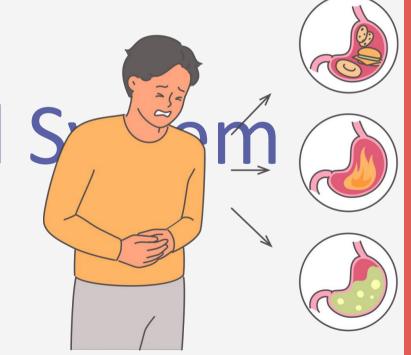
PHARMACOLOGY 201 | DR. MORA

# Gastrointestinal S

H2 Blockers, PPIs, Anti-Emetics



# Learning Objectives

- 1. Explain the physiological regulation of gastric acid secretion, including the roles of histamine (H2), acetylcholine (M3), and gastrin (CCK-B) receptors.
- 2. Describe the mechanism of action of H2 receptor antagonists and their role in decreasing gastric acid production.
- 3. Compare the different types of antacids, their mechanisms of action, and their respective side effects.
- 4. Discuss the pharmacokinetics and mechanism of action of proton pump inhibitors (PPIs) and their role in acid suppression.
- 5. Identify the adverse effects of long-term PPI use, including increased risk of fractures, hypomagnesemia, and C. difficile infection.

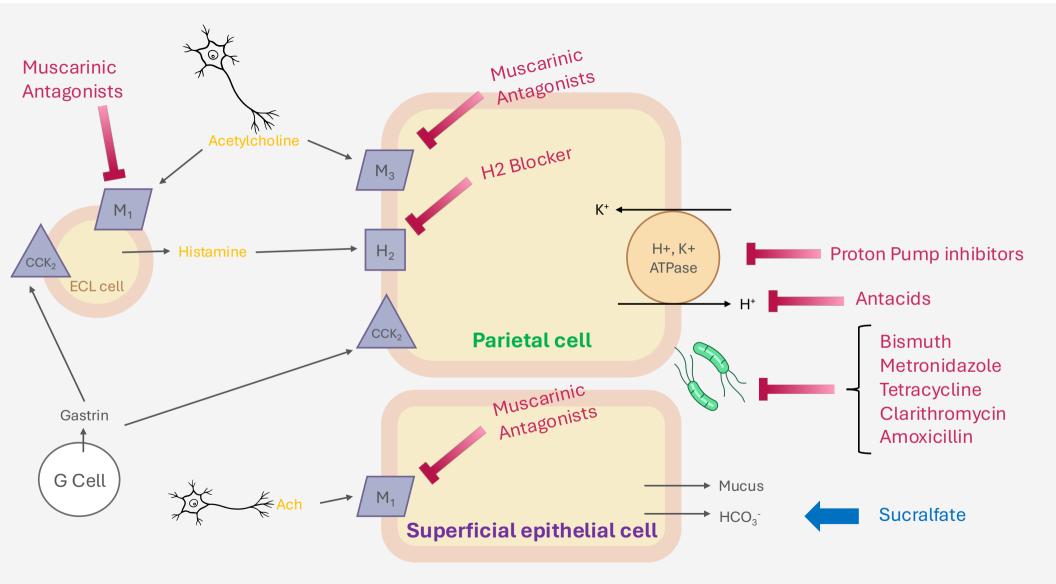
# Learning Objectives

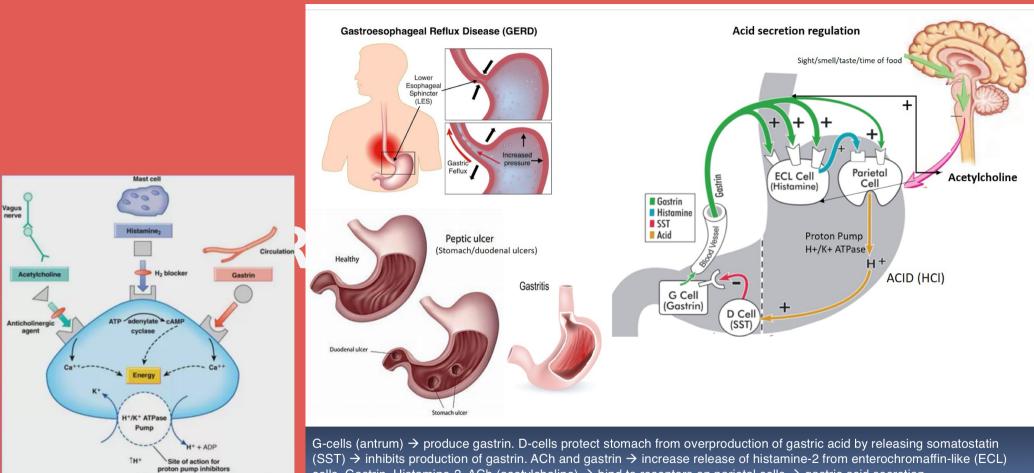
- 6. Describe the central pathways involved in nausea and vomiting, including the chemoreceptor trigger zone (CTZ) and vomiting center.
- 7. Explain the mechanism of action of 5-HT3 receptor antagonists and their use in chemotherapy-induced and postoperative nausea.
- 8. Describe the role of dopamine (D2) receptor antagonists in nausea control and their potential extrapyramidal side effects.
- 9. Compare the mechanisms and indications of antihistamines (H1 blockers) and anticholinergics (M1 blockers) in motion sickness treatment.
- 10. Apply knowledge of acid suppression and antiemetic pharmacology to select appropriate treatment options based on patient presentation.

# **Acid Production**

### Background

- Parietal cells contain receptors for gastrin (CCK-B), histamine (H<sub>2</sub>), acetylcholine (M<sub>3</sub>)
- Acetylcholine (via vagal nerve) and gastrin (released from antral G cells into the blood) bind to parietal cell receptors
- Cause increase in cytosolic calcium → stimulates protein kinases that stimulate acid secretion from a H+/K+-ATPase (proton pump)
- Enterochromaffin-like cells have receptors for gastrin and Ach, which stimulate histamine release





cells. Gastrin, Histamine-2, ACh (acetylcholine)  $\rightarrow$  bind to receptors on parietal cells  $\rightarrow$  gastric acid secretion

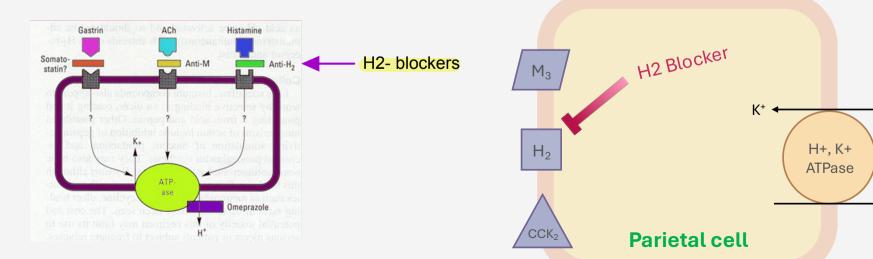
Fig. 51-2. Parietal cell stimulation and secretion. ADP, Adenosine diphosphate; ATP, adenosine triphosphate; ATPase, denosine triphosphatase; cAMP, cyclic adenosine monophosphate

### H2 Receptor Antagonists

Famotidine, Cimetidine, Ranitidine (withdrawn)

#### **Mechanism of Action**

- Competitively bind histamine (H2) receptors on gastric parietal cells
- Reduce intracellular cAMP levels, decreasing H+/K+ ATPase activation
- Results in reduced acid secretion and gastric pH elevation



### H2 Receptor Antagonists

Famotidine, Cimetidine, Ranitidine (withdrawn)

Indication

- GERD
- Peptic ulcer disease
- Zollinger-Ellison syndrome

### H2 Receptor Antagonists

Famotidine, Cimetidine, Ranitidine (withdrawn)

#### Adverse Effects

• CNS effects (confusion, dizziness in elderly)

#### • Gynecomastia (cimetidine)

- H<sub>2</sub>RAs are remarkably safe
- Oral absorption is rapid  $\rightarrow$  peak serum drug concentration: 1-3 hours
- <u>Side Effects</u> (SEs)
  - GI Discomfort: diarrhea, constipation
  - CNS Effects: headache, dizziness, drowsiness, lethargy
  - Dermatologic Effects: rash
  - Hematologic Effect: thrombocytopenia (1%) is reversible upon discontinuation of H<sub>2</sub>RA
- Cimetidine (Tagamet) has the greatest potential for drug-drug interactions → inhibits hepatic cytochrome P-450 isoenzymes → inhibits metabolism of theophylline, phenytoin, warfarin → drug toxicities

#### **Contraindications**

- CrCl < 15 Famotidine
- Severe renal impairment 20mg Q48H
- Caution in elderly (CNS effects)

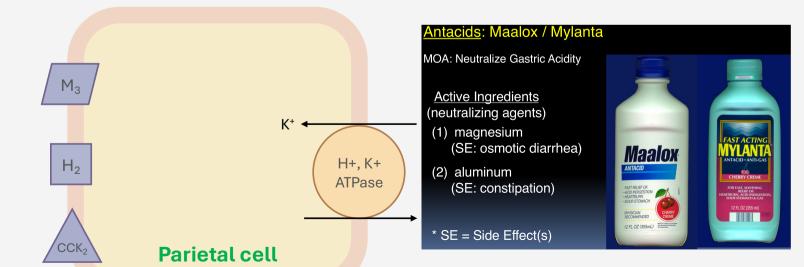
#### Histamine-2 Receptor Antagonists (H<sub>2</sub>RA)

- Tachyphylaxis or tolerance may develop after 2-6 weeks of H<sub>2</sub>RA therapy due to upregulation of H<sub>2</sub> receptor sites.
- Development of tachyphylaxis limits the use of H<sub>2</sub>RAs in management of GERD and other conditions requiring long-term therapy.



Calcium carbonate, Magnesium hydroxide, Aluminum hydroxide Mechanism of Action

- Directly neutralize gastric acid via acid-base chemical reactions
- Increase gastric pH and decrease pepsin activity
- Provide quick symptomatic relief but do not reduce acid production



Calcium carbonate, Magnesium hydroxide, Aluminum hydroxide

Indication

- GERD
- Peptic ulcer disease
- Dyspepsia
- Prevention from bleeding from stress-related gastritis

from stress-related gastritis

Calcium carbonate, Magnesium hydroxide, Aluminum hydroxide

#### **Adverse Effects**

- Constipation (aluminum)
- Diarrhea (magnesium)
- Hypercalcemia (calcium carbonate)

#### Milk of Magnesia (magnesium)

- magnesium  $\rightarrow$  neutralizes hyperacidity
- magnesium  $\rightarrow$  treats constipation

#### Amphojel (aluminum hydroxide)

- aluminum  $\rightarrow$  neutralizes hyperacidity
- neutralizing agent  $\rightarrow$  treats diarrhea



#### Contraindications

- Renal failure (magnesium-containing antacids)
- Metabolic alkalosis

#### Calicum Carbonate (TUMS)

- moderate neutralizing capacity, compared to Maalox/Mylanta
- $\begin{array}{c} \mathsf{CaCO}_3 \twoheadrightarrow \mathsf{gas} \ \mathsf{formation} \\ \twoheadrightarrow \mathsf{burping} \ / \ \mathsf{flatulence} \end{array}$
- high-doses (4-8 grams/day) → hypercalcemia / metabolic alkalosis "milk-alkali syndrome" → kidney failure



#### Antacids (Maalox, Mylanta)

- Onset: immediate (minutes)
- Duration: 30 minutes on an empty stomach, but 3 hours when taken within 1 hour of meals
- Alginic acid may be added to antacids → forms a viscous solution that floats on top of gastric contents → protects the esophageal mucosa from acid reflux
- <u>Simethicone</u> (surfactant) may be added to antacids → "breaks up" gas bubbles → relieves gas
- Caution: small amounts of aluminum and magnesium are absorbed and can accumulate in renal insufficiency → toxicity
  - Magnesium: avoid in patients with CrCl < 30 ml/min
  - Aluminum: avoid in patients with renal failure (CrCl < 15 ml/min)

Antacids (cont.)

### Sodium Bicarbonate (Alka-Seltzer)

High sodium content (567 mg per tablet)  $\rightarrow$  Na<sup>+</sup>/H<sub>2</sub>O retention  $\rightarrow$  exacerbates hypertension, heart failure, chronic kidney disease



# Proton Pump Inhibitors (PPIs)





#### General

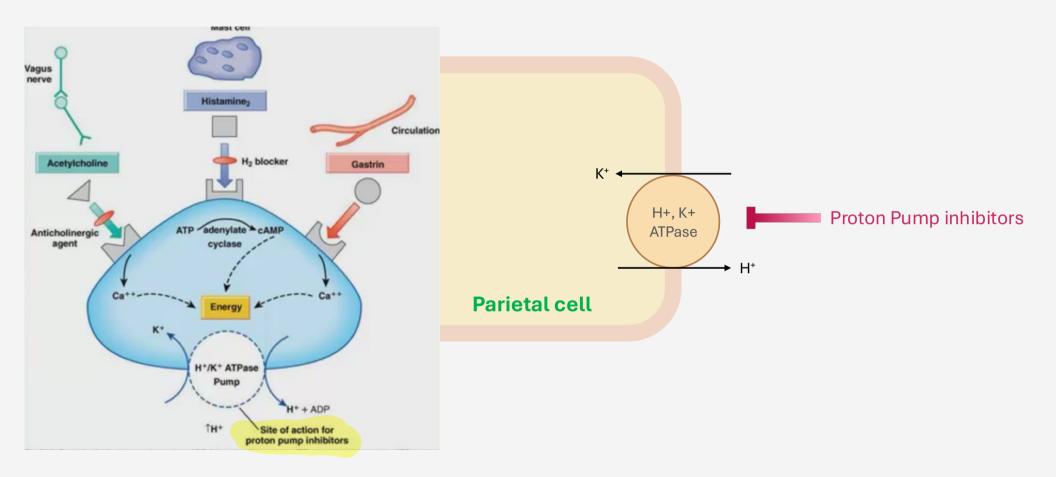
- Most potent suppressors of gastric acid secretions
- 6 available: omeprazole, esomeprazole, lansoprazole, pantoprazole dexlansoprazole, rabeprazole
- All have equivalent efficacy and comparable doses

Drug	Availability	Route of administration	Starting dosage*	Cost of generic (brand)†
Dexlansoprazole (Dexilant)	Prescription	Oral	30 mg per day	NA (\$153)
Esomeprazole (Nexium)	Prescription Over-the-counter	Oral or IV	Oral: 20 mg per day IV: 20 mg per day for 10 days	Oral: NA (\$201) IV: NA (\$381)‡
Lansoprazole (Prevacid)	Prescription	Oral	15 mg per day	\$106 (\$196)
Lansoprazole (Prevacid 24H)	Over-the-counter	Oral	15 mg per day for 14 days§	NA (\$13)
Omeprazole (Prilosec, Zegerid)	Prescription	Oral	20 mg per day	\$33 (\$196)
Omeprazole (Prilosec OTC, Zegerid OTC)	Over-the-counter	Oral	20.6 mg (Prilosec OTC) or 20 mg (Zegerid OTC) per day for 14 days§	\$7 (\$13)
Pantoprazole (Protonix)	Prescription	Oral or IV	Oral: 40 mg per day IV: 40 mg per day for 7 to 10 days	Oral: \$16 (\$186 IV: \$42 (\$42)‡
Rabeprazole (Aciphex)	Prescription	Oral	20 mg per day	NA (\$250)

## PPIs

Omeprazole, Pantoprazole, Esomeprazole, Lansoprazole Mechanism of Action

- Irreversibly inhibit H+/K+ ATPase proton pump in gastric parietal cells
- Prevents final step of acid secretion
- Act regardless of stimulation source (histamine, gastrin, ACh)
- Leads to profound and long-lasting acid suppression (10-48h)
- Amount of proton pumps increase after fasting → best if given in AM before first meal



### PPIs

#### Omeprazole, Pantoprazole, Esomeprazole, Lansoprazole

#### Indication

- Gastroesophageal reflux disease (GERD)
- Peptic ulcers (gastric, duodenal)
- Erosive esophagitis
- *H. pylori* eradication
- NSAID-induced ulcers
- Non-ulcer dyspepsia
- Prevent stress-related musical bleeding
- Zollinger-Ellison syndrome panaratic tumors -> 1 gastrin -> hypersecretory effects

**PPIs** 

#### Omeprazole, Pantoprazole, Esomeprazole, Lansoprazole

#### **Adverse Effects**

- Increased risk of fractures
- Hypomagnesemia
- C. difficile infection
- Rebound acid hypersecretion

Long-Term SEs of PPIs (usually with high doses)

- Atrophic gastritis has been "rarely" associated with patients on long-term therapy PPIs for Helicobacter pylori.
- Risk of *C. difficile* and other enteric infections has been observed due to ability of pathogens to survive in a less acidic GI environment: however the overall risk is low.
- Vit B<sub>12</sub> deficiency, since gastric acid is required to extract Vit B<sub>12</sub> from dietary sources. Monitor Vit B12 levels in PPI patients.

### Contraindications

- Long-term use in osteoporosis
  - Interstitial nephritis AIN u/PPI may be d/t deposits of PPi or metabolites in tubular interstition

#### Long-Term SEs of PPIs

- Hypomagnesemia may occur with long-term use of PPIs due to reduced intestinal absorption. Monitoring serum magnesium levels is recommended in patients on long-term PPI therapy.
- Hypocalcemia and increase risk of fractures is associated with reduced calcium absorption due to hypochlorhydria. Since calcium citrate does not require acid for absorption, it is the recommended calcium supplement in patients on long-term PPI therapy.
- Iron malabsorption secondary to long-term gastric acid suppression with PPIs, however this does not appear to be of clinical significance unless a patient requires oral iron supplementation. Higher doses and longer duration of iron supplementation are recommended in these patients.

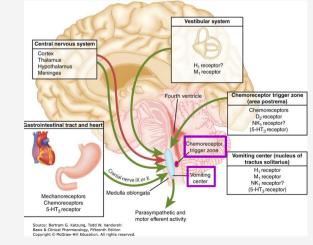


# **Anti-Emetics**

# **Vomiting Centers**

### **General Background**

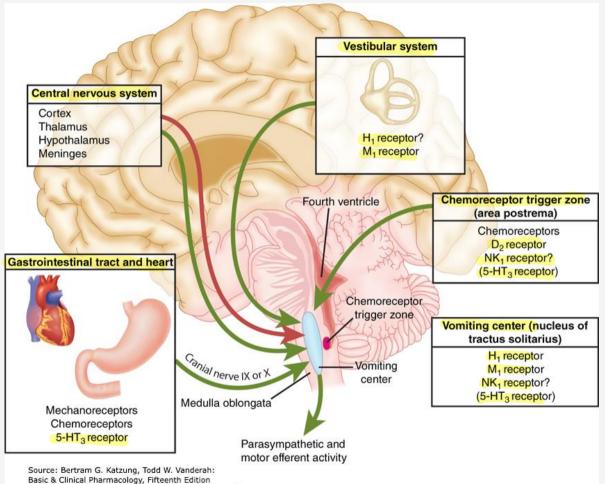
- Brainstem "vomiting center" lateral medullary reticular formation
- Coordinates vomiting with CN VIII, IX, X, neural networks in nucleus tractus solitarius that control respiratory, salivatory, and vasomotor center
- Antiemetics target one of the 5 neurotransmitter receptors at vomiting centers:
  - Muscarinic M1 receptors
  - Histamine H<sub>1</sub> receptors
  - Dopaminergic D<sub>2</sub> receptors
  - Neurokinin 1 (NK1) receptors
  - Serotonin (5-HT3) receptors



# **Vomiting Centers**

### **General Background**

- Alternative medications with antiemetic properties:
  - Glucocorticoids
  - Benzodiazepines
  - Cannabinoids



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### 5-HT3 Antagonists

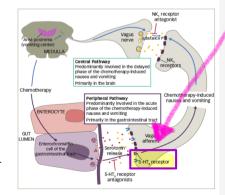
#### **Ondansetron**, Granisetron, Palonosetron

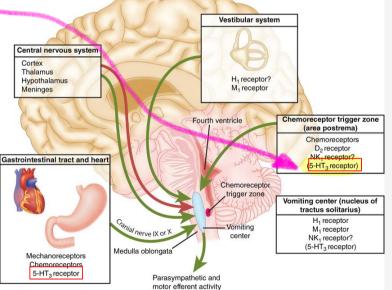
#### **Mechanism of Action**

- Selectively block 5-HT3 receptors in chemoreceptor trigger zone (CTZ) and vagal afferents
- Prevents stimulation of the vomiting reflex

#### Serotonin 5-HT<sub>3</sub> Antagonists

- <u>Ondansetron</u> (Zofran) → mainly blocks 5-HT<sub>3</sub> receptors on intestinal vagal and spinal afferent nerves; also blocks 5-HT<sub>3</sub> receptors in the vomiting center and CTZ.
  - Effective in treating emesis mediated through vagal stimulation (e.g., chemotherapy and postoperative nausea/vomiting)
  - May be combined with corticosteroid (i.e., dexamethasone) for enhanced effects in chemotherapy
  - Side Effects: headache, dizziness, prolongation of QTinterval





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### **5-HT3 Antagonists**

Ondansetron, Granisetron, Palonosetron

Indication

- Chemotherapy-induced nausea/vomiting
- Post-operative nausea/vomiting

### **5-HT3 Antagonists**

**Ondansetron**, Granisetron, Palonosetron

**Adverse Effects** 

- QT prolongation
- Headaches, fatigue, sedation

#### Contraindications

Congenital long QT syndrome

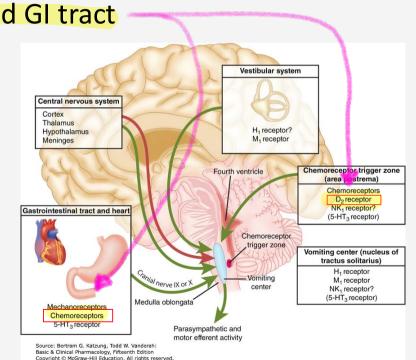
### **Dopamine Antagonists**

Metoclopramide, Prochlorperazine, Promethazine\*

\*Antihistamine activity

### **Mechanism of Action**

- Block dopamine (D2) receptors in the CTZ and GI tract
- Inhibit nausea signals at central and peripheral level
- Increase gastric motility (metoclopramide)



### **Dopamine Antagonists**

Metoclopramide, Prochlorperazine, Promethazine

#### Indication

- Nausea/vomiting
- Gastroparesis (metoclopromide)
- Migraine-associated nausea

Situation	Associated neurotransmitters	Recommended antiemetic	
Migraine headache	Dopamine (probably a primary mediator)	For headache and nausea: metoclopramide or prochlorperazine	
		For nausea: oral antiemetics, metoclopramide, prochlorperazine, serotonin antagonists	
Vestibular nausea	Histamine, acetylcholine	Antihistamines and anticholinergics (equally effective)	
Pregnancy-induced nausea	Unknown	For nausea: ginger, vitamin B6	
		For hyperemesis gravidarum: promethazine (first-line agent); serotonin antagonists and corticosteroids (second-line agents)	
Gastroenteritis	Dopamine, serotonin	First-line agents: dopamine antagonists	
		Second-line agents: serotonin antagonists	
		Use in children is controversial	
Postoperative nausea and vomiting	Dopamine, serotonin	Prevention: serotonin antagonists, droperidol, dexamethasone	
		Treatment: dopamine antagonists, serotonin antagonists, dexamethasone	

## **Dopamine Antagonists**

Metoclopramide, Prochlorperazine, Promethazine

#### **Adverse Effects**

- QT prolongation
- Anticholinergic effects
- Drowsiness
- Extrapyramidal symptoms (rigidity, bradykinesia, akathisia)
- Tardive dyskinesia (delayed response with long-term use of DA gutzgoniste)

#### **Contraindications**

- Parkinson's disease
- Gl obstruction
- History of tardive dyskinesia

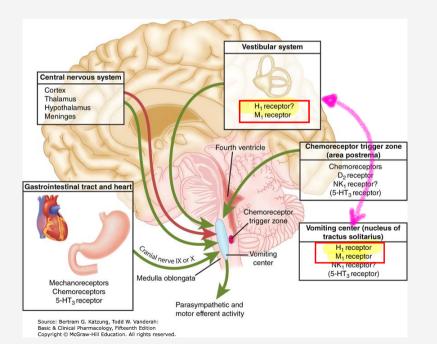


## Antihistamines/Anticholinergics

Diphenhydramine<sup>H1</sup>, Meclizine<sup>H1</sup>, Dimenhydrinate, Scopolamine<sup>M1</sup>

#### **Mechanism of Action**

- Antihistamines: Block H1 receptors from vestibular nuclei vomiting centers of the brain
- Antimuscarinics: Block M1 receptors (cholinergic transmission) from vestibular nuclei to vomiting centers of the brain
- Prevent motion-induced nausea signals to vomiting center



## **Antihistamines/Anticholinergics**

Diphenhydramine<sup>H1</sup>, Meclizine<sup>H1</sup>, Dimenhydrinate, Scopolamine<sup>M1</sup>

### Indication

- Motion sickness
- Vertigo
- Postoperative nausea/vomiting

## Antihistamines/Anticholinergics

Diphenhydramine<sup>H1</sup>, Meclizine<sup>H1</sup>, Dimenhydrinate, Scopolamine<sup>M1</sup>

### **Adverse Effects**

- Drowsiness
- Dry mouth
- Blurred vision
- Urinary retention
- Mydriasis

Anticholinergic properties

### **Contraindications**

- Glaucoma
- BPH
- Elderly (risk of delirium, falls)
- Avoid with other sedatives

**Study Checks** 

A 42-year-old woman is seen because of worsening heartburn during the past week. She was first diagnosed with GERD 1 month ago and treatment was begun with cimetidine 400 mg once daily. Two weeks later the cimetidine dosage was increased to 400 mg twice daily.

- a) What is the reason for the worsening of her GERD symptoms?
- b) What are the mechanisms of action of H<sub>2</sub> receptor blockers and proton pump inhibitors?
- c) What is a rational approach to her treatment?
- d) If the patient is switched to a proton pump inhibitor, of what adverse effects should she be warned?

A 42-year-old woman is seen because of worsening heartburn during the past week. She was first diagnosed with GERD 1 month ago and treatment was begun with cimetidine 400 mg once daily. Two weeks later the cimetidine dosage was increased to 400 mg twice daily.

a) What is the reason for the worsening of her GERD symptoms? Cimetidine is an H<sub>2</sub> receptor antagonist and tolerance to acid suppressing effects of these drugs has been shown to develop as early as 2 to 5 days after beginning treatment. One mechanism for this phenomenon is secondary to the hypergastrinemia that stimulates histamine release and overcomes the H<sub>2</sub> receptor blockade.

A 42-year-old woman is seen because of worsening heartburn during the past week. She was first diagnosed with GERD 1 month ago and treatment was begun with cimetidine 400 mg once daily. Two weeks later the cimetidine dosage was increased to 400 mg twice daily.

- b) What are the mechanisms of action of H<sub>2</sub> receptor blockers and proton pump inhibitors?
- H<sub>2</sub> blockers suppress gastric acid secretion (compete with histamine for binding to H<sub>2</sub> receptors on the basolateral membrane of parietal cells).
- PPI: prodrugs that require activation in an acid environment. Activated form binds covalently with sulfhydryl groups on <u>cysteine</u> in the H<sup>+</sup>,K<sup>+</sup>-ATPase located on the luminal membrane of the parietal cell. Despite the short plasma half-lives (0.5-2 h) of the parent drug, acid suppression continues for 24 to 48 hours or until new pump molecules are synthesized.

A 42-year-old woman is seen because of worsening heartburn during the past week. She was first diagnosed with GERD 1 month ago and treatment was begun with cimetidine 400 mg once daily. Two weeks later the cimetidine dosage was increased to 400 mg twice daily.

- c) What is a rational approach to her treatment?
- Switch her to a proton pump inhibitor. Also cause a hypergastrinemia but does not result in tolerance because inhibition occurs at the H<sup>+</sup>,K<sup>+</sup>-ATPase which is the final step in gastric acid secretion.

A 42-year-old woman is seen because of worsening heartburn during the past week. She was first diagnosed with GERD 1 month ago and treatment was begun with cimetidine 400 mg once daily. Two weeks later the cimetidine dosage was increased to 400 mg twice daily.

- d) If the patient is switched to a proton pump inhibitor, of what adverse effects should she be warned?
- PPI metabolized by hepatic CYPs. May interfere with elimination of other drugs cleared by this route.
- Chronic treatment w/ PPI  $\rightarrow$  decreases absorption of vitamin B<sub>12</sub>.
- Loss of gastric acidity may affect the bioavailability of drugs, most notably iron salts. This may result in an **iron deficiency anemia**.

A 24-year-old woman presents with symptoms of esophageal reflux. She is 6 months pregnant. Which of the following drugs is contraindicated in this patient?

- A. Ranitidine
- B. Lansoprazole
- C. Misoprostol
- D. Sucralfate
- E. Aluminum hydroxide antacid

A 48-year-old man with a duodenal ulcer disease is treated with cimetidine. After 6 weeks of treatment, he complains that his stomach pain is returning and wonders if the dose of cimetidine should be increased. The most likely reason for the decreased effectiveness of cimetidine in this patient is

### A. tolerance.

- B. diminished Gl absorption.
- C. enhanced plasma protein binding.
- D. increased hepatic metabolism.
- E. poor patient compliance.

As the binding of esomeprazole to the (H+, K+)-ATPase enzyme is irreversible and new enzyme needs to be expressed in order to resume acid secretion, esomeprazole's duration of antisecretory effect persists longer than 24 hours.

Esomeprazole has a plasma half-life of a few hours yet suppresses acid secretion for 24 to 48 hours. The reason for this paradox is

- A. acid suppression continues until new H+,K\*-ATPase molecules are synthesized.
- B. gastrin depletion occurs long after esomeprazole disappears from the plasma.
- C. prostaglandin synthesis is enhanced by esomeprazole.
- D. H. pylori is effectively suppressed by esomeprazole for 24 to 48 hours.
- E. acid suppression continues until new H2 receptors are synthesized.

A 48-year-old woman has been diagnosed with a duodenal ulcer that is complicated by H. pylori infection. A suitable therapeutic regimen for this patient would be

- A. a single antibiotic.
- B. a single antibiotic plus a proton pump inhibitor.
- C. misoprostol plus a proton pump inhibitor.
- D. an H2 receptor antagonist.
- E.  $2^{-3}$  antibiotics plus a proton pump inhibitor.

#### Bismuth Quadruple Therapy

- Preferred regimen in patients allergic to penicillin (PCN)
- <u>Bismuth Subsalicylate</u> (Pepto Bismol) + <u>Metronidazole</u> (Flagyl) + <u>Tetracycline</u> + <u>PPI</u> → 14 days
  - $\circ$  PPI (standard dose) PO BID  $\rightarrow$  e.g., <u>Lansoprazole</u> (Prevacid) 30 mg PO BID
  - <u>Bismuth Subsalicylate</u> (300 or 524 mg) PO QID
  - Tetracycline (TCN) 500 mg PO QID
  - Metronidazole: 250 mg PO QID or 500 mg PO TID

Clarithromycin-Based Therapy

.

- <u>Clarithromycin</u> (Biaxin) + <u>Amoxicillin</u> (Amoxil) + <u>Metronidazole</u> (Flagyl) + <u>PPI</u> → 10-14 days
  - $\circ~$  PPI (standard dose) PO BID  $\rightarrow$  e.g., Lansoprazole (Prevacid) 30 mg PO BID
  - Clarithromycin 500 mg PO BID
  - Amoxicillin 1000 mg PO BID
  - $\circ$  Metronidazole 500 mg PO BID

A 60-year-old woman has had symptoms of heartburn for 6 months. She first treated herself with antacids but as the frequency and severity of the pain increased she switched to over-the-counter <u>omeprazole</u> which she has been taking daily for 3 months. She now comes to your office complaining of fatigue and lethargy. Her physical examination is unusual only in that her skin is remarkably pale. An analysis of her blood reveals hypochromic, microcytic red blood cells. The most likely explanation for this finding is

- A. poor absorption of calcium.
- B. poor absorption of vitamin B2.
- C. poor absorption of folic acid.
- D. poor absorption of iron salts.

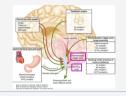
Vit B12 -> macrocytic anemia iron def. -> microcytic anem: a • measure vit B12 Serm levels • iron def. -> + ferritin levels

E. a direct effect of omeprazole on the bone marrow production of red blood cells.

# **Rapid Review**

- Which H2 blocker causes gynecomastia?
- Which H2 blocker has the most drug interactions?
- What is the MoA of PPIs?
- What are the serious adverse drug reactions of PPIs?
- Whare the the 5 neurotransmitter receptor types targeted by antiemetics?
- What are the indications for scopolamine patch?
- What are the 2 main indications for metoclopramide? }
- What is the MoA of metoclopramide? blocks D-2 receptors in CTZ

- Histamine H.



#### • What are the serious adverse drug reactions of PPIs?

#### Long-Term SEs of PPIs (usually with high doses)

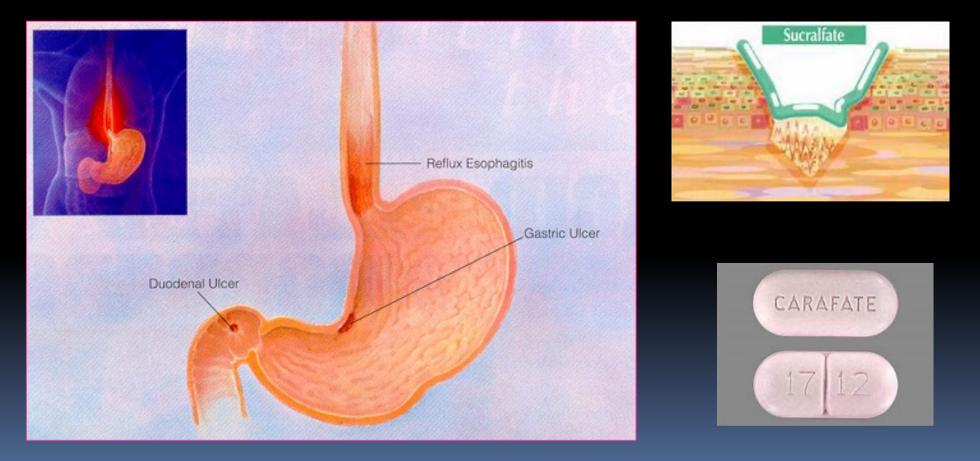
- Atrophic gastritis has been "rarely" associated with patients on long-term therapy PPIs for *Helicobacter pylori*.
- Risk of *C. difficile* and other enteric infections has been observed due to ability of pathogens to survive in a less acidic GI environment; however the overall risk is low.
- Vit B<sub>12</sub> deficiency, since gastric acid is required to extract Vit B<sub>12</sub> from dietary sources. Monitor Vit B12 levels in PPI patients.
- Hypomagnesemia may occur with long-term use of PPIs due to reduced intestinal absorption. Monitoring serum magnesium levels is recommended in patients on long-term PPI therapy.
- Hypocalcemia and increase risk of fractures is associated with reduced calcium absorption due to hypochlorhydria. Since calcium citrate does not require acid for absorption, it is the recommended calcium supplement in patients on long-term PPI therapy.
- Iron malabsorption secondary to long-term gastric acid suppression with PPIs, however this does not appear to be of clinical significance unless a patient requires oral iron supplementation. Higher doses and longer duration of iron supplementation are recommended in these patients.

### References

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### Sucralfate (Carafate)

(cytoprotective agent) MOA: binds to gastric ulcer forming a protective barrier



### Sucralfate (Carafate)

- Sucralfate may also have protective affect by stimulating release of mucosal prostaglandins (PGE)
- SE: constipation (1-3%) due to aluminum content
- Caution: aluminum content may accumulate in patients with renal insufficiency → "aluminum encephalopathy" (i.e., dementia), and anemia
- Aluminum binds dietary phosphate (GI tract)
  → hypophosphatemia
- Sucralfate tablets are large and may be difficult for geriatrics to swallow → use liquid formulation



CARAFATE



### Misoprostol (Cytotec)

MOA: synthetic prostaglandin (PG) analog

- stimulates the production of mucus and bicarbonate ("mucoprotective shield")
- improves mucosal blood flow
- reduces mucosal cell turnover
- mildly inhibits gastric acid secretion (less than H<sub>2</sub>RAs)

<u>SE</u>: diarrhea (up to 30%), abdominal cramping

 take with food and reduce daily dose to minimize incidence of diarrhea

<u>Caution</u>: misoprostol is contraindicated in pregnancy.

 use in women in childbearing years requires negative serum pregnancy test and adequate contraception



#### Antiemetic Agents

There are 4 major sources of afferent input to the vomiting center.

(1) CTZ (chemoreceptor trigger zone)

- located outside the BBB and is subject to stimuli in blood
- receptors: D<sub>2</sub>, opioid, 5-HT<sub>3</sub>, NK<sub>1</sub>
- (2) Vestibular System
  - important in motion sickness
  - receptors: M<sub>1</sub> and H<sub>1</sub>
- (3) Vagal and Spinal Afferent Nerves from the GI tract
  - receptors: 5-HT<sub>3</sub>
  - GI irritates (chemotherapy, distention, infection)
    - $\rightarrow$  release of mucosal serotonin
    - → activate 5-HT<sub>3</sub> receptors

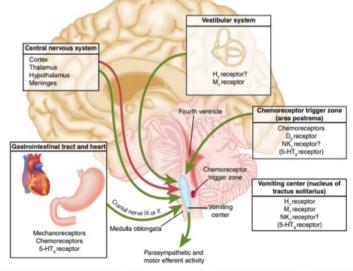
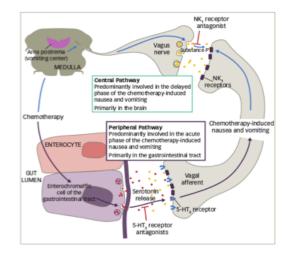


FIGURE 62-6 Neurologic pathways involved in pathogenesis of nausea and vomiting (see text). (Modified and reproduced, with permission, from Knakauer EL et al: Case records of the Massachusetts General Hospital. N Engl J Med 2005;352:817.)

- ightarrow propagate vagal afferent impulses to vomiting center and CTZ
- (4) Central Nervous System (CNS)
  - stress, psychiatric disorders, anticipatory vomiting, etc...

#### Serotonin 5-HT<sub>3</sub> Antagonists

- <u>Ondansetron</u> (Zofran) → mainly blocks 5-HT<sub>3</sub> receptors on intestinal vagal and spinal afferent nerves; also blocks 5-HT<sub>3</sub> receptors in the vomiting center and CTZ.
  - Effective in treating emesis mediated through vagal stimulation (e.g., chemotherapy and postoperative nausea/vomiting)
  - May be combined with corticosteroid (i.e., dexamethasone) for enhanced effects in chemotherapy
  - Side Effects: headache, dizziness, prolongation of QTinterval



<u>Phenothiazines</u>

- <u>Prochlorperazine</u> (Compazine) and <u>Promethazine</u> (Phenergan)
  - $\rightarrow$  block D<sub>2</sub>, M<sub>1</sub>, and H<sub>1</sub> receptors in CTZ and vomiting center
- Side Effects: extrapyramidal symptoms (EPS), hypotension, sedation (d/t antihistaminic property)
  - EPS is treated with diphenhydramine (Benadryl) 25 mg IV or IM

#### **Benzamides**

- Metoclopramide (Reglan) and Trimethobenzamide (Tigan)
  - $\rightarrow$  block D<sub>2</sub> receptors
  - $\rightarrow$  stimulate cholinergic receptors on GI smooth muscle  $\rightarrow$  increases GI motility (Prokinetic)
  - $\rightarrow$  increases lower esophageal sphincter (LES) tone (tx: GERD)
- Side Effects: anxiety, restlessness, EPS (due to CNS dopamine blocking effects)

#### <u>Antihistamines</u>

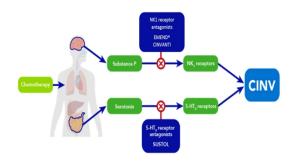
- <u>Diphenhydramine</u> (Benadryl) 25-50 mg PO/IV/IM Q6H and <u>Dimenhydrinate</u> (Dramamine) 50 mg PO Q4H → 1<sup>st</sup> generation antihistamines → block H<sub>1</sub> receptors with potent anticholinergic properties (SE: dizziness, sedation, dry mouth, blurred vision, urinary retention, etc...)
  - $H_1$  blocking effect  $\rightarrow$  prevents motion sickness and vertigo (d/t vestibular dysfunction)
- Meclizine (Antivert) 25-50 mg PO Q24H → blocks H<sub>1</sub> receptors with minimal anticholinergic properties (less sedation) → prevents motion sickness and vertigo

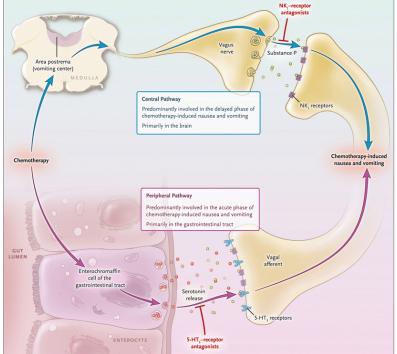
#### Anticholinergic Drugs

- <u>Scopolamine</u> (Transderm Scop) → highly effective M<sub>1</sub> receptor antagonist for the prevention of motion sickness (vestibular dysfunction)
- Scopolamine Patch: Apply to clear area behind the ear every 72 hours (1.5 mg Q72H)
- Side Effects: anticholinergic adverse effects are minimized d/t localized effects with transdermal application

Neurokinin-1 (NK<sub>1</sub>) Receptor Antagonists

- <u>Aprepitant (Cinvanti)</u> PO/IV
  → blocks substance P from binding to NK<sub>1</sub> receptors in vomiting center and CTZ
- Indicated for combination therapy with 5-HT<sub>3</sub> receptor antagonists and corticosteroids for prevention acute and delayed emesis in patients treated with highly-emetogenic chemotherapy agents







#### Selection of Antiemetics by Clinical Situation

Situation	Associated neurotransmitters	Recommended antiemetic
Migraine headache	Dopamine (probably a primary mediator)	For headache and nausea: metoclopramide or prochlorperazine
		For nausea: oral antiemetics, metoclopramide, prochlorperazine, serotonin antagonists
Vestibular nausea	Histamine, acetylcholine	Antihistamines and anticholinergics (equally effective)
Pregnancy-induced nausea	Unknown	For nausea: ginger, vitamin B6
		For hyperemesis gravidarum: promethazine (first-line agent); serotonin antagonists and corticosteroids (second-line agents)
Gastroenteritis	Dopamine, serotonin	First-line agents: dopamine antagonists
		Second-line agents: serotonin antagonists
		Use in children is controversial
Postoperative nausea and vomiting	Dopamine, serotonin	Prevention: serotonin antagonists, droperidol, dexamethasone
		Treatment: dopamine antagonists, serotonin antagonists, dexamethasone

Adapted from: Flake ZA, Scalley RD, Bailey AG. Practical selection of antiemetics. Am Fam Physician 2004; 69:1169.