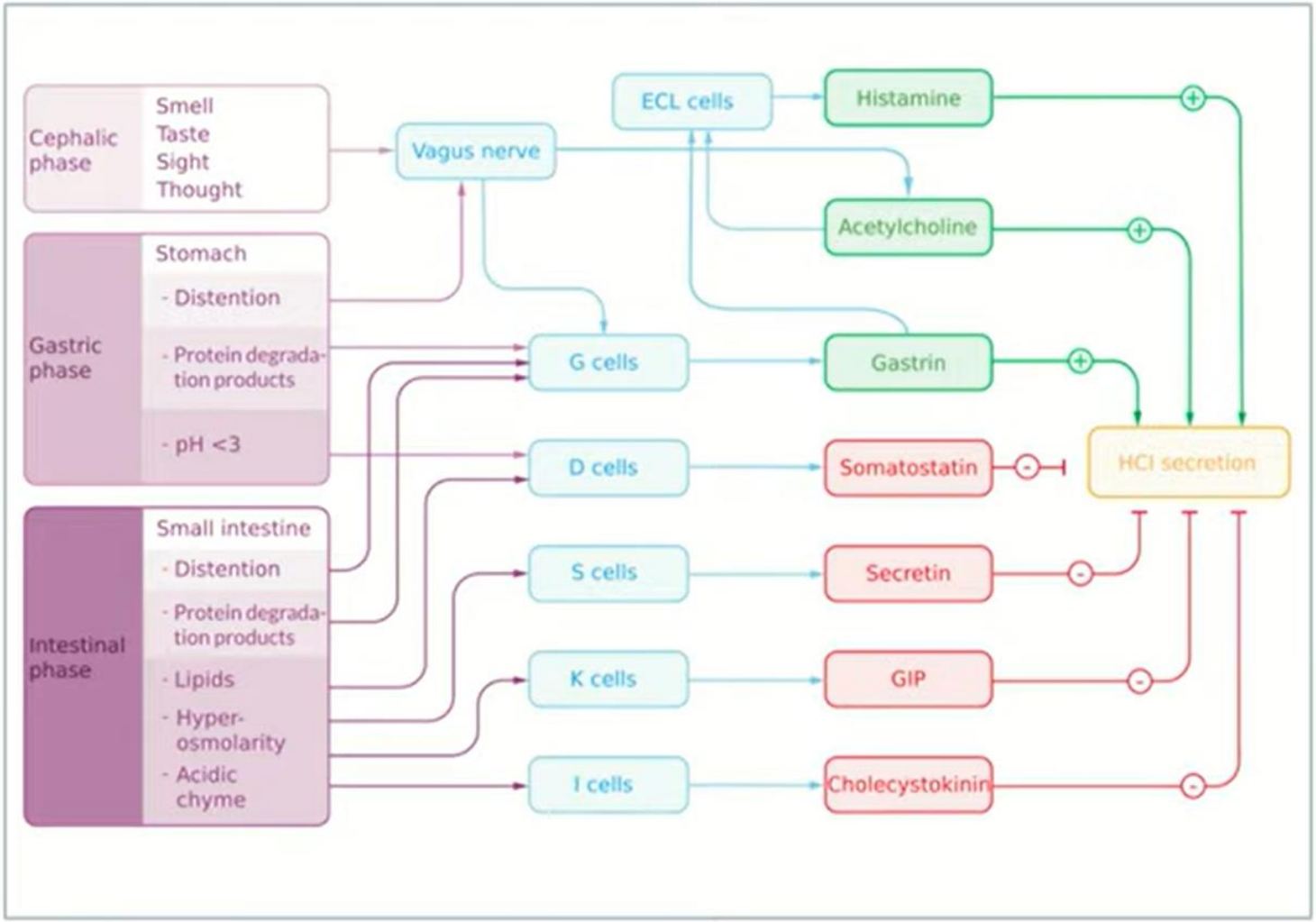
- Before the course
  - Fill the definitions in the glossary
    - https://docs.google.com/document/d/1ZYVIwgAKfTYUZuXg6GvYBuL8gmAITtOOzP0cdrU2vao/edit?usp=sharing
  - View the youtube video on acid secretion physiology
    - https://www.youtube.com/watch?v=XcrnbUwM88M
  - View the tutorial on how to use mindmeister to build mindmaps
    - https://support.mindmeister.com/hc/en-us/articles/360017492920-Getting-Started-with-MindMeister#h_01FHB2NS8A8YEZBCQTF776N2XA

LECTURE

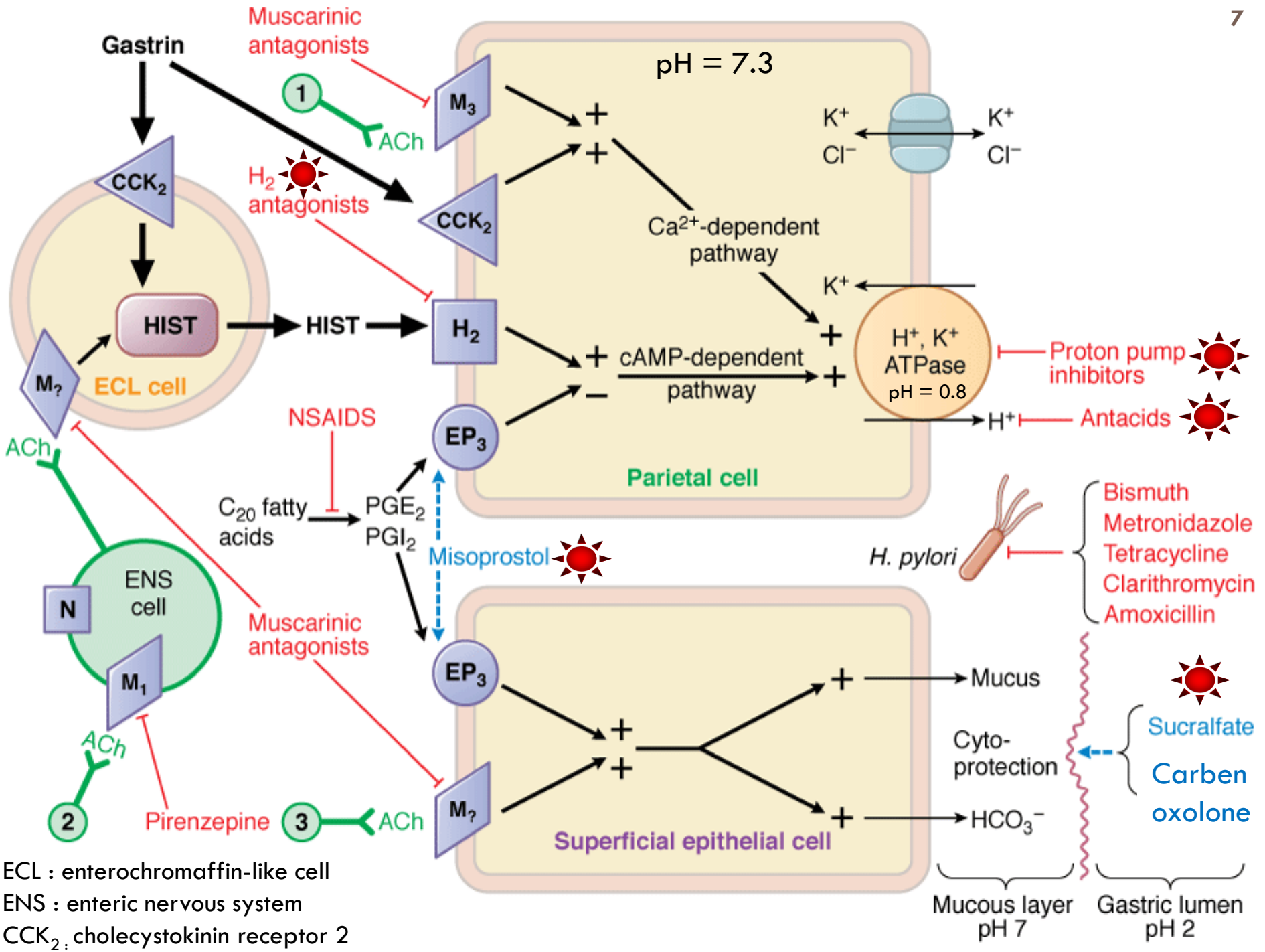
Outline

- Physiology of gastric secretion
- Antacids
- Histamine H_2-receptor antagonists
- Proton pump inhibitors (PPI)
- Sucralfate
- Synthetic prostaglandins

General mechanisms regulating acid secretion



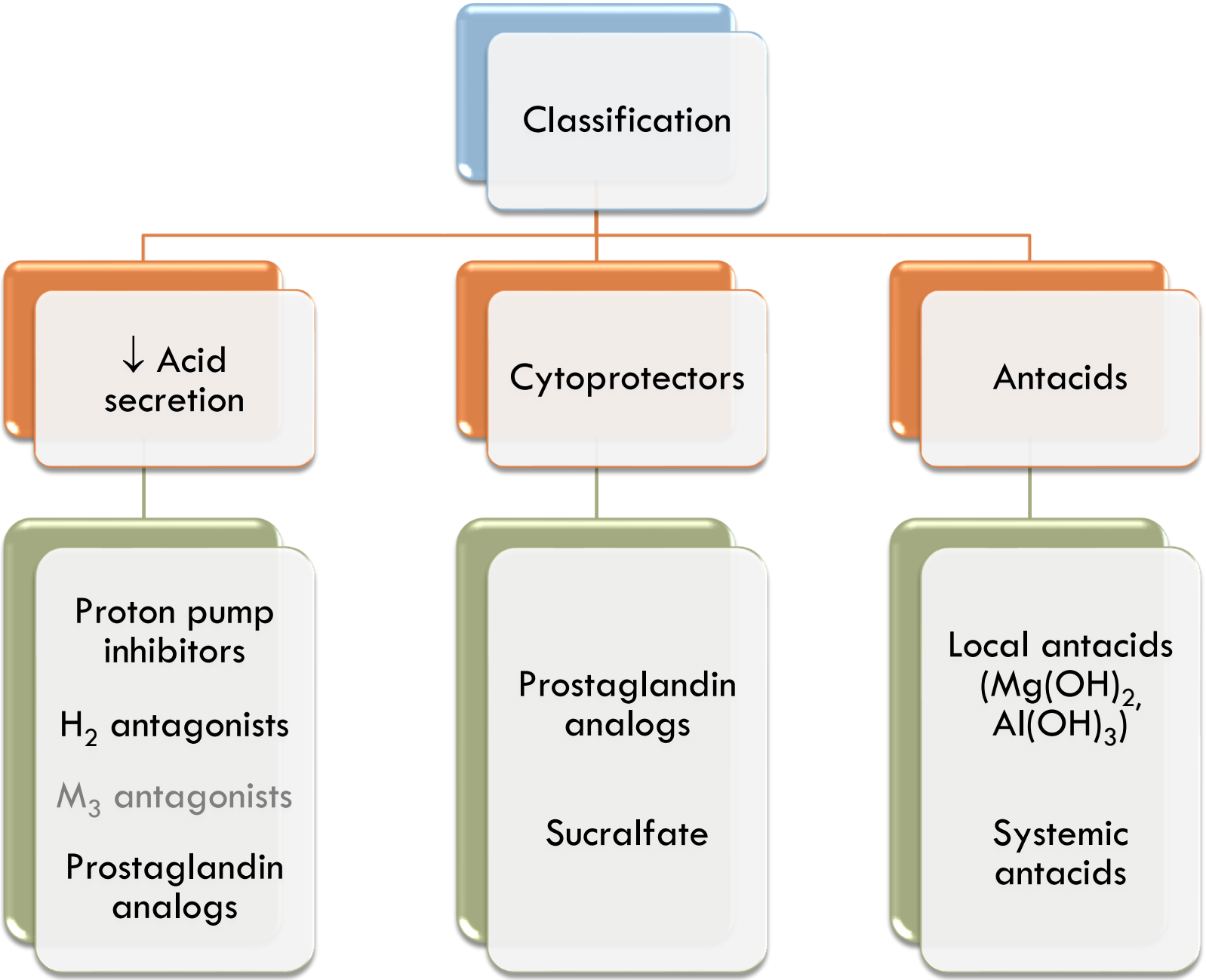
https://www.youtube.com/watch?v=XcrnbUwM88M



ECL : enterochromaffin-like cell

ENS : enteric nervous system

CCK_2 : cholecystokinin receptor 2


Classification
↓ Acid secretion
Cytoprotectors
Antacids
Proton pump inhibitors
H_2 antagonists
M_3 antagonists
Prostaglandin analogs
Prostaglandin analogs
Sucralfate
Local antacids ($Mg(OH)_2$, $Al(OH)_3$)
Systemic antacids

Class adverse effects

Highly clinically significant with PPIs

- Absorption of drugs
  - ↓ absorption of drugs requiring acidity : itraconazole, domperidone, thyroxine, isoniazid, protease inhibitors and **iron** salts
  - PK change in drugs with pH-sensitive release from a dosage form
- Susceptibility to infections
  - ↑ gastric pH → promotes bacterial growth → risk of aspiration pneumonia & *Clostridium difficile* gastroenteritis
- Hypergastrinemia
  - Chronic use → lack of negative feedback on gastrin secretion (PPI > anti-H_2)
  - Predispose to **rebound hypersecretion** of gastric acid upon discontinuation of therapy
  - May promote the growth of GI **tumors**

Antacids

- Non specific mechanism of action :
  - Chemical neutralization of HCl
  - Inactivation of pepsin
  - Binding to bile acids
  - Stimulation of local PG production

- Commonly used OTC for intermittent heartburn, dyspepsia & GERD
  - S**uspension** form → greater neutralizing capacity than powder or tablet dosage forms.
  - **Tablets should be thoroughly chewed for maximum effect**
  - **Short acting (1 - 2 hours)**

- Alteration of rates of dissolution and absorption, bioavailability, and renal elimination of other drugs
  - By altering gastric and urinary pH
  - By binding to the drugs in the GI → should not be given **within 2 hours** of other drugs

Antacids

- Systemic / absorbable antacid : Na HCO_3
  - Reacts rapidly with HCl & rapidly absorbed
  - Na^+ → exacerbates fluid retention in patients with heart failure, hypertension , renal insufficiency
  - HCO_3^- → High doses / renal failure → metabolic alkalosis

- Non-Systemic / non-absorbable antacid : $CaCO_3$ (15-30%)
  - Slower action than $NaHCO_3$
  - Stimulates peristalsis in the oesophagus
  - May be used for calcium supplementation
  - Calcium also may induce rebound acid secretion → more frequent administration

- Bicarbonate & carbonate salts
  - CO_2 release → nausea, gastric distention, flatulence & belching
  - *May induce milk-alkali syndrome* = Metabolic alkalosis, hypercalcemia & renal insufficiency
    - Rare syndrome that occurs after chronic ingestion of large quantities of Ca^{2+} containing dairy products with Na HCO_3 or $CaCO_3$

Antacids : Adverse effects

- Local /Non-systemic antacids = Combination of Mg^{2+} and Al^{3+} hydroxides $Mg(OH)_2 + Al(OH)_3$ (5-10%)
  - Preferred combinations because of balanced effects
  - Mg^{2+} (rapidly reacting) and Al^{3+} (slowly reacting)
  - Mg^{2+} (laxative) and Al^{3+} (constipating)
  - Poorly absorbed $\rightarrow$ sustained antacid effect
  - Mg & Al are absorbed & excreted by the kidneys $\rightarrow$ should not be given to patients with renal insufficiency

Table 2. Features and limitations of different types of antacid salts.

	Salts[a]			
	Calcium	Sodium	Magnesium	Aluminum
Species[b]	Carbonate	Bicarbonate, citrate	Hydroxide, carbonate, oxide, trisilicate	Hydroxide, carbonate, phosphate, glycinate
Category	Non-absorbable	Absorbable	Non-absorbable	Non-absorbable
ANC (mEq/15 mL)[c]	58	17	35	29
Maximum daily dosage limit (mEq)[d]	160	200 (≤60 years old) and 100 (>60 years or older)	50	NA
Limitations	• Constipation and flatulence • Systemic alkalosis and hypercalcemia on long term use • Occasional milk-alkali syndrome in patients taking more than the recommended dose	• Non-serious, stomach/gut irritations that could cause gas or bloating	• Dose-related diarrhea • Flushing • Hypotension • Vasodilation • Hypermagnesemia	• Hypomagnesemia • Hypophosphatemia • Constipation • Anemia
FDA category for antacid use in pregnancy[e]	None	None	None	None
Contraindications				
Renal impairment	No	Yes	Yes	Yes
Hepatic impairment	No	Yes	No	No
Others	• Patients with hypercalcemia, hypercalciuria, nephrocalcinosis, and nephrolithiasis • Patients on a low-phosphate diet	• Patients on a sodium- restricted diet, e.g., those with hypertension or congestive heart failure	• Patients with severe diarrhea • Patients with neuromuscular disease such as myasthenia gravis	• Patients with constipation

[a]A salt is a chemical compound consisting of an ionic assembly of positively charged cations and negatively charged anions. The specific salts of active pharmaceutical ingredients are often formed to achieve desirable formulation properties.[96]
[b]Chemical species are specific forms of a particular element, such as an atom, molecule, ion, or radical. For example, chloride is an ionic species.[97]
[c]The potency of an antacid is generally expressed in terms of its ANC, which is defined as the number of mEq of 1 N HCl that are brought to pH 3.5 in 15 minutes (or 60 minutes in some tests) by a unit dose of the antacid preparation.[98]
[d]As per the federal register of the US FDA[99]
[e]Antacids carry a FDA pregnancy category of None (N), meaning these drugs have not been classified by the FDA.[65]
mEq, milliequivalents; ANC, acid-neutralizing capacity.

H_2 receptor antagonists – anti-H_2

- Agents

	Relative potency
Cimetidine	1
Ranitidine ZANTAC	4-10
Nizatidine AXID	4-10
Famotidine FAMODAR	20-50

FDA Safety Communication

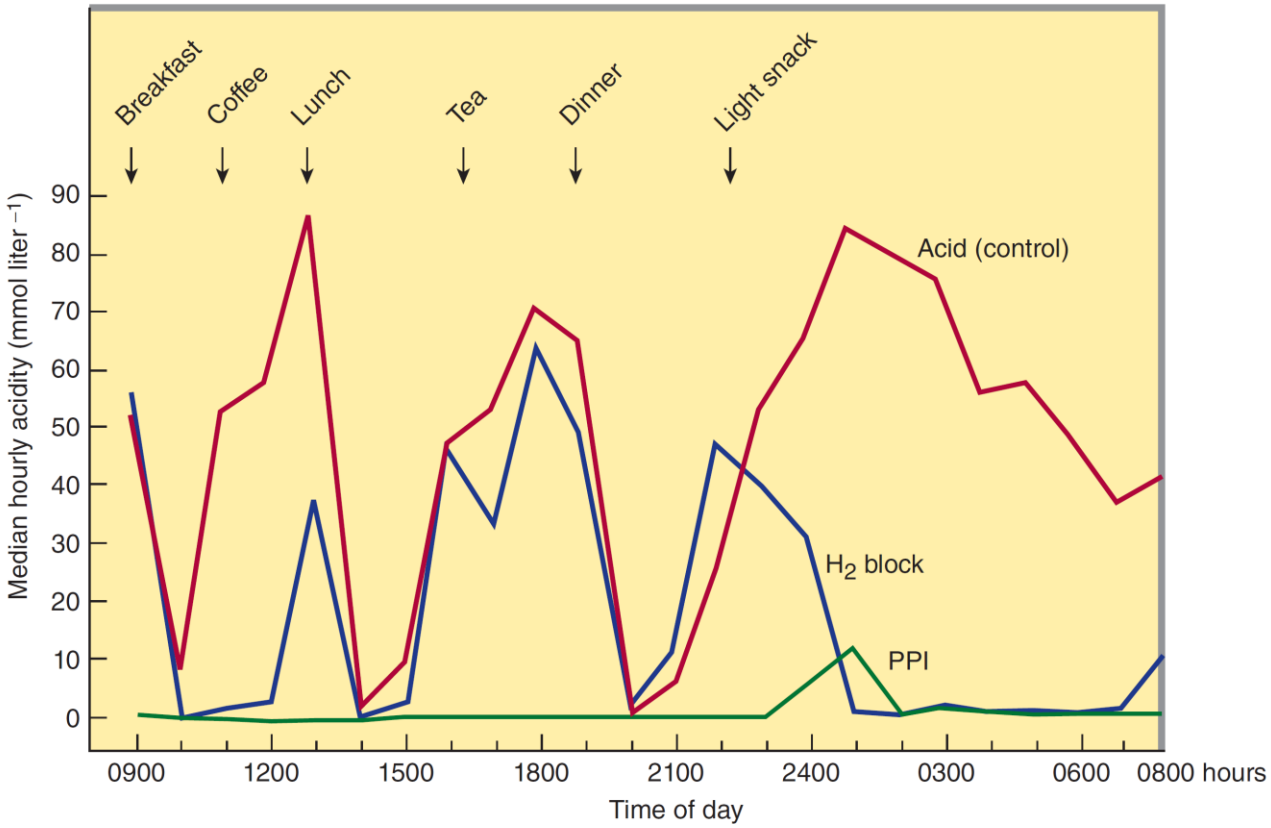
On April 1, 2020, FDA requests removal of all ranitidine products (Zantac) from the market

For more information, see FDA Drug Safety Communication (link https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market)

Health care professionals should stop prescribing and dispensing ranitidine to patients

- **Highly selective & Competitive** antagonists of the H_2 receptor on the basolateral membrane of parietal cells
- Efficacy
  - Inhibition of 60-70% of total 24-hour gastric acid secretion
  - Major efficacy in suppressing **nocturnal acid secretion** → administration in the **evening** at bedtime
  - Modest activity in suppressing meal stimulated acid secretion
- Ranitidine and nizatidine also may **stimulate GI motility**

PPI versus H_2 antagonists



Twenty-four-hour median intragastric acidity **pretreatment** (red) and after 1 month of treatment with either **ranitidine**, 150 mg twice daily (blue, H2 block), or **omeprazole**, 20 mg once daily (green, PPI). Note that H2-receptor antagonists have a marked effect on nocturnal acid secretion but only a modest effect on meal-stimulated secretion. Proton-pump inhibitors (PPIs) markedly suppress meal-stimulated and nocturnal acid secretion.

H_2 receptor antagonists – anti-H_2

- PK
  - Oral bioavailability ~ 50% (may be **enhanced** by food)
  - Variability in duration of action
    - Cimetidine (4-5h) < ranitidine (6-8h) < Famotidine=nizatidine (10-12h)
  - Mild hepatic metabolism
  - Renal clearance of drug + metabolites → dose should be ↓ in renal impairment

- Therapeutic uses
  - Uncomplicated GERD (OTC 60 min before meals / BID if frequent)
  - Treatment of gastric and duodenal ulcers (less effective than PPI)
  - Prevention of stress ulcers in critically ill patients

- **Tolerance** to the acid-suppressing effects of anti-H_2 → diminished therapeutic effect with continued drug administration
  - Mechanism : secondary hypergastrinemia → stimulate histamine release from ECL cells

anti-H_2 : adverse effects + drug interactions

- Adverse effects
  - Well tolerated : minor adverse effects → **headache**, diarrhea, drowsiness, fatigue, muscular pain, and constipation
  - IV or in elderly or renal/hepatic dysfunction→ confusion, delirium, hallucinations, slurred speech, and headaches
  - Rapid IV → bradycardia (slow infusions over 30 minutes)
  - Cimetidine : anti-androgenic effects
    - Long term treatment with high doses
    - Decreases testosterone binding to the androgen receptor and inhibits estradiol metabolism
    - Women → galactorrhea
    - Men → gynecomastia, reduced sperm count, and impotence

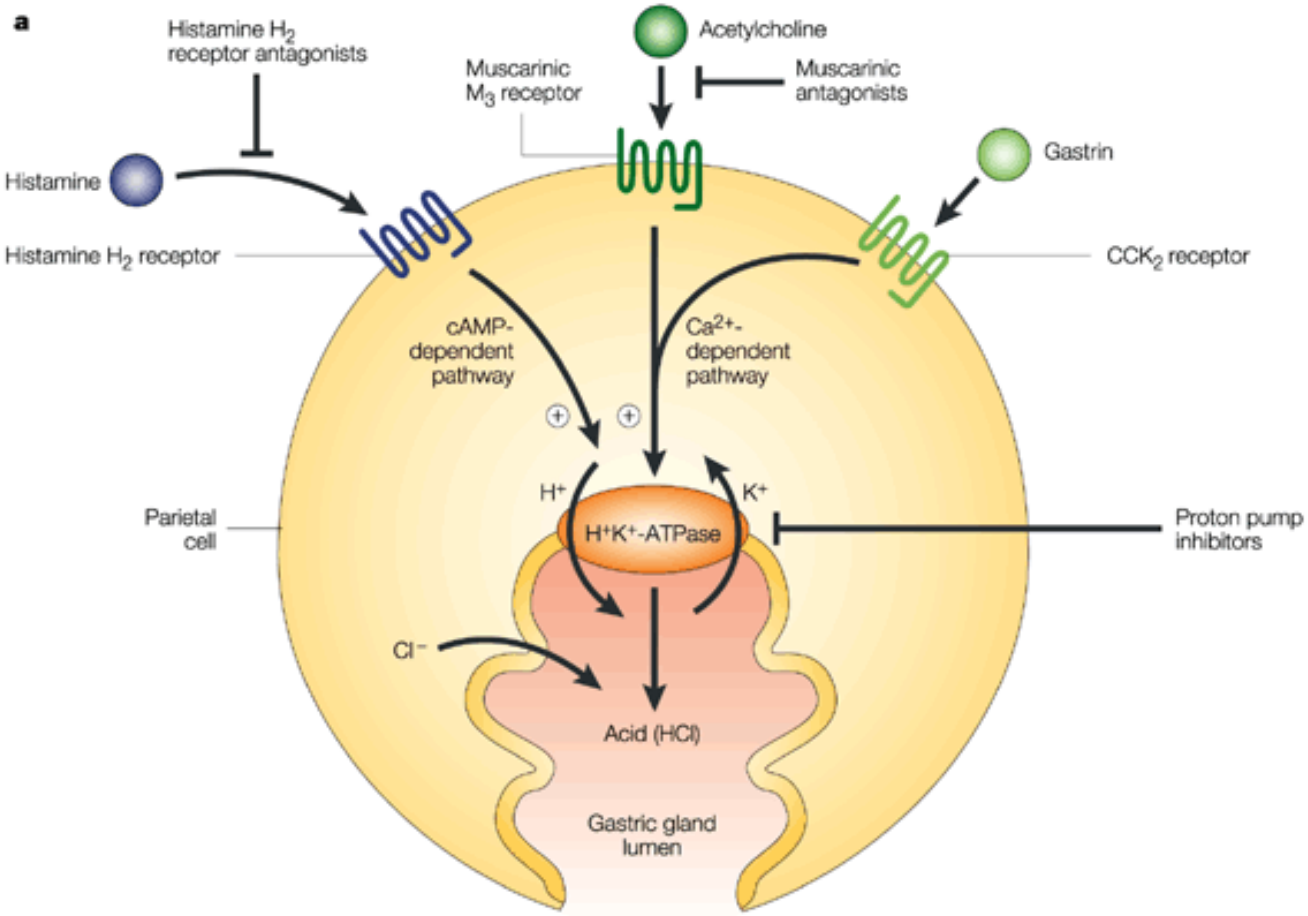
- Drug interactions
  - Cimetidine → potent CYP inhibitor (e.g., CYP1A2, CYP2C9, and CYP2D6)
  - Cimetidine >> Ranitidine >>> Famotidine & nizatidine

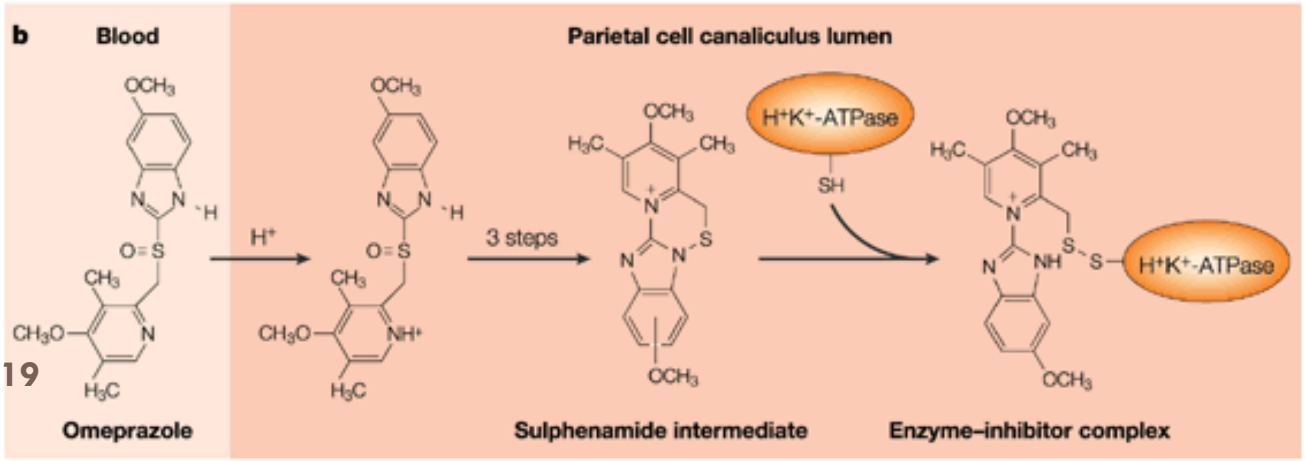
Proton pump inhibitors PPI

- Agents
  - Omeprazole **GASTRIMUT**
  - Esomeprazole **NEXIUM** = S-isomer of omeprazole
  - Lansoprazole **LANZOR**
  - Dexlansoprazole **DEXILANT**= R-enantiomer of lansoprazole
  - Rabeprazole **PARIET**
  - Pantoprazole **GASTROPAN**

- The **most effective suppressors of gastric acid secretion** → ↓ daily production of acid (basal and stimulated) by > 90%

- All proton pump inhibitors
  - Have similar pharmacological properties
  - Have equivalent efficacy at comparable doses
  - Induce prolonged (24 hours) suppression of acid secretion, despite the much shorter plasma half-lives (0.5-2 hours)



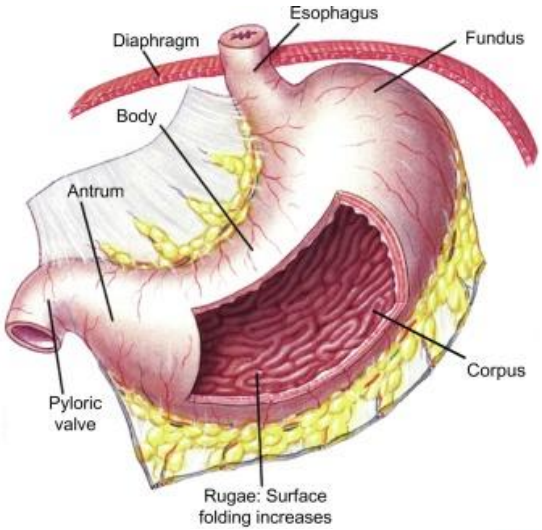


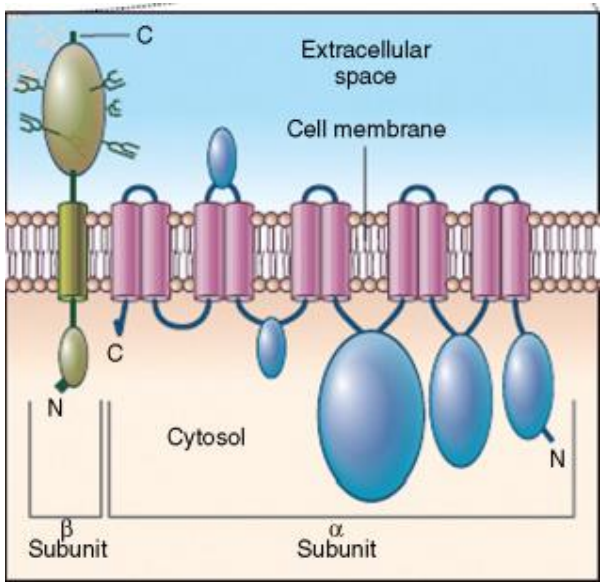
1. **Prodrugs** diffuse into the parietal cells of the stomach and accumulate in the acidic secretory canaliculi

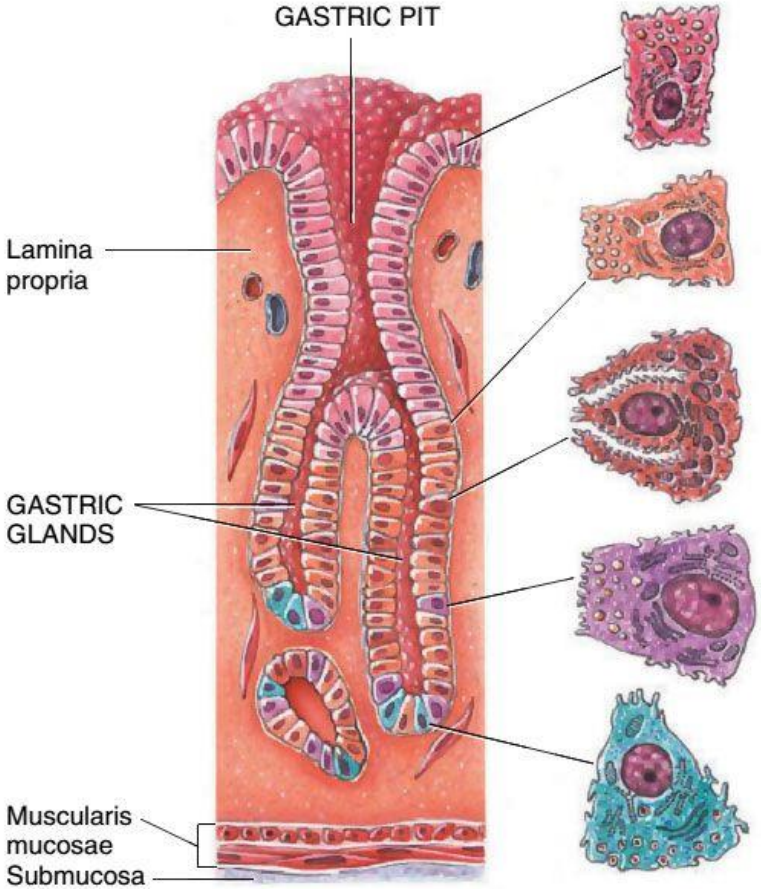
2. They are **protonated** to a tetracyclic **sulfenamide** compound which cannot diffuse back across the canalicular membrane

3. Bind covalently with SH – PP & **irreversibly** inhibit the proton pump

4. Acid secretion resumes after new PP are synthesized







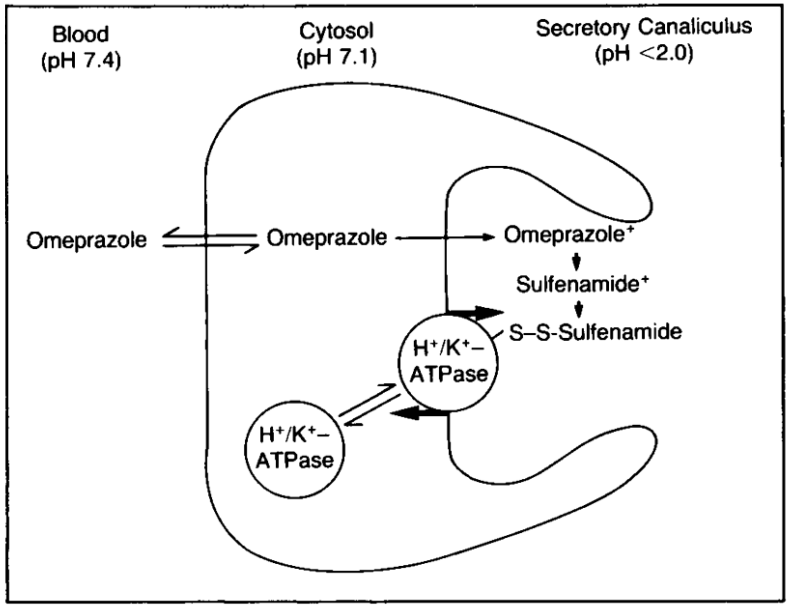
SURFACE MUCOUS CELL (secretes mucus)

MUCOUS NECK CELL (secretes mucus)

PARIETAL CELL (secretes hydrochloric acid and intrinsic factor)

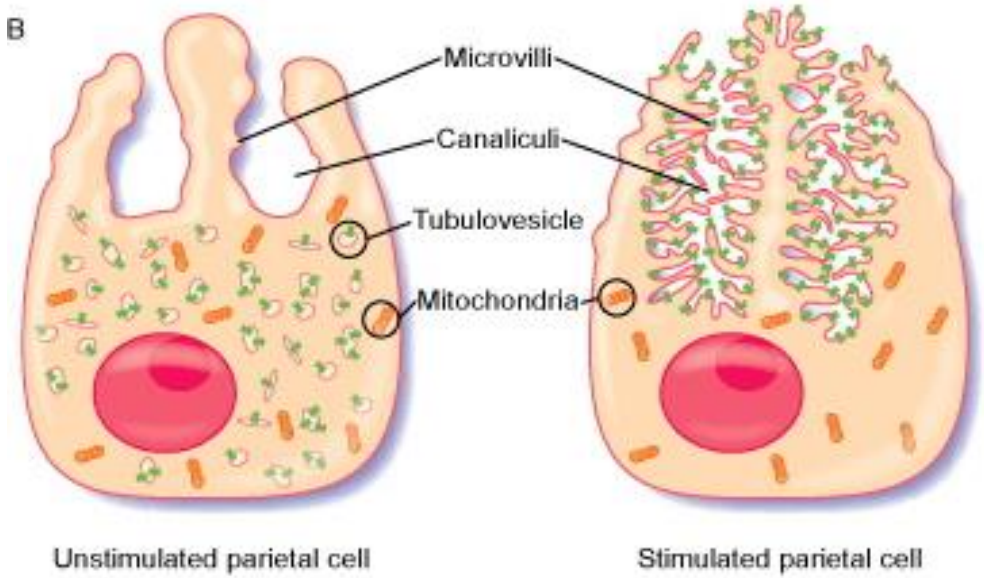
CHIEF CELL (secretes pepsinogen and gastric lipase)

G CELL (secretes the hormone gastrin)

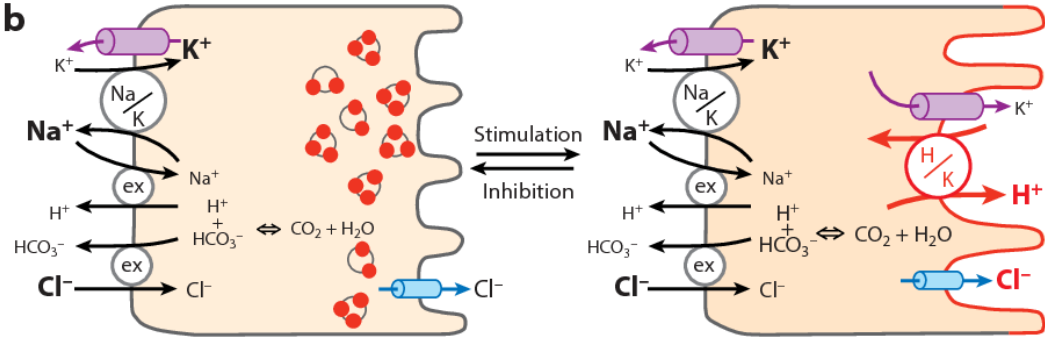


PPIs : PK/PD

- PPIs only inhibit **active** pumps
  - In a fasting state, only 10% of pumps are actively secreting acid and susceptible to inhibition → **administer PPIs 0.5 ~ 1 hour before a meal,** so that peak serum concentrations coincide with maximal pump activity
  - Not all pumps are inactivated with first dose → Full acid inhibiting potential is seen after 3-4 days of daily medication (similarly, 3-4 days are required for acid secretion to return to normal when drug is stopped)



- Bioavailability ↓ 50% by food → PPIs **must be administered** in the **fasting** state
  - Larger amplitude movements crush the protective coatings → expose the prodrugs to the stomach acid → activation → irreversible binding to gastric content → ↓ absorption
  - Food stimulates acid secretion

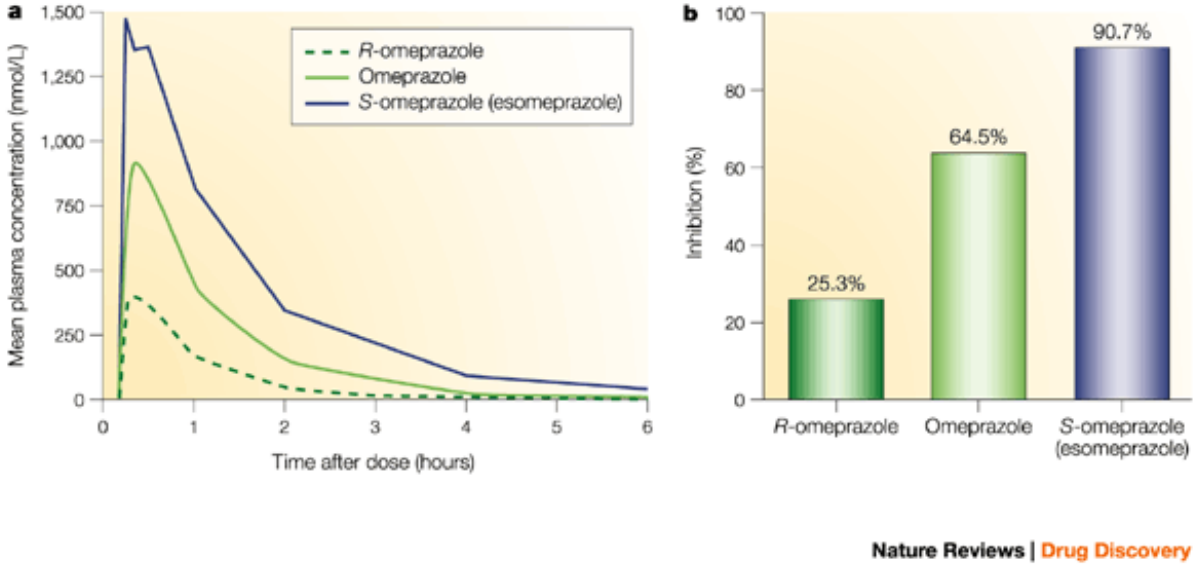


PPIs : PK

- Absorption
  - Acid labile **prodrugs** → gastro-resistant formulations (**enteric-coated** or combined with sodium bicarbonate)
  - Enteric coat → dissolution at alkaline pH → absorption
  - IV formulations, oral suspensions, powders are available
- Metabolism
  - **Extensive** metabolism particularly **CYP2C19** and **CYP3A4**
- Excretion
  - Renal excretion of metabolites → Chronic renal failure does not lead to drug accumulation

Proton pump inhibitor (PPI)	Cytochrome P450 metabolism	Interaction potential*
Omeprazole	Major: CYP2C19 Minor: CYP3A4	High
Esomeprazole	Major: CYP2C19 Minor: CYP3A4	Moderate
Pantoprazole	Major: CYP2C19 Minor: CYP3A4	Low
Lansoprazole	CYP2C19 CYP3A4	Moderate
Rabeprazole	Major: Non-enzymatic Minor: CYP2C19 Minor: CYP3A4	Low

PPIs : PK



a | Drug plasma concentrations and **b** | inhibition of pentagastrin-stimulated gastric acid secretion in healthy subjects (n = 4) after oral administration of 15 mg of *R*-omeprazole, omeprazole and esomeprazole at time 0

- CYP2C19 pharmacogenetics → variation in level of gastric acid suppression (especially omeprazole)
- Omeprazole & esomeprazole are both metabolized by CYP2C19 but S : slower metabolism → higher bioavailability, 2x potency & less PK variability

https://www.nature.com/articles/nrd1010#Fig4

- Same idea for lansoprazole & dexlansoprazole

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4697039/#:~:text=Also%2C%20dexlansoprazole%20has%20a%20lower,isomer%20%5B7%E2%80%9310%5D.

PPIs : adverse effects

- Remarkably few adverse effects
- Most common : headache, abdominal pain, constipation, flatulence, and diarrhea
- Chronic treatment may lead to
  - ↓ Vit B12 absorption
  - Hypomagnesemia → muscle weakness, muscle cramps, tetany, arrhythmias, hypotension and seizures
  - ↑ risk of bone fracture & osteoporosis (↓ Ca^{2+} absorption)
  - Hypergastrinemia, respiratory & enteric infections, dementia, nephritis

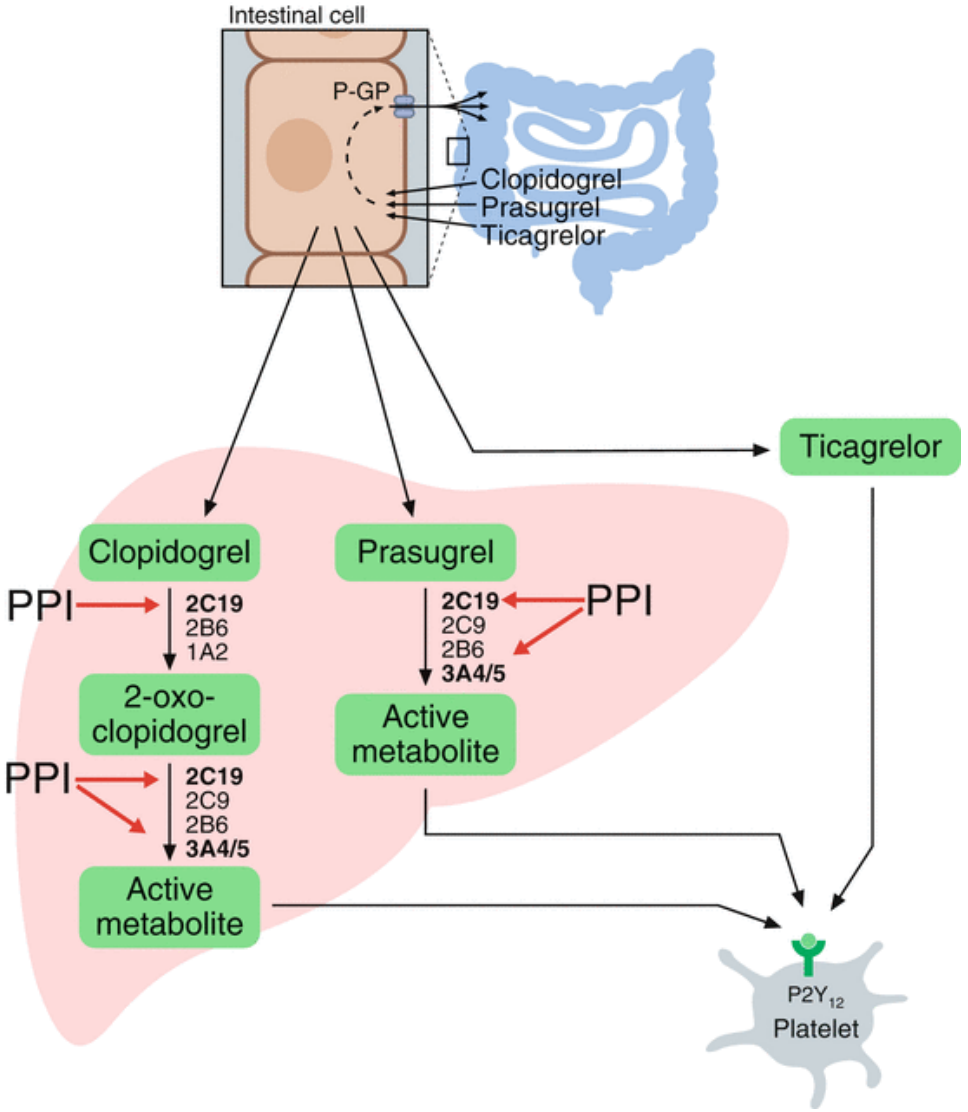
https://www.uspharmacist.com/article/proton-pump-inhibitors-considerations-with-longterm-use

PPIs : drug interactions

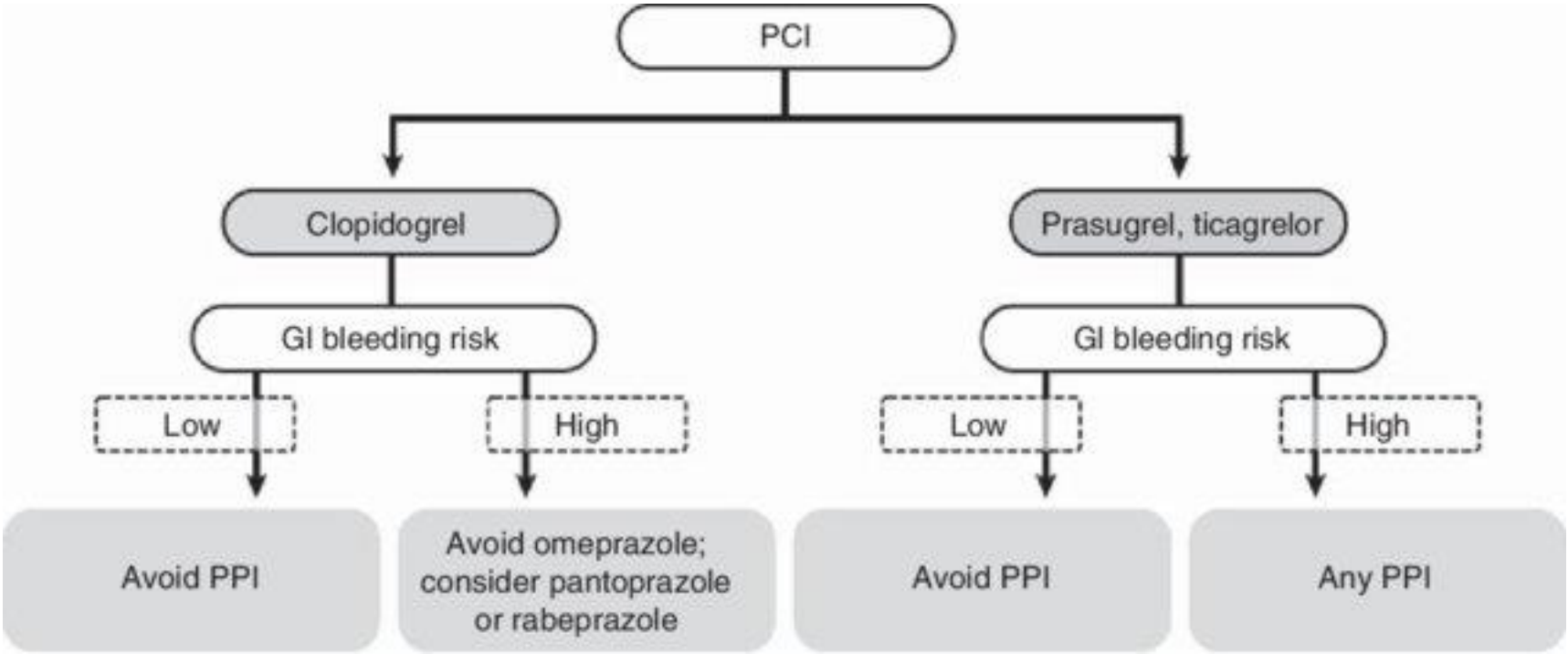
- Metabolism of drugs
  - Competitive inhibition
    - Warfarin (esomeprazole, lansoprazole, omeprazole, and rabeprazole), diazepam (esomeprazole and omeprazole), and cyclosporine (omeprazole and rabeprazole).
  - Omeprazole
    - **CYP2C19 inhibitor** → ↓ clearance of disulfiram, phenytoin, and other drugs
    - **CYP1A2 inducer** → ↑ clearance of imipramine, several antipsychotic drugs, and theophylline
  - Rabeprazole & pantoprazole : least significant DDI

PPIs : drug interactions

- Omeprazole + clopidogrel
  - Clopidogrel = prodrug → active anticlotting agent by CYP2C19
  - Omeprazole would ↓ clopidogrel activity → ↑ risk of cardiovascular events (clinical relevance ?)



PPIs : drug interactions



PPIs : therapeutic uses

- Gastroesophageal *r*eflux *d*isease (GERD)
  - Most effective agents
  - QD use → Symptom relief & tissue healing in 85-90% patients
  - May be used OTC for heartburn
- Peptic ulcers
  - 90% of duodenal ulcers heal in 4 weeks & gastric ulcers in 6-8 weeks
- *H. pylori* infections
  - Dual or triple therapy with antibiotics (amoxicillin, clarithromycin, metronidazole)
  - Quadruple therapy (if clarithromycin resistance)
- Prevention and treatment of NSAID-associated gastric ulcers
- Prevention of stress related mucosal bleeding in critically ill patients
- Treatment of pathological hypersecretory conditions (Zollinger-Ellison syndrome)

Table 3. Recommended Length of Therapy for FDA-Approved Indications in Adults

Indication	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Symptomatic GERD	4 wk; may consider additional 4-wk course	8 wk	4 wk	NA[a]	4 wk; may consider additional 4-wk course
Heartburn (OTC)	14 days; may repeat in 4 mo	14 days; may repeat in 4 mo	14 days; may repeat in 4 mo	NA	NA
Healing of erosive esophagitis	4-8 wk; may consider additional 4-8–wk course based on response. Maintenance: not studied >6 mo	8 wk; may consider additional 8-wk course. Maintenance: not studied >12 mo	4-8 wk; may consider additional 4-8–wk course based on response. Recurrence: may consider additional 4-8 wk	8 wk; may consider additional 8-wk course based on response	4-8 wk; may consider additional course up to 8 wk based on response
Helicobacter pylori eradication	10 days	Dual therapy: 14 days; triple therapy: 10-14 days	Dual therapy: 14 days; triple therapy: 10-14 days[b]	NA	7 days
Hypersecretory conditions	Long-term	Long-term	Long-term	Long-term	Long-term
Risk reduction for NSAID-associated gastric ulcer	6 mo	12 wk	NA	NA	NA
Healing of NSAID-associated gastric ulcer	NA	8 wk	NA	NA	NA
Gastric ulcer	NA	8 wk	4-8 wk	NA	NA
Duodenal ulcer	NA	4 wk. Maintenance: open-ended	4 wk; may consider additional 4-wk course	NA	4 wk; additional therapy may be required

[a] "NA" indicates that the medication is not FDA-approved for the condition listed.
[b] An additional 14 or 18 days of omeprazole therapy should be used if an ulcer is present at initiation of dual or triple therapy, respectively.
GERD: gastroesophageal reflux disease; NA: not applicable; NSAID: nonsteroidal anti-inflammatory drug.
Source: References 2-7.

https://www.uspharmacist.com/article/appropriate-use-and-safety-concerns-of-proton-pump-inhibitors

Sucralfate ULCAR

- Sucralfate consists of the octasulfate of sucrose + $Al(OH)_3$
- In an acid environment (pH <4), sucralfate undergoes extensive cross-linking to produce a viscous, sticky polymer that adheres to epithelial cells and ulcer craters for up to 6 hours after a single dose.
- Sucralfate **cytoprotective** effects
  - Mechanical : Inhibition of hydrolysis of mucosal proteins by pepsin
  - Stimulation of local production of prostaglandins and epidermal growth factor
  - Binding to bile salts
  - No direct ↓ in gastric acidity
- Used to prevent/treat peptic ulcer
  - Less effective than antisecretagogues
  - Advantage in preventing aspiration pneumonia, radiation ulcers, biliary esophagitis or gastritis

Sucralfate ULCAR

- Activated by acid → should be taken on an empty stomach at least 1 hour before meals
- Onset : 1 – 2 hours
- Duration up to 6 hours (Q6)
- **Not absorbed significantly** from the gut → primarily excreted in the feces (and safety)
- Patients absorb a small amount of aluminum from the drug → used cautiously in patients with renal impairment
- Most common adverse effect : constipation (2% of patients)
- Inhibits absorption of other drugs e.g., phenytoin, digoxin, cimetidine, ketoconazole, and fluoroquinolone antibiotics
- Taken 2 hours after administration of other drugs

Prostaglandin analog : Misoprostol

- Misoprostol is a synthetic analog of PGE_1.
  - Decreases gastric acid secretion (basal 90% and food-stimulated 80%)
  - Prevents gastric injury by cytoprotective effects that include
    - Stimulation of mucin and bicarbonate secretion
    - Increased mucosal blood flow.
- PK : rapid absorption and extensive metabolism into active misoprostol acid
  - $T_{1/2}$ < 30 minutes → administered Q6-8h
- Adverse effects
  - **Diarrhea** (up to 40%) , abdominal pain and cramps , headache
  - Can cause clinical exacerbations of inflammatory bowel disease
  - Contraindicated during pregnancy
- Used to **prevent** NSAID-induced mucosal injury
  - Rarely used because of its adverse effects and the inconvenience of QID daily dosing (short duration of action)
- Other uses : pregnancy termination, induction of uterine contractions (off label)

ACTIVITIES DURING THE CLASS

Mindmap

- We will use The **mindmeister** to summarize the key concepts learned in this chapter

- Activity
  - Click on the following link and begin constructing the mindmap
  - https://mm.tt/2437168741?t=SPiO7Jzrgi
  - Each student has to add one idea about one drug class, this could be a mechanism of action, PK, … be sure to put only the key concepts, the ones you want to always remember about each drug

ACTIVITIES AFTER THE CLASS

Crosswords

Individual work

- Learn by playing : crosswords

- Download Activeinspire (if you don't have it already) following the instructions on
  - https://support.prometheanworld.com/s/article/1052?language=en_US

- You may now open the joined application and search for the words !

Case report : Deprescribing PPI

By pairs

- Read the article : Dharmarajan TS. The Use and Misuse of Proton Pump Inhibitors: An Opportunity for Deprescribing. J Am Med Dir Assoc. 2021 Jan;22(1):15-22. doi: 10.1016/j.jamda.2020.09.046. Epub 2020 Dec 13. PMID: 33321078.
- This article explains the misuse of PPI and offers an algorithm to help deprescribing the PPI from patients regimens.

- This activity is done by pairs (one case per pair of students)
- Look among your family, relatives, neighbours, friends, community pharmacy … of patients who consume regularly and chronically PPIs (continuously for at least one year)
- Describe his clinical case (refer to the **rubric** to see the details that should be inserted)
  - Rubric link : https://docs.google.com/document/d/1n0mQYwrqc39XHdjOs8XDqbkah98ie2-8IfI4wpsOKAw/edit?usp=sharing
- Use Dharmarajan's algorithm to analyse his PPI use and conclude whether he is a candidate for deprescribing PPI or not
- A report should be written on a word document and should contain all the elements mentioned in the grid
- Your report should be written on a word document and uploaded on the following padlet : https://padlet.com/rakaraky/xfdpt5xt4m3eeg7m
- This is a tutorial to help you with how to handle padlet
  - https://www.youtube.com/watch?v=YsV4ShNddYY