Digestive System

University of Jordan

Faculty of Medicine

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Medical Committee
The University of Jordan

◯ Slide ◉ Sheet ◯ Handout ◯ Other

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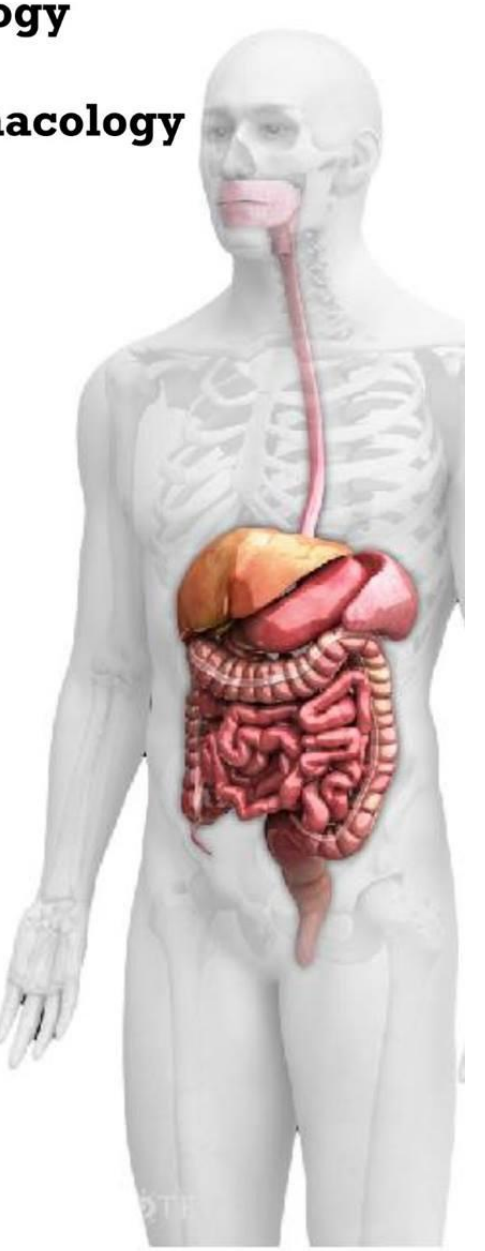
☐ Pathology ☒ Pharmacology

☐ Microbiology ☐ PBL



Lecture # : 2

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Prostaglandin Analogs

They have a short half life around 30 minutes which is not good because patients have to take the drug several times a day (3-4 times daily).

Misoprostol is the drug used to protect from ulcer for people who are suffering from arthritis and taking antisteroidal drugs and cortics, since these antisteroidals can affect the stomach and cause ulcers since they prevent formation of prostaglandin.

Prostaglandin in the stomach is essential for protecting the stomach; providing mucus and bicarbonate secretion so people who must take NSAIDs like aspirin they can take this drug (Misoprostol) to protect the stomach.

Because it is an Analog it stimulates prostaglandin receptors and this:

1) Starts secretions and enhances mucosal blood flow which provides protection for the stomach

2) It has a modest inhibitory effect on the secretion of acids, it acts on parietal cells reducing histamine-stimulated cAMP production causing Modest acid Inhibition.

3) It acts on the intestine and it stimulates the secretion of chloride and electrolyte and this increases the water content and causes diarrhea. Another effect is that it increases intestinal motility and this causes diarrhea too.

4) Stimulation of the uterine contractions and this affects pregnant woman, it can cause abortion.

Because of these reasons this drug is not widely used and again it's indicative for prevention of NSAID-induced ulcers in high risk patients.

Another reason for it not being widely used is it needs multiple daily dosing.

PPI maybe as effective and better tolerated, it doesn't cause diarrhea and it's administered once a day.

Another option is cyclooxygenase2-selective NSAIDs, they do the required effect without prostaglandin production in the stomach.

Prostaglandin Analogs have no significant drug interactions and one of the side effects is **cramping abdominal pain** and diarrhea.

Colloidal Bismuth Compounds:

Bismuth subsalicylate and Bismuth Subcitrate these two drugs are mucosal protective agents they provide a coat on the ulcer and they are minimally absorbed from the GIT.

Not only physical function they also have chemical function, they effect gastric HCL secretion reducing the secretion of acid, also it has an antimicrobial action it helps eradicate H. pylori, another effect it stimulates PGE (Prostaglandin type E) secretion which increases mucous secretions and protection, it reduces Pepsin secretion and decreases H+ ion back diffusion.

Bismuth subsalicylate has additional effect because it has salicylate. In the intestines, this compound splits and the salicylate is released, it inhibits intestinal prostaglandin and chloride secretion so it reduces stool frequency and liquidity in acute infectious diarrhea, that's why it's used for diarrhea (remember prostaglandin stimulates electrolyte and fluid secretions in intestines)

Question: How does the Bismuth stimulate PGE secretions in the stomach and inhibits prostaglandins in the intestine?

In the stomach it was the effect of the compound, down in the intestines it splits and the **salicylate** itself inhibits the prostaglandin secretion.

Bismuth subsalicylate is very useful in preventing and treating **traveler's diarrhea**, because it has antimicrobial effects and binds enterotoxins.

The intestinal flora has some microorganisms, and when someone travels a long distance, between continents, the new bacteria causes disturbance and this causes the diarrhea.

It is also used for the nonspecific **treatment of dyspepsia** and acute **diarrhea**, even if you have no ulcers.

It has a direct antimicrobial activity against H pylori and it is used for second-line therapy for the eradication of H pylori infection, it is used with PPI, tetracycline and metronidazole.(This is given for people who tried first line and failed)

Adverse effects:

Minor such as blackening of the tongue and stool, but for people who take it for a long time it may lead to bismuth toxicity and it results in Enecephalopathy, but it's very rare.

Another topic: Drugs stimulating GI motility

Prokinetic agents:

It has many potential uses for example:

-Drugs that increase the lower esophageal sphincter pressure causing closure of the sphincter they prevent the gastroesophageal reflux.

-Drugs that improve gastric emptying, useful for gastroparesis (when the stomach stops contracting and doesn't evacuate it's content) this happens sometimes after surgery (postsurgical gastric emptying delay.)

-Stimulation of the small intestine is useful for postoperative ileus (when the intestines activities stop) so you need to stimulate it again, we use these drugs, not any drug there are drugs for the upper GIT and drugs for the lower.

-Drugs enhancing colonic transit, useful in the treatment of constipation.

The main stimulus of the GIT is the presence of food, so when the person eats the food moves along the intestines and get absorbed and contents that are not needed gets out of the body.

1-Pressure done by food in the Gut lumen stimulates the secretion of 5-HT (5 Hydroxytryptamine or Serotonin; very potent neurotransmitter present in brain and GIT) from the EC cells.

(5-HT) has 14 different receptors in the body, we know actions of some of these receptors but many of these receptors are still unknown.

2- **Stimulation of 5-HT3 receptors** on the extrinsic afferent nerves which are sensory nerves of vagus and this stimulation reaches the CNS and this goes to the vomiting centers and causes nausea, vomiting or abdominal pain, so what blocks these receptors prevents nausea and vomiting.

3- **Stimulation of 5-HT1P receptors** of the intrinsic primary afferent nerves (IPANs) and this stimulates the enteric nervous system which activates the enteric neurons and this is responsible for peristaltic and secretory reflex activity so it increases peristaltic activity and increases the secretions, so when someone has diarrhea we can block these receptors and the problem is done.

4- **Stimulation of 5-HT4 receptors** on the neurons so they are presynaptic receptors, they stimulate the release of other neurotransmitters like ACh and calcitonin gene related peptide (CGRP), and this stimulates the reflex activity.

When someone eats so much he gets Nausea, and this depends on the strength of the stimulus and it has direct relation with nausea and vomiting.

Also the receptors do not have the same sensitivity they depend on the stimulus.

-The enteric nervous system can independently control or regulate motility and secretion.

The myenteric interneurons control:

Peristaltic reflex, promoting release of excitatory mediators proximally, and inhibitory mediators distally.

Motilin which stimulates excitatory neurons or muscle cells directly.

Dopamine which acts as an inhibitory neurotransmitter in the upper GI (on the stomach and Esophagus) it decreases the intensity of esophageal and gastric contractions.

Cholinomimetic Agents:

In the past they were used, but because of the presence of other drugs with fewer side effects they are not much used anymore.

Bethanechol Stimulates muscarinic M3 receptors on muscle cells and at myenteric plexus synapses.

It treats **GERD and gastroparesis**.

Neostigmine is still used, AChE inhibitor enhances gastric, small intestine and colonic emptying and stimulates GIT.

IV neostigmine used for the treatment of acute large bowel distention (acute colonic pseudo-obstruction) it means there is no mechanical activity = the mass is not moving, so we can stimulate it by neostigmine, administration of 2 mg results in prompt colonic evacuation of flatus gases and feces.

It has cholinergic side effects : Bradycardia, excessive salivation, nausea, vomiting and diarrhea.

Dopamine D2-receptor antagonists:

Metoclopramide and Domperidone are D2 Antagonists.

Dopamine acts as an inhibitory neturotransmitter in the GIT, it decreases the intensity of esophageal and gastric contractions, so if you block D2 receptors the opposite happens so we increase the intensity of esophageal and gastric contractions.

so it increases esophageal peristaltic amplitude, and increases lower esophageal sphincter pressure so it closes the sphincter preventing Gastroesophageal reflux.

In addition to that it enhances gastric emptying to treat gastroparesis.

Remember: they have no effect on small intestine or colonic motility (lower GIT)

Also blocking D2 receptors in the chemoreceptor trigger zone results in an antiemetic effect, in addition to gastric emptying so it has Anti nausea and Antiemetic actions.

Clinical uses:

They are used for the treatment of GERD, they are not effective with erosive esophagitis.

They are not superior to antisecretory agents, so when we lose PPI we add these drugs, so it's used in combination with atnisecretory drugs in patients with refractory heartburn (they are not responding to Antisecretory drugs)

The main use is Impaired Gastric emptying (Gastroparesis).Widely used in postsurgical and diabetic gastroparesis.

We can use it in Nonulcer dyspepsia.

Used in prevention of vomiting (Anti Nausea, Anti vomiting)

Another use is Postpartum lactation stimulation, when the mother wants to breastfeed the infant these drugs can be given. Because when we block D2 receptors we block Dopamine from blocking the release of prolactin, so this drug helps prolactin to promote postpartum lactation, the drug used is **Domperidone**.

Adverse effects:

Metclopromide passes through the blood brain barrier so it blocks dopamine receptors and this causes extrapyramidal symptoms (Parkinsons's desease) when we block dopamine receptors, it effects the balance and may cause schizophrenia, also dystonia, Akathisia, restlessness, drowsiness, insomnia, anxiety.

Domperidone does not cross the BBB so it doesn't cause CNS effects.

Both drugs can elevate serum prolactin levels because they are blocking dopamine receptors but some dopamine is there too, so side effects do not

appear from the first or second or even tenth dose, but for people who take it for prolonged times it causes galactorrhea, gyneomastia, impotence and menstrual disorders.

The End

اهداء الى كل من: علي التميمي المدريري, اب مالك الصغير, جماعة لعبة الطابة كل يوم اثنين, شركس الدفعة, لجان الدفعات, ميدتيم, ابو الطنجور, الرفاعي, الخياط و حمزة.

حبوا بعض

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