

Acid Suppression Therapy

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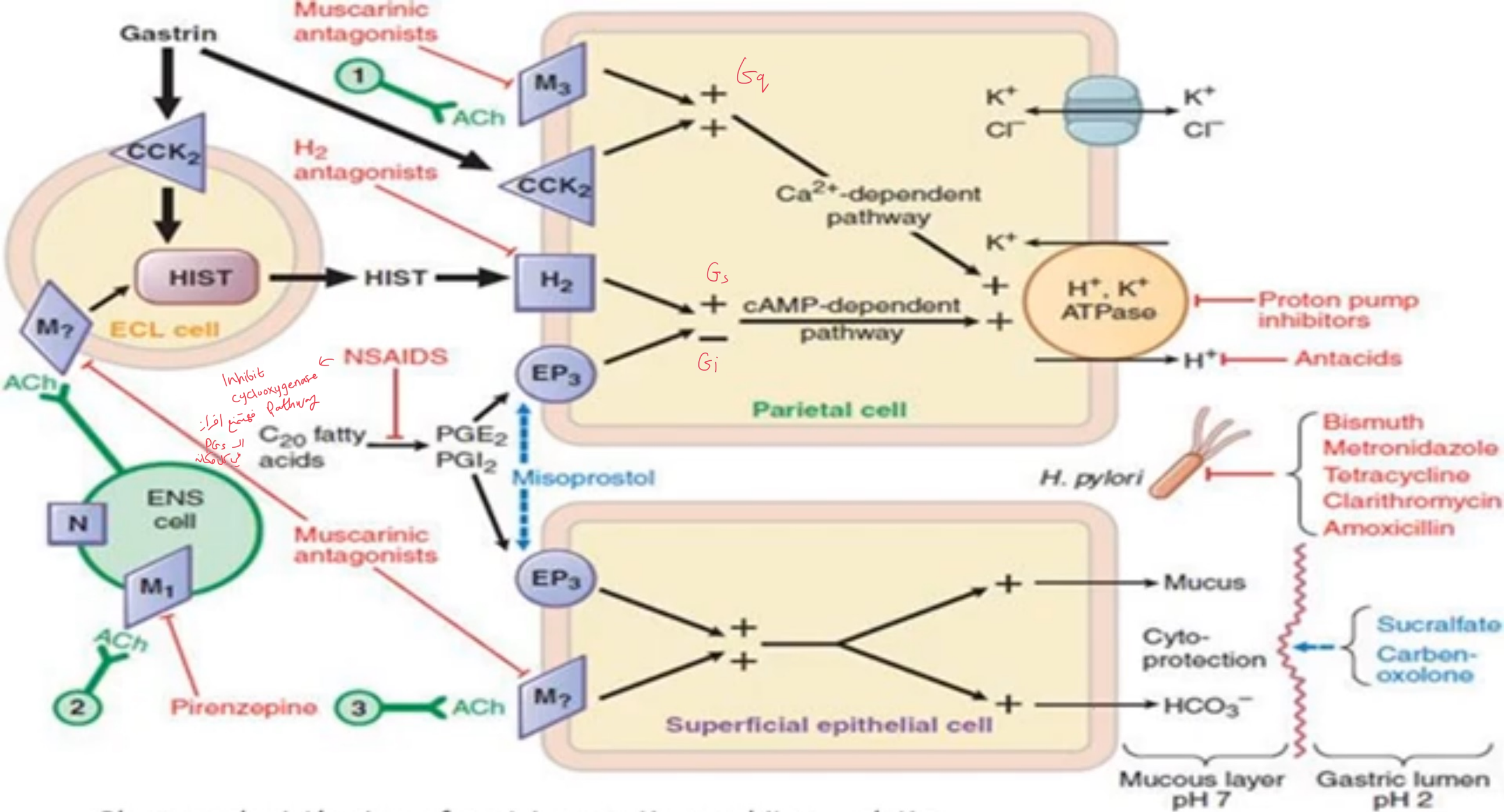
BCPS

Acid Suppression Therapy

- The treatment and prevention of acid-related disorders are accomplished by decreasing gastric acidity and enhancing mucosal defense. The appreciation that an infectious agent,*Helicobacter pylori*, plays a key role in the pathogenesis of acid-peptic diseases has stimulated new approaches to prevention and therapy.
- **PHYSIOLOGY OF GASTRIC SECRETION**
- Gastric acid secretion is a complex and continuous process: neuronal (acetylcholine, ACh), paracrine (histamine), and endocrine (gastrin) factors all regulate the secretion of H^+ by parietal cells



Pharmacologist's view of gastric secretion and its regulation

- Shown are the interactions among an enterochromaffin-like (ECL) cell that secretes histamine, a ganglion cell of the enteric nervous system (ENS), a parietal cell that secretes acid, and a superficial epithelial cell that secretes mucus and bicarbonate. Physiological pathways, shown in solid black, may be stimulatory (+) or inhibitory (–). 1 and 3 indicate possible inputs from postganglionic cholinergic fibers; 2 shows neural input from the vagus nerve. Physiological agonists and their respective membrane receptors include acetylcholine (ACh), muscarinic (M), and nicotinic (N) receptors; gastrin, cholecystokinin receptor 2 (CCK_2); histamine (HIST), H_2 receptor; and prostaglandin E_2 (PGE_2), EP_3receptor. A red indicates targets of pharmacological antagonism. A light blue dashed arrow indicates a drug action that mimics or enhances a physiological pathway. Shown in red are drugs used to treat acid-peptic disorders. NSAIDs are nonsteroidal anti-inflammatory drugs, which can induce ulcers via inhibition of cyclooxygenase.

- Specific receptors (M_3, H_2, and CCK_2, respectively) are on the basolateral membrane of parietal cells in the body and fundus of the stomach. Some of these receptors are also present on *enterochromaffin-like* (ECL) cells, where they regulate the release of histamine. The H_2 receptor is a GPCR that activates the G_s–adenylyl cyclase–cyclic AMP pathway. ACh and gastrin signal through GPCRs that couple to the G_q–PLC-IP_3–Ca^{2+} pathway in parietal cells. In parietal cells, the cyclic AMP and the Ca^{2+}-dependent pathways activate H^+, K^+-ATPase (the proton pump), which exchanges H^+ and K^+ across the parietal cell membrane. This pump generates the largest ion gradient known in vertebrates, with an intracellular pH of ~7.3 and an intracanalicular pH of ~0.8.
- ACh release from postganglionic vagal fibers directly stimulates gastric acid secretion through muscarinic M_3 receptors on the basolateral membrane of parietal cells. The CNS predominantly modulates the activity of the enteric nervous system via ACh, stimulating gastric acid secretion in response to the sight, smell, taste, or anticipation of food (the "cephalic" phase of acid secretion). ACh also indirectly affects parietal cells by increasing the release of histamine from the ECL cells and of gastrin from G cells. ECL cells, the source of gastric histamine, usually are in close proximity to parietal cells. Histamine acts as a paracrine mediator, diffusing from its site of release to nearby parietal cells, where it activates H_2 receptors to stimulate gastric acid secretion.

- *Gastrin*, produced by antral G cells, is the most potent inducer of acid secretion. Multiple pathways stimulate gastrin release, including CNS activation, local distention, and chemical components of the gastric contents. Gastrin stimulates acid secretion indirectly by inducing the release of histamine by ECL cells; a direct effect on parietal cells also plays a lesser role. *Somatostatin* (SST), which is produced by antral D cells, inhibits gastric acid secretion. Acidification of the gastric luminal pH to <3 stimulates SST release, which in turn suppresses gastrin release in a negative feedback loop. SST-producing cells are decreased in patients with *H. pylori* infection, and the consequent reduction of SST's inhibitory effect may contribute to excess gastrin production.

- GASTRIC DEFENSES AGAINST ACID. The extremely high concentration of H^+ in the gastric lumen requires robust defense mechanisms to protect the esophagus and the stomach. The primary esophageal defense is the lower esophageal sphincter, which prevents reflux of acidic gastric contents into the esophagus. The stomach protects itself from acid damage by a number of mechanisms that require adequate mucosal blood flow. One key defense is the secretion of a mucus layer that helps to protect gastric epithelial cells by trapping secreted bicarbonate at the cell surface. Gastric mucus is soluble when secreted but quickly forms an insoluble gel that coats the mucosal surface of the stomach, slows ion diffusion, and prevents mucosal damage by macromolecules such as pepsin. Mucus production is stimulated by prostaglandins E_2 and I_2, which also directly inhibit gastric acid secretion by parietal cells. Thus, drugs that inhibit prostaglandin formation (e.g., NSAIDs, ethanol) decrease mucus secretion and predispose to the development of acid-peptic disease.

Acid Suppression Therapy

- PROTON PUMP INHIBITORS PPIs
- H_2 RECEPTOR ANTAGONISTS H2RAs
- AGENTS THAT ENHANCE MUCOSAL DEFENSE

  1-misoprostol

  2-Sucralfate

  3-Antiacids

PROTON PUMP INHIBITORS PPIs

- Six proton pump inhibitors are available for clinical use: *omeprazole* and its isomer, *esomeprazole* (NEXIUM),*lansoprazole* and its R-enantiomer, *dexlansoprazole*, *rabeprazole*, and *pantoprazole*. All proton pump inhibitors have equivalent efficacy at comparable doses

PROTON PUMP INHIBITORS (PPIs)

- The most potent suppressors of gastric acid secretion are inhibitors of the gastric H^+, K^+-ATPase (proton pump). These drugs diminish the daily production of acid (basal and stimulated) by 80-95%.
- *Activation of **prodrug** proton pump inhibitor*. Omeprazole is converted to a sulfenamide in the acidic secretory canaliculi of the **parietal cell**. The sulfenamide interacts **covalently** with sulfhydryl groups in the proton pump, **thereby irreversibly inhibiting** its activity. Lansoprazole, rabeprazole, and pantoprazole undergo analogous conversions. * لاحظ انه ال PPIs ال absorption تاعها بصير في ال dudenum ← الـ portal vein ← liver ← systemic circulation ← ترجع مرة ثانية للمعدة.
- Proton pump inhibitors (PPIs) are prodrugs that require activation in an acid environment. After absorption into the systemic circulation, the prodrug diffuses into the parietal cells of the stomach and accumulates in the acidic secretory canaliculi

- Acid secretion resumes only after new pump molecules are synthesized and inserted into the luminal membrane, providing a prolonged (up to 24- to 48-h) suppression of acid secretion, despite the much shorter plasma $t_{1/2}$ ~ 0.5-2 h of the parent compounds. ← تأثيره الي اداني اياه في الجسم مازال مستمر Biological half-life: up to 48-h
- Enteric-coated drugs contained inside gelatin capsules, IV
- The FDA-approved dose of intravenous pantoprazole for gastroesophageal reflux disease is 40 mg daily for up to 10 days. Higher doses (e.g., 160-240 mg in divided doses) are used to manage hypersecretory conditions such as the Zollinger-Ellison syndrome.

In upper GI Bleeding

- Loading dose 80mg then infusion 8 mg /hr for 72 hr

- Because an acidic pH in the parietal cell acid canaliculi is required for drug activation and food stimulates acid production, these drugs ideally should be given ~30 min before meals. Concurrent administration of food may reduce somewhat the rate of absorption of PPIs.
- Because not all pumps and all parietal cells are active simultaneously, maximal suppression of acid secretion requires several doses of the PPIs. For example, it may take 2-5 days of therapy with once-daily dosing to achieve the 70% inhibition of proton pumps that is seen at steady state.

- **ADVERSE EFFECTS**

عموماً اي بياخدوا ل short period مش كتير بشكو من ال side effect

- PPIs generally cause remarkably few adverse effects. The most common side effects are nausea, abdominal pain, **constipation, flatulence, and diarrhea**. Subacute myopathy, arthralgias, headaches, and skin rashes also have been reported.

اكتشكية في ال chronic use اي بياخدوه اشهر او سنوات.

- Chronic treatment with omeprazole decreases the absorption of **vitamin B_{12}**, but the clinical relevance of this effect is not clear. Chronic use of PPIs has been reported to be associated with an increased risk of **bone fracture** and with increased susceptibility to certain **infections** (e.g., hospital-acquired pneumonia, community-acquired *Clostridium difficile*). **Hypomagnesemia** is reported.

خاصة عند ال elderly (فوق 65 سنة)

HAP

- Long-term use of proton pump inhibitor (PPI) acid-suppressing agents, such as omeprazole, has been associated with an increased risk of **stomach cancer** (also called gastric cancer). This is based on the results of several observational studies and is thought to be because PPIs such as omeprazole are potent gastric acid suppressants that may increase the risk of gastric cancer by causing atrophy (thinning) of the stomach lining, elevating levels of a hormone called gastrin, and an overgrowth of bacteria in the stomach.

يفضل ما ناخد PPI متواصل فترة طويلة.

لازم حتى الناس اي محتاجه تاخده فترات طويلة انها تقطع، يعني مثلاً ياخد لمدة شهرين واقطع شهر بعدين ارجع مرة تانية خود وهكذا.

- **DRUG INTERACTIONS** omeprazole الحاجة تعرفال
- PPIs are metabolized by hepatic CYPs and therefore may interfere with the elimination of other drugs cleared by this route. PPIs have been observed to interact with **warfarin** (esomeprazole, lansoprazole, omeprazole, and rabeprazole), **diazepam** (esomeprazole and omeprazole), and **cyclosporine** (omeprazole and rabeprazole). Among the PPIs, only **omeprazole inhibits CYP2C19** (thereby decreasing the clearance of disulfiram, phenytoin, **tacrolimus** and other drugs) and induces the expression of CYP1A2 (thereby increasing the clearance of imipramine, several antipsychotic drugs, tacrine, and theophylline). There is emerging evidence that **omeprazole can inhibit conversion of clopidogrel (at the level of CYP2C19) to the active antiplatlets form**. **Pantoprazole** is less likely to result in this interaction; concurrent use of clopidogrel and PPIs (mainly pantoprazole) significantly reduces GI bleeding without increasing adverse cardiac events
- Loss of gastric acidity also may affect the bioavailability of such drugs as **ketoconazole, ampicillin esters, and iron salts**.

H_2 RECEPTOR ANTAGONISTS H2RAs

- The H_2 receptor antagonists inhibit acid production by reversibly competing with histamine for binding to H_2 receptors on the basolateral membrane of parietal cells.
- Four different H_2 receptor antagonists are available in the U.S.: ***cimetidine***, ***ranitidine*** **(ZANTAC)**, ***famotidine***, **and** ***nizatidine***. These drugs are less potent than PPIs but still suppress 24-h gastric acid secretion by ~70%. Because the most important determinant of duodenal ulcer healing is the level of **nocturnal acidity,** evening dosing of H_2 receptor antagonists is adequate therapy in most instances.

drug drug interaction

مش موجود الآن انسحب قبل سنوات طويلة لانه بيعمل

مش موجود الآن انسحب من سنتين

عادة نستخدمها لـ GERD

ممكن لو اخدتها بالليل او كذا ممكن تحسن الاعراض اي تيجي للارتجاع المرئي بالليل.

جدید قبلا
سنتین

- The U.S. Food and Drug Administration today announced it is requesting manufacturers withdraw all prescription and over-the-counter (OTC) ranitidine drugs from the market immediately. This is the latest step in an ongoing investigation of a contaminant known as N-Nitrosodimethylamine (NDMA) in ranitidine medications (commonly known by the brand name Zantac). The agency has determined that the impurity in some ranitidine products increases over time and when stored at higher than room temperatures and may result in consumer exposure to unacceptable levels of this impurity. As a result of this immediate market withdrawal request, ranitidine products will not be available for new or existing prescriptions or OTC use in the U.S.

Pharmacokinetics

- The H_2 receptor antagonists are rapidly absorbed after oral administration, with peak serum concentrations within 1-3 h. Absorption may be **enhanced** by food or decreased by antacids, but these effects probably are unimportant clinically. **Therapeutic** levels are achieved rapidly after intravenous dosing and are maintained for 4-5 h (cimetidine), **6-8 h (ranitidine)**, or 10-12 h (famotidine). Only a small percentage of H_2 receptor antagonists are protein bound. Small amounts (from <10% to ~35%) of these drugs undergo metabolism in the liver, but liver disease per se is not an indication for dose adjustment. **The kidneys excrete** these drugs and their metabolites by filtration and renal tubular secretion, and it is important to **reduce drug** doses in patients with **decreased creatinine clearance**. Neither hemodialysis nor peritoneal dialysis clears significant amounts of these drugs

ADVERSE REACTIONS

في صيدلية امريكية حكت انه الناس اللي فوق 65 سنة ممنوع ياخذوا هاي المجموعة الافضل ياخذو PPI لانه ممكن تسبب الخرف dementia وغيره ..

- Side effects are minor and include diarrhea, headache, drowsiness, fatigue, muscular pain, and constipation. Less common side effects include those affecting the CNS (confusion, delirium, hallucinations, slurred speech, and headaches), which occur primarily with intravenous administration of the drugs or in elderly subjects. Several reports have associated H_2 receptor antagonists with various blood dyscrasias, including thrombocytopenia. H_2 receptor **antagonists cross the placenta and are excreted in breast milk**. Although no major teratogenic risk has been associated with these agents, caution is warranted when they are used in **pregnancy.**

GERD للي عندهم

most safest

PREGNANCY:

ANTIACIDS THEN H2RAs THEN PPIs

DRUG INTERACTIONS

- Drug interactions with H_2 receptor antagonists occur mainly with cimetidine, and its use has decreased markedly. Cimetidine inhibits CYPs (e.g., CYP1A2, CYP2C9, and CYP2D6), and thereby can increase the levels of a variety of drugs that are substrates for these enzymes. Ranitidine also interacts with hepatic CYPs, but with an affinity of only 10% of that of cimetidine. Famotidine and nizatidine are even safer in this regard.

اكتاح في قطاع غزة

TOLERANCE AND REBOUND WITH ACID-SUPPRESSING MEDICATIONS

- Tolerance to the acid-suppressing effects of H_2 receptor antagonists may develop within 3 days of starting treatment and may be resistant to increased doses of the medications. Diminished sensitivity to these drugs may result from the effect of the secondary hypergastrinemia to stimulate histamine release from ECL cells. PPIs do not cause this phenomenon; however, rebound increases in gastric acidity can occur when either of these drug classes is discontinued

في H2 blockers بصوحتا من غير ما تعمل stop

AGENTS THAT ENHANCE MUCOSAL DEFENSE

- **PROSTAGLANDIN ANALOGS: MISOPROSTOL**

لا تقارنه بال PPI

- Prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2) are the major prostaglandins synthesized by the gastric mucosa. Contrary to their cyclic AMP-elevating effects on many cells via EP_2 and EP_4 receptors, these prostanoids bind to the EP_3 receptor on parietal cells and stimulate the G_i pathway, thereby decreasing intracellular cyclic AMP and gastric acid secretion. PGE_2 also can prevent gastric injury by cytoprotective effects that include stimulation of mucin and bicarbonate secretion and increased mucosal blood flow. Acid suppression appears to be the most important effect clinically.

ما بنقدر نستخدمه لعلاج Peptic ulcer لانه full of side effects و untollerated

مثال Severe side effects: Severe diarrhea ، Severe Gastric upset ، لما توصل لل Therapeutic dose من هالدوا بتكون وصلت لكل اعراض حتى المريض ما بيقدر يكمل العلاج من كتر هالاعراض المزعجة untollerated side effects

Sucralfate

- In the presence of acid-induced damage, pepsin-mediated hydrolysis of mucosal proteins contributes to mucosal erosion and ulcerations. This process can be inhibited by **sulfated polysaccharides**. Sucralfate consists of the octasulfate of sucrose to which $Al(OH)_3$ has been added. 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 h after a single dose. In addition to inhibiting hydrolysis of mucosal proteins by pepsin, sucralfate may have additional cytoprotective effects, including **stimulation of local production of prostaglandins and EGF**.

هيكون طبقة
gel like الـ
(Insoluble)

Antiacids

عشان تعادل الحموضة الموجودة بالمعدة

Class	Generic Name	Trade Name
Calcium salts	calcium carbonate	Tums, Rolaids
Sodium bicarbonate		Alka-Seltzer
Aluminum salts	aluminum hydroxide	Amphojel
	aluminum carbonate	Basaljel
Magnesium salts	magnesium hydroxide	Milk of Magnesia
	magnesium oxide	Uro-Mag, Mag-Ox
Combination products	aluminum hydroxide and magnesium hydroxide	Maalox, Mylanta, Gelusil
	alginic acid, magnesium trisilicate, calcium stearate	Gaviscon

SPECIFIC ACID-PEPTIC DISORDERS AND THERAPEUTIC STRATEGIES

- **GASTROESOPHAGEAL REFLUX DISEASE (GERD)**
- **PEPTIC ULCER DISEASE** (PUD)

    1-TREATMENT OF *HELICOBACTER PYLORI* INFECTION.

    2-TREATMENT OF NSAIDs induced ULCER

- **Upper GI bleeding**

GASTROESOPHAGEAL REFLUX DISEASE

- Regimens for the treatment of GERD with PPIs and histamine H_2 receptor antagonists are listed in Table_. Although some patients with mild GERD symptoms may be managed by nocturnal doses of H_2 receptor antagonists, twice-daily dosing usually is required. Antacids are recommended only for the patient with mild, infrequent episodes of heartburn.

DRUG	DOSAGE (twice daily)
H_2 Receptor Antagonists	
Cimetidine	400[a]/800[a] mg
Famotidine	20/40 mg
Nizatidine	150[a]/300[a] mg
Ranitidine	150/300 mg
Proton Pump Inhibitors	
Esomeprazole	20/40 mg daily/40[a] mg
Lansoprazole	30[a]/60[a] mg daily/30[a] mg
Omeprazole	20/40[a] mg daily/20[a] mg
Pantoprazole	40/80[a] mg daily/40[a] mg
Rabeprazole	20/40[a] mg daily/20[a] mg

- Mild cases of GERD during pregnancy should be treated conservatively; antacids or sucralfate are considered the first-line drugs. If symptoms persist, H_2 receptor antagonists can be used, with ranitidine having the most established track record in this setting. PPIs are reserved for women with intractable symptoms or complicated reflux disease. In these situations, lansoprazole is considered the preferred choice.

Peptic ulcer treatment(H.pylori, NSAIDs)

- **Treatment of *H. pylori*–associated ulcers**
- General recommendations, are to include an antisecretory agent (preferably a PPI) plus at least two antibiotics (clarithromycin and amoxicillin or metronidazole) in the eradication regimen.

لو واجه اجابته حرجة باحدة وتشخص لازم نفحص ال #Pylori موجودة ولا لا ؟ الاحسن من ال Stool antigen صفى الدم

وشوف ال History اذا بياخذ NSAIDs .

Regimen	Drugs and doses	Notes
Clarithromycin triple	PPI (standard or double dose) BID + amoxicillin 1000 mg BID or metronidazole 500 mg TID + clarithromycin 500 mg BID for 14 days	Avoid if clarithromycin resistance rate is known to be > 15% or in patients with prior macrolide exposure
Bismuth quadruple	PPI (standard dose) BID + Bismuth subsalicylate 300 mg QID or Bismuth subcitrate 120-300 mg QID + metronidazole 250 QID or 500 mg TID-QID + tetracycline 500 mg QID[d] + PPI BID x 10-14 days	Initial treatment choice if clarithromycin resistance rates are high or patient has prior macrolide exposure
Concomitant	PPI (standard dose) BID + clarithromycin 500 mg BID + amoxicillin 1000 mg BID + metronidazole or tinidazole 500 mg BID for 10-14 days	Appears at least as effective as clarithromycin triple therapy, although not validated in North America
Sequential	PPI (standard dose) BID + amoxicillin 1000 mg BID for 5–7 days; then PPI BID + clarithromycin 500 mg BID + metronidazole or tinidazole 500 mg BID for 5–7 days	Efficacy subject to geographic variation of resistance rates; complexity of regimen makes it less desirable as first line therapy

Hybrid	PPI (standard dose) BID + amoxicillin 1000 mg BID for 7 days; then PPI BID + amoxicillin 1 g BID + clarithromycin 500 mg BID + metronidazole or tinidazole 500 mg BID for 7 days	Regimen not studied in North America; complexity of regimen makes it less desirable as first line therapy
Levofloxacin triple	PPI (standard dose) BID + levofloxacin 500 mg daily + amoxicillin 1000 mg BID for 10–14 days	Lack of North American data; concerns for high levofloxacin resistance rates
Levofloxacin sequential	PPI (standard or double dose) BID + amoxicillin 1000 mg BID for 5-7 days; then PPI BID + amoxicillin 1000 mg BID + levofloxacin 500 mg daily + metronidazole or tinidazole 500 mg BID for 5-7 days	Lack of North American data; may be more effective than levofloxacin triple therapy
LOAD	PPI (double dose) daily + levofloxacin 250 mg daily + metronidazole or tinidazole 500 mg BID + doxycycline 100 mg daily	Lack of North American data; may be more effective than levofloxacin triple therapy

BID = twice daily; PPI = proton pump inhibitor; QID = four times daily; TID = three times daily.

Treatment and secondary prevention of NSAID-induced ulcers

- Discontinue or lower NSAID dose, if possible. Ulcers will heal with appropriate treatment, but healing may take longer with continued NSAID use.
- Test for *H. pylori* and treat, if present.
- Drug therapy

a. PPIs: Drug of choice for healing and secondary prevention of NSAID-induced ulcers

Upper GI bleeding

في اي كالتينه بلاحيا المريض بستفرغ دم
لكنه بقه راحة من الاعراض

* **Management of ulcer-related GI bleeding**

1-Volume resuscitation and hemodynamic stabilization

2-Endoscopic therapy

3-PPI therapy

في الجمعية نفس الاشي

loading

Use of a pre-endoscopic dose (**80-mg intravenous bolus, followed by an 8-mg/hour** intravenous infusion) of PPI may be considered. This does not result in reduced mortality, surgery, or rate of rebleeding

* **Management of acute variceal bleeding**

1-Somatostatin analog: **Octreotide**

2-Preferred agent in combination with endoscopic interventions because of more favorable

3-adverse effect profiles; main adverse effects include hyperglycemia and abdominal cramping

loading

4-Dosing: **50-mcg intravenous bolus, then 50 mcg/hour intravenously** for 3–5 days