Drugs Used in Gastrointestinal disorders
Part 1

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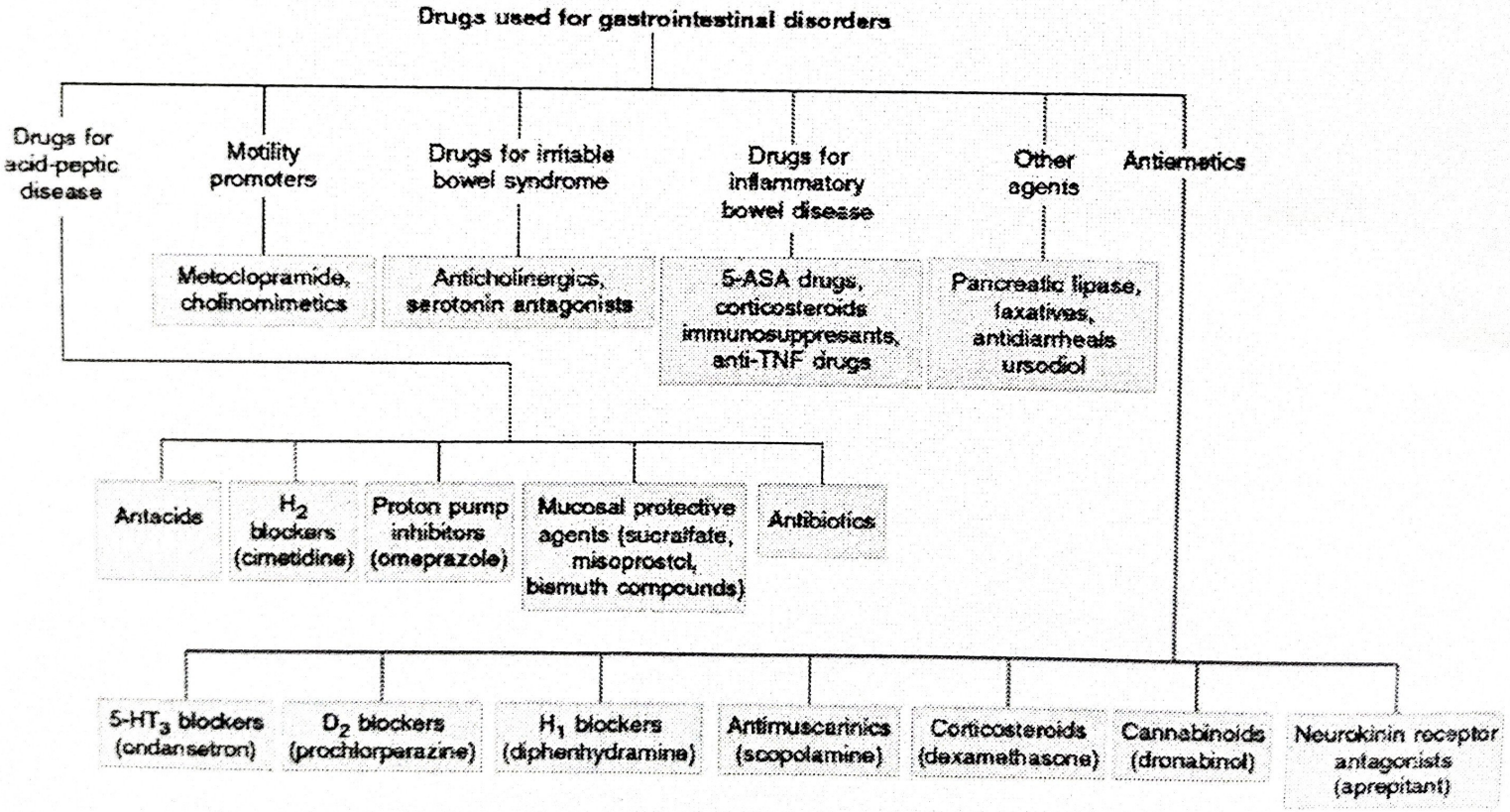
ينحل سكيب وبنوجبل ~



Ulcer هدول بتعملوا (Acid, Pepsin) ومثال عليهم

Protection of GI هدول بتعملوا وإشي يمنع بدنا إياه

Aggressive factor (limit لفيدة) (محدد فقط) > defensive factor

هاد الجرب بيشتركوا بالمسبب ← وهو أنه

A. Acid-Peptic Diseases

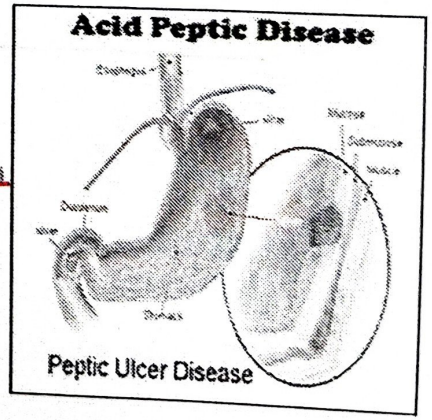
=Ulceration of the GI

GERD
Peptic ulcer
nonUlcer dyspepsia
stress related gastritis

- Acid-peptic diseases are a group of disorders involving erosion or ulceration of the mucosal lining of the gastrointestinal tract; includes:
  1. GERD = gastroesophageal reflux disease.
  2. peptic ulcer (gastric and duodenal ulcers)
  3. nonulcer dyspepsia
  4. stress-related gastritis

إشي بالشرك

- In all these conditions, mucosal erosions or ulceration arise when the caustic effects of aggressive factors (acid, pepsin) overwhelm the defensive factors of the gastrointestinal mucosa (mucus and bicarbonate secretion, prostaglandins).



* هيك عرفنا شو العرض الأول إنو بصيب الـ GI؟ شو سببه؟ شو الأمراض بهاد الجروب؟ وبس

(Acid, Pepsin) Aggressive factor

١- إما بتقلل من ال

٢- " بتزيد من ال defense factor

A. Drugs Used in Acid-Peptic Diseases

- Drugs used in the treatment of acid-peptic disorders may be divided into:

1) Agents that reduce intragastric acidity: (↓ aggressive factor)
   1. Antacids
   2. H2 blockers
   3. proton pump inhibitors

2) Agents that promote mucosal defense (Prostaglandin analogs).
(↑ defensive factor)

3) Or, in the case of peptic ulcers, eradicate the bacterium *Helicobacter pylori.*

(Over 90% of peptic ulcers are caused by infection with the bacterium ① *Helicobacter pylori* or by use of nonsteroidal anti-inflammatory drugs ② (NSAIDs)).

في عدد كبير من الحوالي إذا ما كان مسبب الـ Ulceration هو NSAIDs
و ح يكون السبب هو الـ H.Pylori

②

ال Mechanism of action هون الهم موجة!!

Physiology of acid secretion

Dicyclomine blocks the cholinergic receptor. | Cimetidine blocks the H_2 histamine receptor | Misoprostol stimulates the ...

① PPI :- بيمنع دخول ال HCL باتجاه ال lumen of stomach عن طريق ال Proton Pump.

② في مجموعة signal بتحفز ال Proton Pump وبتنظم ال secretion of HCl

Ⓐ Acetylcholine :- وقت يرتبط بال receptor تبعه بال Parietal cell ح يحفز إفراز ال HCL فبنعطي Acetyl cholin Antagonist

أي Dicyclamine مثل cholinergic receptor antagonist

Ⓑ Histamin :- وقت يرتبط بال receptor ح تحفز ال Protein Kinase حتى تنتج HCL

و بنعطي بهاي الحالة H2-blocker مثل ال cimetidine.

Ⓒ Prostaglandin :- لما يرتبط بال receptor ح يعمل inhibition لإفراز ال HCL

فهون بنعطي إشي يعمله stimulation

لأنها تعتبر defensive factor

مثل Misoprostol

(1) weak base + HCL → salt + H2O

(2) pH ارتفاع ال ... inactivation of Pepsin

Antacids

- Antacids are weak bases that react with gastric hydrochloric acid to form a salt and water.
- Their principal mechanism of action is reduction of intragastric acidity.
- Because pepsin (a proteolytic enzyme) is inactive at a pH greater than 4, antacids also reduce pepsin activity.
- The efficacy of an antacid depends on its capacity to neutralize gastric HCl and on whether the stomach is full or empty (food delays stomach emptying allowing more time for the antacid to react).

- They include:
  1. Sodium bicarbonate
  2. Calcium carbonate
  3. Magnesium hydroxide
  4. Aluminum hydroxide

* فعالية الدوا مرتبطة بأنه قديش قدر أعمل neutralize of gastric HCL
efficacy لكن وكمان أحصل على أعلى
لازم ناخذه بعد الأكل على معدة full!
ليش؟ حتى يظل هالدواء أطول
(حيض ال Antacid بالمعدة أكثر)

Antacids

gastric distention → belching

fluid retention →

1. **Sodium bicarbonate** [NaHCO3] + HCL → carbon dioxide + Sodium Chloride

- Reacts rapidly with hydrochloric acid (HCL) to produce carbon dioxide and sodium chloride.

1. Formation of carbon dioxide results in gastric distention and belching. (انتفاخ — تجشؤ)

2. **Unreacted alkali** is readily absorbed, potentially causing metabolic alkalosis when given in high doses or to patients with renal insufficiency.

3. Sodium chloride absorption may exacerbate fluid retention in patients with heart failure, hypertension, and renal insufficiency.

- This antacid is not recommended for long-term use.

إذا كان عندك مريض ١- عنده renal insufficiency ٢- أعطه جرعات عالية منه ← ح يصير امتصاص لـ unreacted alkali ← Metabolic Alkalosis

Antacids

② **Calcium carbonate** + HCL → carbon dioxide + calcium chloride

- is less soluble and reacts more slowly than sodium bicarbonate with HCl to form carbon dioxide and calcium chloride (CaCl2). ميزته ده

- Like sodium bicarbonate, calcium carbonate may cause ① belching or ② metabolic alkalosis.

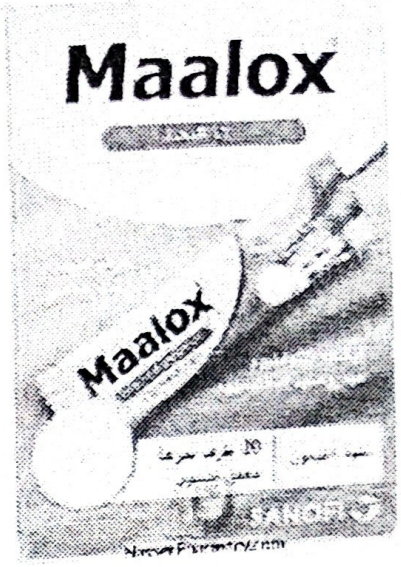
بتشابه مع الأعراض بس ما رح يعمل fluid retension لأنه ما فيه صوديوم

- Excessive doses of either sodium bicarbonate or calcium carbonate with calcium-containing dairy products can lead to hypercalcemia, renal insufficiency, and metabolic alkalosis (milk-alkali syndrome).

لو شخص كان بياخذ sodium bicarbonate أو calcium carbonate وبنفس الوقت بياخذ منتجات فيها كالسيوم مش الحليب ← بنسميها Milk-Alkali syndrome وأعراضها :-

① hypercalcemia ② renal insufficiency ③ Metabolic Alkalosis

Antacids



- **Magnesium hydroxide** or **aluminum hydroxide**
  - React slowly with HCl to form magnesium chloride or aluminum chloride and water.
  - Because no gas is generated, belching does not occur.
  - Metabolic alkalosis is also uncommon because of the efficiency of the neutralization reaction.
  - Because unabsorbed magnesium salts may cause an osmotic diarrhea and aluminum salts may cause constipation, these agents are commonly administered together in branded formulations (eg, Gelusil, Maalox, Mylanta) to minimize the impact on bowel function.
  - Both magnesium and aluminum are absorbed and excreted by the kidneys. Hence, patients with renal insufficiency should not take these agents long-term.

* contrainelication for renal insufficiency patient.

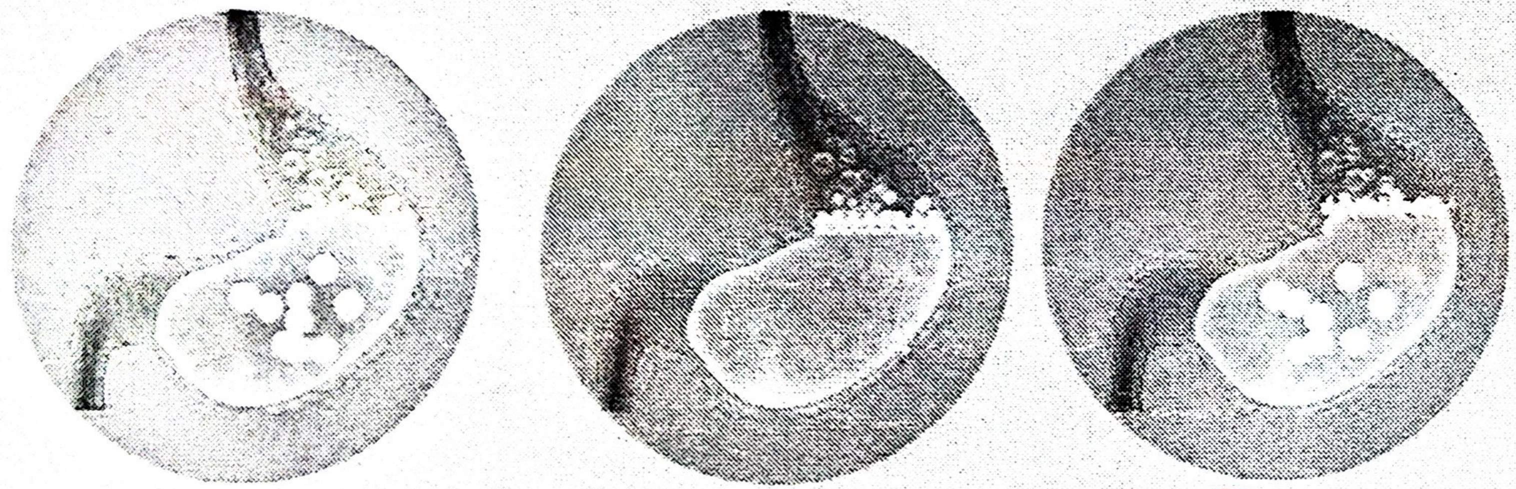
Neutralized with gastric HCL

Alginic acid/antacid

تركيبته :-

له بشكل raft
تطفو على سطح محتويات المعدة
فبتمنع انه يطلع هاد ال acid لل esophagous وبعمل heart burn او "GERD"

لينمضغ كان وجبتها مع الطعام



Antacids work by counteracting, or neutralising, any excess stomach acid

Alginates form a 'raft' that floats on top of stomach contents

Combo products contain an antacid & a raft-forming alginate = Gaviscon

H2- receptor antagonists

extra side effect ← قل استخدامه لإنه كنت

- Four H2 antagonists are in clinical use: **cimetidine, ranitidine, famotidine,** and **nizatidine.**
- From their introduction in the 1970s until the early 1990s, H2-receptor antagonists (commonly referred to as H2 blockers) were the most commonly prescribed drugs in the world.
- With the recognition of the role of *H pylori* in ulcer disease (which may be treated with appropriate antibacterial therapy) and the advent of proton pump inhibitors, the use of prescription H2 blockers has declined markedly. H2 blocker قل استخدام ال PPI بعد ما تم اكتشاف ال
- However, the over-the-counter preparations of the H2 antagonists are heavily used by the public. OTC

H2- receptor antagonists

cimetidine: AE → antiandrogenic effect / → prolactin-stimulating " / → inhibition of CYP450

Adverse effects and drug interactions:

- In general, the H2 antagonists are well tolerated.
- The other agents do not produce the antiandrogenic (1) and (2) prolactin-stimulating effects of cimetidine.
- Cimetidine inhibits several cytochrome P450 (3) isoenzymes and can interfere with the metabolism of many other drugs, such as warfarin, phenytoin, and clopidogrel. interaction with cimetidine
- All H2 antagonists may reduce the efficacy of drugs that require an acidic environment for absorption, such as ketoconazole. anti fungal

→ هاي سايد افيكت مشتركة بين كلهم ال H2 blocker

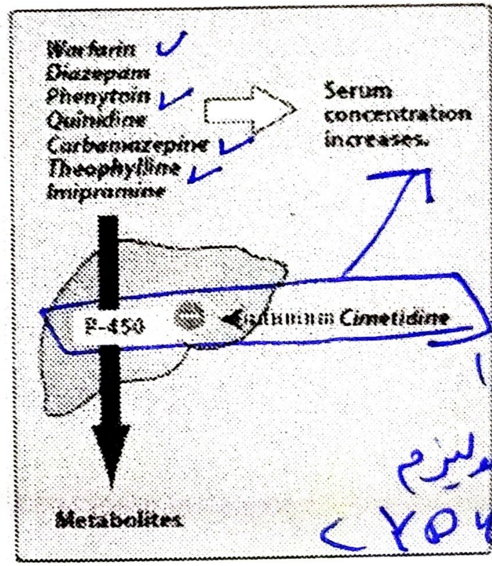


Figure 31.5
Drug interactions with cimetidine.

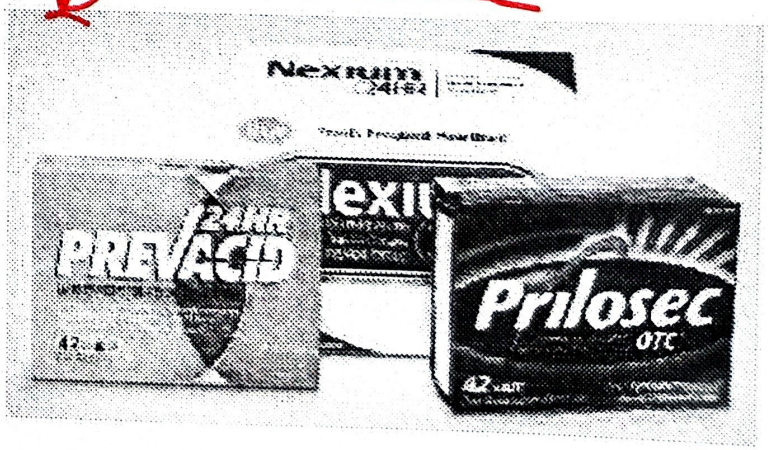
ح يزيد تركيز اي دوا بصير له ميتابوليزم بواسطة ال CYP450

aggressive factor اخر كلاس رح يشتغل على تقليل الـ

Proton Pump Inhibitors

- Since their introduction in the late 1980s, these efficacious acid inhibitory agents have assumed the major role for the treatment of acid-peptic disorders.
- Proton pump inhibitors (PPIs) are now among the most widely prescribed drugs worldwide due to their outstanding efficacy and safety.
- Six proton pump inhibitors are available for clinical use: **omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole,** and **pantoprazole.**
- All are available in oral formulations. Esomeprazole and pantoprazole are also available in intravenous formulations.

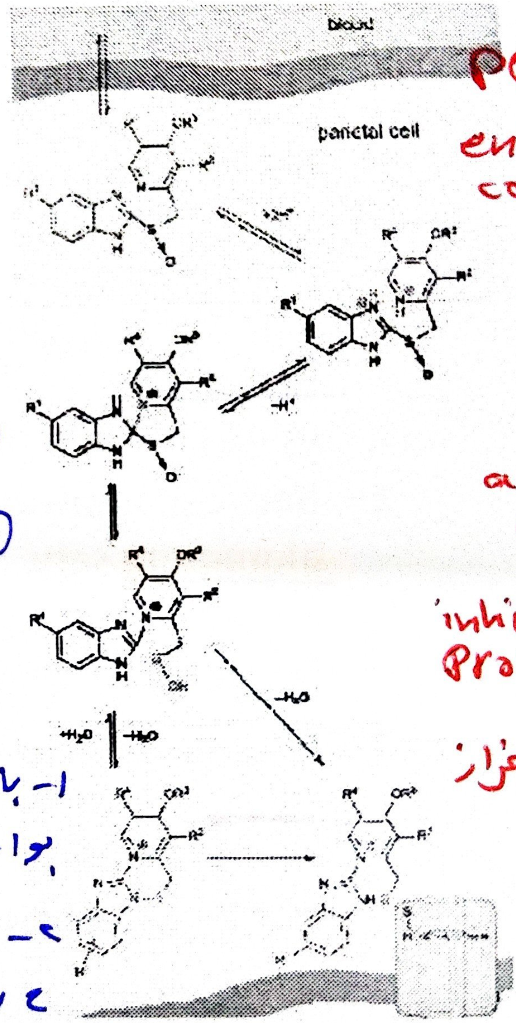
esomeprazole
Pantoprazole + oral



MOA

Proton Pump Inhibitors

- Proton pump inhibitors are administered as inactive prodrugs.
- Oral formulations of these drugs are enteric coated to prevent acid inactivation in the stomach. ①
- PPIs are lipophilic weak bases that diffuse into the parietal cell, where they become protonated and ② concentrated more than 1000-fold. There they undergo conversion to compounds that irreversibly ③ inactivate the parietal cell H+/K+ ATPase, the transporter that is primarily responsible for producing stomach acid.



PPI
enteric coated الدوا
↓
دخل جوا الـ Parietel cell
↓
active form صار هون
↓
inhibition of Proton pump
↓
ما حيصير إفراز للـ HCl

١- بأخدهم على شكل enteric coated لحتى ما يصير لهم inactivation بواسطة عصارة المعدة

٢- بدخلوا لداخل الـ Parietel cell وبشكل irreversible ع يعملوا تثبيط للـ Proton pump المسؤولة عن ضخ الـ HCl

بجوا الخلية ٥ ميزاتهم ← ١- lipophilic ٢- weak base

وبعد دخولهم للخلية بصيروا protonated.

Proton Pump Inhibitors

- All of these agents are effective orally.
- For maximum effect, PPIs should be taken 30 to 60 minutes before breakfast or the largest meal of the day. so that the peak serum concentration coincides with the maximal activity of proton pump secretion.
  - In a fasting state, only 10% of proton pumps are actively secreting acid and susceptible to inhibition.
- **Dexlansoprazole** has a dual delayed release formulation and can be taken without regard to food.

① ②

تركيبة متطورة وما بتتأثر بالأكل وبرّها delyeed release.

* إذا اخذنا الـ PPI على معدة فاضية بحالة الصيام بكون ما حتعطينا أكتر من ١٠٪ من الـ effect تبعها
* بينما إذا حدّ كان أكل بعد بعض ساعة وهاد رح يشتغل عليه و يعطونا أعلى efficacy.

Proton Pump Inhibitors

- The drugs have a short serum half-life of about 1.5 hours, but acid inhibition lasts up to 24 hours owing to the irreversible inactivation of the proton pump.
- At least 18 hours are required for synthesis of new H + /K + -ATPase pump molecules.
  - Because not all proton pumps are inactivated with the first dose of medication, up to 3–4 days of daily medication are required before the full acid inhibiting potential is reached.

- From a pharmacokinetic perspective, proton pump inhibitors are ideal drugs:

1. they have a short serum half-life (1,5 h)
2. they are concentrated and activated near their site of action
3. they have a long duration of action.

ليش تعتبر ideal؟

مش كلهم بقدروا يتعاملوا مع أول جرعة من proton pump لـ inactivation

لهيك بنحتاج لـ ٣ أو ٤ أيام لحتى نحصل كامل effect

(5)

Proton Pump Inhibitors

- **Adverse effects and drug interactions:**
- Adverse effects of proton pump inhibitors occur infrequently and include diarrhea, abdominal pain, and headache. (1) (2) (3)
- Proton pump inhibitors may decrease the oral bioavailability of vitamin B12 and certain drugs that require acidity for their gastrointestinal absorption (eg, digoxin, ketoconazole). drugs - drug interaction.
- The FDA has issued a warning about a potentially important adverse interaction between clopidogrel and PPIs.
  - Clopidogrel is a prodrug that requires activation by the hepatic P450 CYP2C19 isoenzyme, which also is involved to varying degrees in the metabolism of proton pump inhibitors (especially omeprazole, esomeprazole, lansoprazole, and dexlansoprazole).
  - Thus, proton pump inhibitors could reduce clopidogrel activation (and its antiplatelet action) in some patients.

بقلل امتصاص B12 + الحديد
acidity بتحتاج
حتى يصير سهل امتصاصها

خطرين اعطي البنج سوا

activation of clopidogrel ← CYP450 انزيم بتحتاج
metabolism of PPI ←

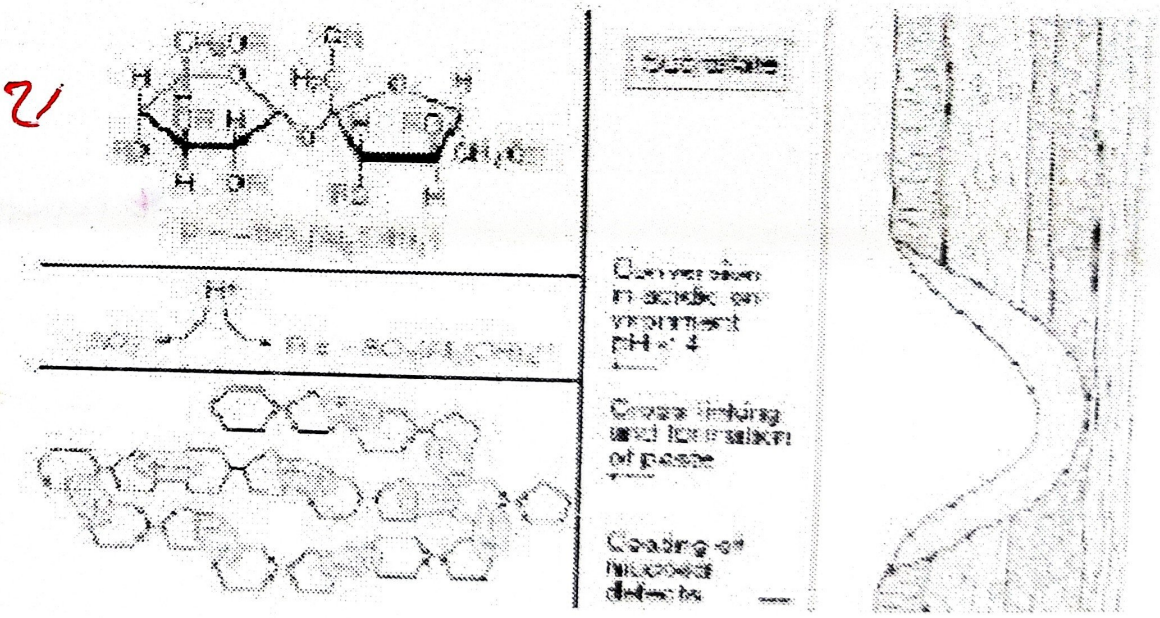
Mucosal Protective Agents

1. Sucralfate
2. Misoprostol
3. Bismuth compounds

معون حنستخدمهم
لحتى نزيد من ال
defense factor
(Prostaglandin
analoug)

Sucralfate

- **Sucralfate** is a salt of sucrose complexed to sulfated aluminum hydroxide.
- It polymerizes in the acid environment of the stomach.
- By forming complex gels with epithelial cells, sucralfate creates a physical barrier that protects the ulcer from pepsin and acid, allowing the ulcer to heal.



Sucralfate mechanism of action

PPI + H2 blocker + Antacied → increased of PH
→ sucralfate → need low PH for activation.

Sucralfate

لأن الدواء بتعارض مع بعض

- Sucralfate must be taken 4 times daily on an empty stomach (at least 1 hour before meals).
- Because it requires an acidic pH for activation, *sucralfate* should not be administered with PPIs, H2 antagonists, or antacids.

هاد الادوية ع ترفع ال pH

- Sucralfate is too insoluble to have significant systemic effects when taken by the oral route; toxicity is very low.

- Limitations of sucralfate include:
  - the need for multiple daily dosing (< 4 time daily)
  - large tablet size صعوبة بالبلع
  - interaction with a number of other medications (eg, digoxin and fluoroquinolones). drug - drug interaction.

Prostaglandin analog
Misoprostol

وظيفته:

- Prostaglandin E, produced by the gastric mucosa, inhibits secretion of acid and stimulates secretion of mucus and bicarbonate (cytoprotective effect). defensive factor
- An analog of PGE1, **misoprostol** increases mucosal protection [1] and inhibits acid secretion. [2]

متى يكون؟

- Prophylactic use of misoprostol should be considered in patients who are taking NSAIDs and are at moderate to high risk of NSAID-induced ulcers, such as elderly patients and those with previous ulcers.

شخص بياخذ NSAIDs ومعرض للإصابة بالقرحة بسببها.

- Misoprostol is contraindicated in pregnancy, since it can stimulate uterine contractions and cause miscarriage. → Abortion يمكن يعمل

- Dose-related diarrhea [1] and nausea [2] are the most common adverse effects and limit the use of this agent. Thus, PPIs are preferred agents for the prevention of NSAID-induced ulcers.

سايد افيكت

إذا شخص بياخذ NSAIDs ومعرض لـ ulcer → لازم ياخذ PPI

Bismuth Compounds

- Two bismuth compounds are available:
  1. **Bismuth subsalicylate**
  2. **Bismuth subcitrate potassium.**

- Bismuth subsalicylate undergoes rapid dissociation within the stomach, allowing absorption of salicylate.

- Over 99% of the bismuth appears in the stool. excretion .

لهيك أي شخص عنده مشاكل من
المعدة ما بعطيه salicylates!
Bismuth sub salicylate
لأنه بيتكسر بالمعدة ويعطيني
salicylate.

Ulcer
diarrhea
H. pylori

Bismuth Compounds

MOA

- The precise mechanisms of action of bismuth are unknown.

sucralfate

1. Bismuth coats ulcers and erosions, creating a protective layer against acid and pepsin.

Misoprostol

2. It also stimulate prostaglandin, mucus, and bicarbonate secretion. (defensive factor)
3. Bismuth subsalicylate reduces stool frequency and liquidity in acute infectious diarrhea.
4. Bismuth has direct antimicrobial effects and binds enterotoxins, accounting for its benefit in preventing and treating traveler's diarrhea.
5. Bismuth compounds have direct antimicrobial activity against *H pylori.*

Bismuth Compounds

Adverse Effects

- All bismuth formulations have excellent safety profiles.

1. Bismuth causes **harmless blackening of the stool**, which may be confused with gastrointestinal bleeding.
2. **Liquid** formulations may cause **harmless darkening of the tongue.**

لونه غامق وا

blacking of the stool بشخصون إنه عادة وجود ال

GI bleeding ، لكن لحالما المريض بياخد bismuth فـ هو

ح يكون السبب هدول

Antibiotics

- Chronic infection with *H pylori* is present in most patients with recurrent non-NSAID-induced peptic ulcers.
- Eradication of this organism greatly reduces the rate of recurrence of ulcer in these patients.

- One regimen of choice "**triple therapy**" consists of:
  1. A proton pump inhibitor
  2. A course of clarithromycin
  3. A course of amoxicillin (or metronidazole in patients with penicillin allergy) twice daily for 14 days.

- Bismuth-based **quadruple therapies** are commonly used as second-line therapies (PPI+ bismuth subsalicylate or subcitrate+ tetracyclin+ metronidazole)

Triple therapy of H. pylori => PPI + clarithromycin + Amoxicillin (or Metro)

Three-drug regimen

Table 18–2

Drug Regimens to Eradicate *Helicobacter pylori*[a]

Treatment Regimen	Cure Rates
First Line: Three Drugs[b]	
Daily for 10 days: bismuth 300 mg + tetracycline 500 mg + metronidazole 500 mg, each given four times daily, + omeprazole 20 mg each given twice daily	Good to excellent
Daily for 10 days: clarithromycin 500 mg + amoxicillin 1 g + omeprazole 20 mg each given twice daily	Good to excellent

بتجنب استخدامهم:-

- Amoxicillin should not be used in penicillin-allergic patients
- Metronidazole should be avoided if alcohol is going to be consumed (disulfiram-like reaction).
- A single daily PPI dose is less effective than twice-daily dosing when used in a triple-drug regimen.
- Substitution of one PPI for another is acceptable and does not affect eradication rates.

العلاج الثلاثي أقل
بإضافة كرة مرتين باليوم

استبدال ال PPI (تركيبة بتركيبة أخرى من نفس ال PPI)
عادي ما فيا شر

Four-drug regimen

- Bismuth-based four-drug regimens have clinical cure rates similar to three-drug PPI-based regimens.
- Disadvantages of bismuth-based regimens include frequency of administration (four times a day), risk for salicylate toxicity in renal impairment, and bothersome side effects (eg, stool and tongue discoloration, constipation, nausea, vomiting).
- Therefore, bismuth-based quadruple therapy is usually considered second-line treatment.

First Line: Four Drugs	
Pylera® (bismuth subcitrate potassium 140 mg + metronidazole 125 mg + tetracycline 125 mg) three capsules two times daily + omeprazole 20 mg twice daily x 10 days	Good to excellent

بالعلاج الثلاثي مرتين باليوم

" الرباعي مرة باليوم

Metronidazole

Anti protozoal
Anti bacterial

- **Antiprotozoal** drug that also has potent **antibacterial** activity.
- Metronidazole is indicated for treatment of:

1. **anaerobic** or mixed intra-abdominal infections
2. vaginitis (trichomonas infection, bacterial vaginosis)
3. *Clostridium difficile* infection
4. brain abscess.

- Adverse effects include nausea, headache, dry mouth and a metallic taste in the mouth occur commonly. Peripheral neuropathy with prolonged use
- Dark brown urine discoloration has also been documented

Figure 43.3
Adverse effects of metronidazole

- Metronidazole has a disulfiram-like effect, and patients should be instructed to avoid alcohol.

Metronidazol + Alcohol → disulfiram-like effect.

B. Drugs That Promote Upper Gastrointestinal Motility

وظيفتها

- Drugs that can selectively stimulate gut motor function (**prokinetic** agents) have significant potential clinical usefulness.

تزيد ال gi motility

✓ Agents that increase lower esophageal sphincter pressures may be useful for **GERD**.

✓ Drugs that improve gastric emptying may be helpful for

① **gastroparesis** and **postsurgical gastric emptying delay**.②

– Gastroparesis: Paralysis of the muscles of the stomach and possibly other parts of the gastrointestinal tract due to damage to gastrointestinal nerves or muscle; common in advanced diabetes and advanced Parkinson's disease.

urokinin receptor
antagonists
(aprepitant)

B. Drugs That Promote Upper Gastrointestinal Motility

1. Cholinomimetic agents
2. Metoclopramide and domperidone
3. Macrolide antibiotics

① Cholinomimetic agents

كان استخدامهم زمان

- In the past, cholinomimetic agonists such as **bethanechol** (A) were used for GERD and gastroparesis, but the availability of less toxic agents has supplanted their use.

استخدام

- The acetylcholinesterase inhibitor **neostigmine** (B) is still used for the treatment of hospitalized patients with acute large bowel distention.

استخدام

- Cholinergic side effects include excessive salivation (1), nausea (2), vomiting, diarrhea (4), and bradycardia (5).

(3)

Metoclopramide and Domperidone

- Metoclopramide and domperidone are dopamine D2 receptor antagonists.
- Within the gastrointestinal tract activation of dopamine receptors inhibits cholinergic smooth muscle stimulation; blockade of this effect is believed to be the primary prokinetic mechanism of action of these agents.
- Metoclopramide and domperidone also block dopamine D2 receptors in the chemoreceptor trigger zone of the medulla, resulting in potent anti-nausea and anti-emetic action.
- When used chronically, metoclopramide can cause symptoms of parkinsonism, other extrapyramidal effects, and hyperprolactinemia.
- Domperidone is less likely to cause CNS toxicity, because it does not cross the blood-brain barrier.

Meto

- Clinical u

1. Gastroe
2. Impaire
3. Nonulc
4. Prevent
5. Postpar

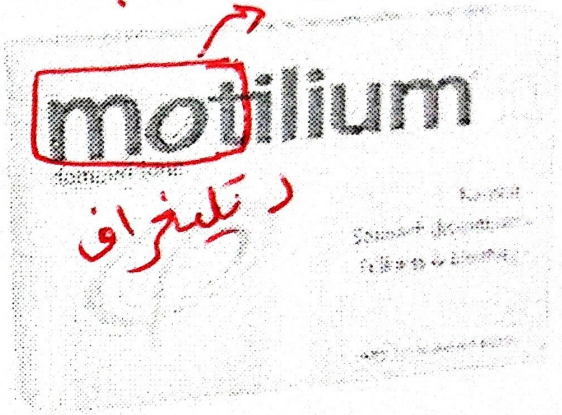
Metoclopramide and Domperidone

- **Clinical uses:**

1. Gastroesophageal reflux disease GERD
2. Impaired gastric emptying
3. Nonulcer dyspepsia
4. Prevention of vomiting
5. Postpartum lactation stimulation → due to hyperprolactinemia

Metoclopramide and Domperidone

Domperidone use is associated with an increased risk of sudden cardiac death



Contraindications

Domperidone is now contraindicated in people:

1. with conditions where cardiac conduction is, or could be, impaired
2. with underlying cardiac diseases such as congestive heart failure
3. receiving other medications known to prolong QT interval or potent CYP3A4 inhibitors (azole antifungals, macrolides antibiotics, grapefruit juice)
4. with severe hepatic impairment

Macrolides

- Macrolide antibiotics such as **erythromycin** directly stimulate motilin receptors on gastrointestinal smooth muscle.
  - **Motilin receptor** is a G protein-coupled receptor that binds motilin. Motilin in turn is an intestinal peptide that stimulates contraction of gut smooth muscle.

- Intravenous erythromycin (3 mg/kg) is beneficial in some patients with gastroparesis; however, tolerance rapidly develops.

Artery Academy

Done By Mariam Yacoub