The GI System

Pharmacology

☑ Sheet ☐ Slide ☐ Handout

Number: 3

Subject: Antidiahreal, Antiematic **Pancreatic Enzyme Supplements & Bile Acid Therapy for Gallstones**

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Price: .....

The sheet is a copy from the slide. However here it is more comprehensive, colorful & some notes were mentioned..

Antidiarrheal Agents

Should not be used in patients with bloody diarrhea, high fever, or systemic toxicity because of the risk of worsening the underlying condition.

Used to control chronic diarrhea caused by irritable bowel syndrome (IBS) or inflammatory bowel disease.

(I) Opioid Agonists (Loperamide, Diphenoxylate)

- ✓ Increase colonic transit time and fecal water absorption.
- ✓ They also decrease mass colonic movements
- ✓ CNS effects and potential for addiction limit the usefulness of most.

<u>Loperamide</u>

Does not cross BBB, so No analgesic or addiction potential.

<u>Diphenoxylate</u>

Not analgesic in standard doses.

Higher doses have CNS effects.

Can cause dependence.

Commercial preparations contain atropine (Lamotil).

Each Lomotil tablet contains: diphenoxylate hydrochloride 2.5 mg atropine sulfate 0.025 mg which contribute to the antidiarrheal action.

N

(II) Bile Salt-Binding Resins

How does these work as anti-diarrheal agents ?

Malabsorption of bile salts cause diarrhea so these compounds bind to certain components of bile in the gastrointestinal tract. They disrupt the enterohepatic circulation of bile acids by combining with bile constituents and preventing their reabsorption from the gut.They are used in the treatment of chronic diarrhea due to bile acid malabsorption.

Include:

- Cholestyramine
- Colestipol
- Colesevelam

What's a Resin?a sticky flammable organic substance, insoluble in water, exuded by some trees and other plants .

Here is the rule :

Malabsorption of bile salts cause diarrhea.

(Crohn's disease or after surgical resection),

These drugs bind bile salts and decrease diarrhea

caused by excess fecal bile acids.

Can cause bloating, flatulence(نفخة), constipation and fecal impaction.
*((fecal impaction : is a solid, immobile bulk of human feces that can develop in the rectum as a result of chronic constipation))

Cholestyramine and colestipol reduce absorption of drugs and fat, but Colesevelam does not.

(III) Octreotide:

(mimic Somatostatin –SS-)

Carcinoid:

is a slow-growing type of neuro-endocrine tumor

Wiki:

VIPoma: A pancreatic neuroendocrine tumor which secretes vasoactive intestinal peptide (VIP)

Synthetic octapeptide (consist of 10 peptides) with actions similar to somatostatin.
It has a longer half life than SS,
think of SS as an Inhibitory peptide .

<u>Clinical Uses</u>

-Inhibition of Endocrine Tumor Effects. (carcinoid, VIPoma*) that cause secretory diarrhea and systemic symptoms such as flushing and wheezing.

-Octreotide decreases secretory diarrhea and systemic symptoms through inhibition of hormonal secretion and may slow tumor progression.

-Octreotide inhibits intestinal secretion and has dose-related effects on bowel motility. In low doses it stimulates motility, whereas at higher doses it inhibits motility.

-Octreotide is effective in **higher doses** for the treatment of diarrhea due to:

1. vagotomy (when u remove the vagus innervation among the stomach)
2. dumping syndrome (when the stomach empty its contents very fast)
3. diarrhea caused by short bowel syndrome or AIDS.

-Octreotide used in **low doses** to stimulate small bowel motility in patients with small bowel bacterial overgrowth or intestinal pseudo-obstruction secondary to scleroderma. (pseudo-obstruction: when there's no real obstruction , but there's no peristaltic movement//scleroderma : sclerosis of the skin but it is systemic >>with GI involvement)

Other Uses

-Because it inhibits pancreatic secretion, octreotide may be of value in patients with pancreatic fistula (when there's a leakage of pancreatic enzymes)

-used in the treatment of pituitary tumors (acromegaly)

Octreotide is sometimes used in gastrointestinal bleeding to reduce portal venous pressures (reduce blood flow)

Adverse Effects

1. Impaired pancreatic secretion may cause **steatorrhea**, leading to **fat-soluble vitamin deficiency**. Loss of bile acids , cause diarrhea!
2. Alterations in gastrointestinal motility cause nausea, abdominal pain, flatulence, and diarrhea. (It's anti diarrheal but one of the side effects is diarrhea)
3. long-term use of octreotide can cause formation of sludge or gallstones in over 50% of patients.
4. octreotide alters the balance among insulin, glucagon, and growth hormone, hyperglycemia or, less frequently, hypoglycemia (usually mild) can occur.
5. Prolonged treatment with octreotide may result in hypothyroidism.
6. Octreotide also can cause bradycardia.

IBS

Drugs Used in the Treatment of Irritable Bowel Syndrome(IBS)

IBS is an idiopathic chronic, relapsing disorder characterized

by: Abdominal discomfort pain, bloating, distention, or cramps with alterations in bowel habits diarrhea, constipation, or both.

There are no drugs to diminish IBS, we treat the symptoms.

Pharmacologic therapies for IBS are directed at relieving abdominal pain and discomfort and improving bowel function.

Antispasmodics (Anticholinergics) for (IBS)

Dicyclomine and Hyoscyamine .

Block muscarinic receptors in the enteric plexus and on smooth muscle.

Their efficacy for relief of abdominal symptoms has never been convincingly demonstrated. (not used frequently)

Low doses cause minimal autonomic effects.

Higher doses cause anticholinergic effects, including dry mouth, visual disturbances, urinary retention, and constipation.

For these reasons, antispasmodics are infrequently used.

Alosetron

anti-diarrheal for IBS

Potent & selective antagonist of the 5-HT3 receptor.
(5-hydroxytryptamine, or serotonin receptor , recall what serotonin does when is that it stimulate afferent fibers that cause nausea vomiting & diarrhea as reflex of pre-stretching of the stomach wall)

Rapidly absorbed, half-life of 1.5 hours (short half life) but has a much longer duration of effect(more than 1.5 hours).

Alosetron is restricted to women with severe diarrhea-predominant IBS not responding to conventional therapies.

Its efficacy in men has not been established.

Prucalopride (anti-constipation in IBS)

High-affinity 5-HT4 agonist. No cardiovascular toxicity

Used for the treatment of chronic constipation in women.
(these receptor are pre-synapsing receptor stimulating it will stimulate the enteric system to decrease the GIT activity >>treat constipation
what this drug really does >> that it targets the impaired motility associated with chronic constipation, thus normalizing bowel movements)

Chloride Channel Activator (Anti-consipitation)

PG stimulate chloride channels ,

Chloride channels are critical to the digestive process because they promote

fluid to release into the intestines.

Lubiprostone is PG analog stimulates type 2 chloride channel (ClC-2)

in the small intestine & this increases liquid secretion in the

intestine which stimulates intestinal motility & bowel movement within 24 hours of taking one dose.

Used in the treatment of chronic constipation.

Approved for the treatment of women with IBS with predominant constipation.

Its efficacy for men with IBS is unproven.

Should be avoided in women of child-bearing age.

Causes nausea (30%) due to delayed gastric emptying.

Antiemetic Agents

Antiemetic=drug that prevent vomiting

Nausea and vomiting may be manifestations of a wide variety of conditions, including:

- ✓ Adverse effects of medications.
- ✓ systemic disorders or infections.
- ✓ Pregnancy.
- ✓ Vestibular dysfunction.
- ✓ CNS infection or increased pressure.
- ✓ Peritonitis.
- ✓ Hepatobiliary disorders.
- ✓ Radiation or chemotherapy.
- ✓ GIT obstruction, dysmotility, or infections.

Pathophysiology (indicated in the figure below)

The brainstem "**vomiting center**" coordinates vomiting through interactions with cranial nerves VIII and X and neural networks in the nucleus tractus solitarius that control respiratory, salivatory, and vasomotor Centers.

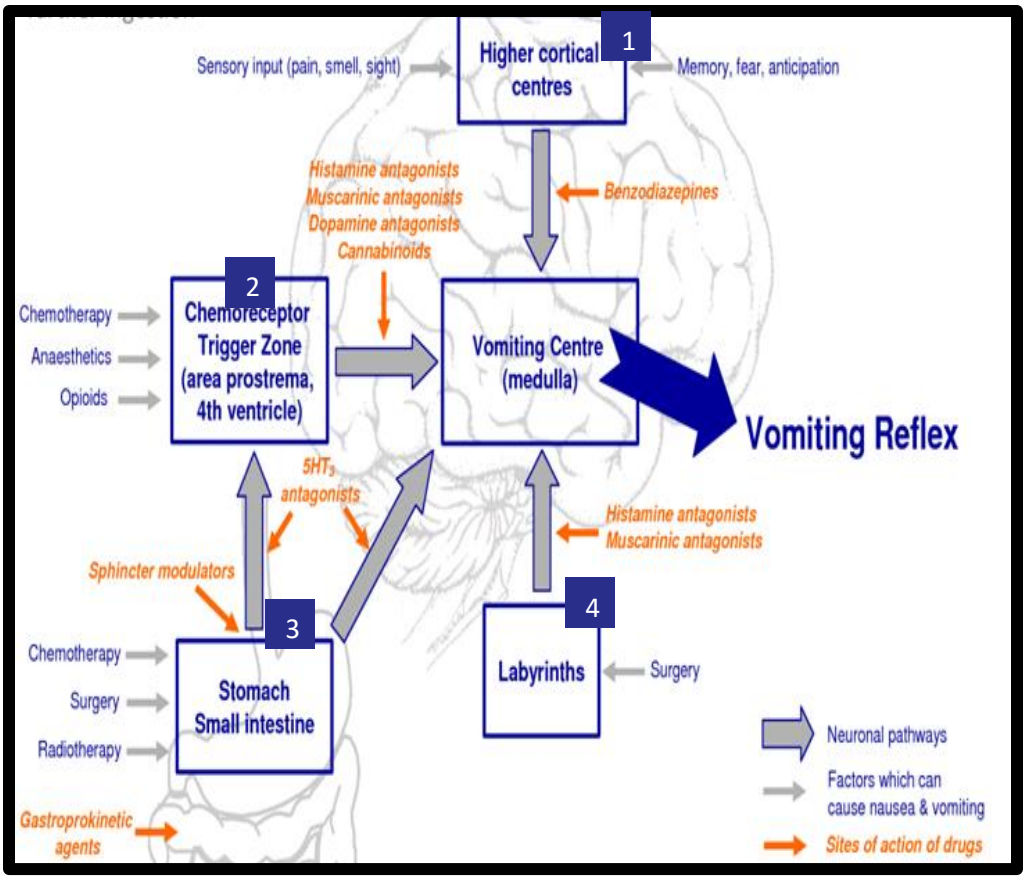
(many systems are involved in vomiting /the diaphragm raise up the , the abdominal muscles contract ..)

Vomiting center contains high concentrations of:
*the function of each receptor were not mentioned just for the sake of understanding

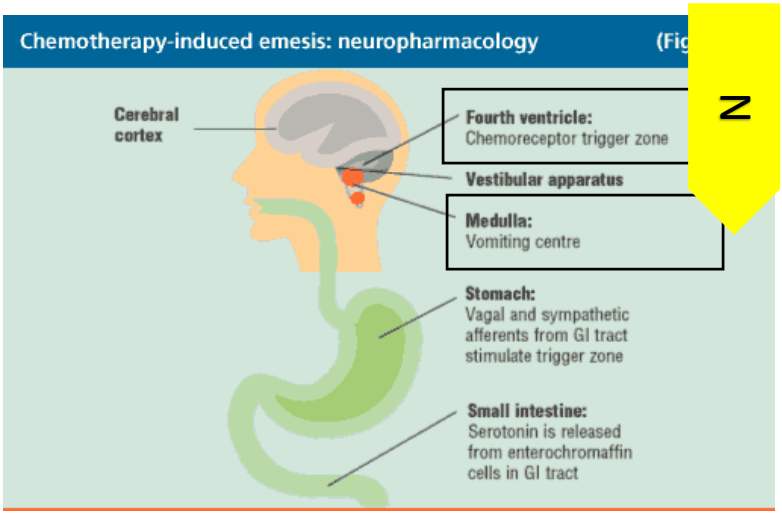
1. **M1 receptors**. (muscarinic Ach receptor , has a lot of functions in the GI it's responsible for mediating the Secretion from salivary glands and Gastric acid secretion from stomach)
2. **H1 receptors**. (histamine receptors /for allergy)
3. **Neurokinin 1** (NK1) receptors.
4. **5-HT3 receptors**. (for serotonin)

NNK-1

Vagal efferent neurons innervating the digestive tract are mainly contained in the dorsal motor nucleus of the vagus. Previous studies have suggested that neurokinins and their neurokinin-1 and neurokinin-3 receptors are involved in the parasympathetic control of digestive functions



Let us try to read this image
it represents the inputs of the vomiting center in the brain
1: from higher cortical centers (that include both Memory –like when you remember sth bad- and sensory –like when u smell sth bad-)
2:chemoreceptor trigger zone (it is an area "prosterema 4th ventricle indicated in a figure below ,out the BBB , when it's treated by chemotherapy for example u will vomit)
3:stomach (like when a chemotherapy is applied on the stomach u vomit)
4:Labyrinth (Inner ear) >>when applying a surgery to it u are really stimulating the vomiting centers .
(different drugs are used for each "pathway")



we will talk about 6 types of antiemetic drugs (Serotonin "5-HT3" Antagonists, Neurokinin 1 Receptor (NK1) Antagonists , Cannabinoids, Antipsychotic drugs ,Benzodiazepines and H1 Antihistamines & Anticholinergic Drugs)

first: Serotonin "5-HT3" Antagonists

1. **Ondansetron**
2. **Granisetron**

Block central 5-HT3 and peripheral (main effect) 5-HT3 receptors.

Prevent emesis due to vagal stimulation and chemotherapy.

Other emetic stimuli such as motion sickness are poorly controlled

Uses

Prevention of acute chemotherapy-induced nausea and emesis and postoperative nausea and vomiting.

Their efficacy is enhanced by combination therapy with dexamethasone and NK1-receptor antagonist.

Adverse effects: Headache, dizziness, and constipation.

Second: Neurokinin 1 Receptor (NK1) Antagonists

Block central NK1 receptors in the area postrema (indicated above).
one NK1 antagonist was mentioned which is :

- Aprepitant
  Used in combination with 5-HT3-receptor antagonists and corticosteroids for the prevention of acute and delayed nausea and vomiting from chemotherapy.

Third: Cannabinoids مخدرات

1. Dronabinol
2. Nabilone

Psychoactive agents.

Used for chemotherapy-induced vomiting. Mechanisms for these effects are not understood.

Adverse effects

Euphoria, dysphoria, sedation, hallucinations, dry mouth, and increased appetite.
منتشٍ ،رأسه مُطبّل ،خَدِر ،يهذي ،فمه جاف ،و شهيته مفتوحة !

forth: Antipsychotic drugs

a class of psychiatric medication primarily used to manage psychosis (including delusions, hallucinations, paranoia or disordered thought)

1. **Prochlorperazine**
2. **Promethazine**
3. **Droperidol**

Antiemetics due to blocking dopamine and muscarinic receptors.

Sedative effects due to antihistamine activity.

Fifth :Benzodiazepines

1. **Lorazepam**
2. **Diazepam**

Reduce anticipatory vomiting caused by anxiety.(not a true antiemetic effect)

anticipatory vomiting"occurring before a new cycle of chemotherapy in response to conditioned stimuli, such as the smells, sights, and sound of the treatment room. It usually occurs after the person has experienced acute nausea and vomiting."

Wiki

Sixth: H1 Antihistamines & Anticholinergic Drugs

Particularly useful in **motion sickness**.

May cause dizziness, sedation, confusion, dry mouth, cycloplegia, and urinary retention.

1. **Diphenhydramine**,
2. **Dimenhydrinate**
   Have significant anticholinergic properties.
3. **Meclizine**

Minimal anticholinergic properties and less sedating.

Used for the prevention of motion sickness and the treatment of **vertigo دوخة due to labyrinth dysfunction.**

Hyoscine (scopolamine)

Very high incidence of anticholinergic effects.

It is better tolerated as a transdermal patch.

Pancreatic Enzyme Supplements

Contain a mixture of **amylase, lipase, and proteases.**

Used to treat pancreatic enzyme insufficiency.
one drug in this category :

- **Pancrelipase.**
  Available in both non-enteric-coated (given with acid suppression therapy) & enteric-coated preparations(a capsule not affected by the acidity of the stomach)
  Administered with each meal and snack.
  Adverse effect:

Excessive doses may cause diarrhea and abdominal pain.
The high purine content of pancreas extracts may lead to hyperuricosuria (goat) and renal stones.

Bile Acid Therapy for Gallstones

Like:

- **Ursodiol** (ursodeoxycholic acid)
  when there's stones in the gallbladder some patients do not prefer surgeries so we give them this drug (acts slowly)..
  here what was mention in the slide about it :

a naturally occurring bile acid that makes up less than 5% of the circulating bile salt pool in humans.

Ursodiol decreases the cholesterol content of bile by reducing hepatic cholesterol secretion.

Ursodiol also stabilizes hepatocyte canalicular membranes.

Ursodiol is used for dissolution of small cholesterol gallstones in patients with symptomatic gallbladder disease who refuse **cholecystectomy** or who are poor surgical candidates.

Given for 12–24 months, dissolution occurs in up to 50% of patients with small noncalcified gallstones.
Bile salt-induced diarrhea is uncommon.

-DO NOT REFER , I HAVE COPIED EVERYTHING

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