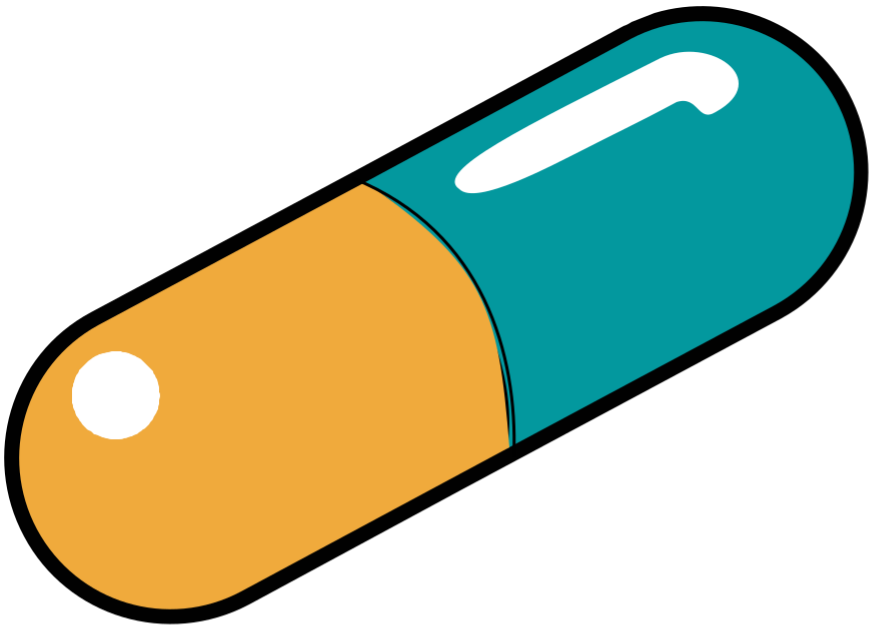
GIS

Sheet no.4

Pharmacology



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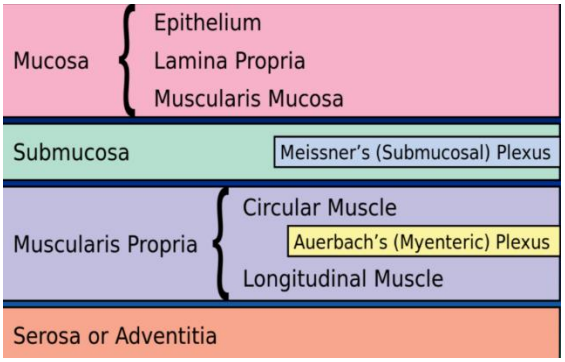
Doctor: Munir Gharaibeh

😊Before we start here are some notes regarding this sheet:

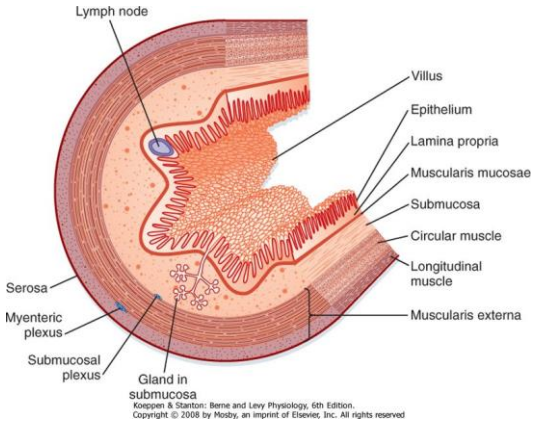
- The black colour for what was wrote in the slides.
- The blue colour for what the doctor said.
- The purple colour for things we add to extra illustration.

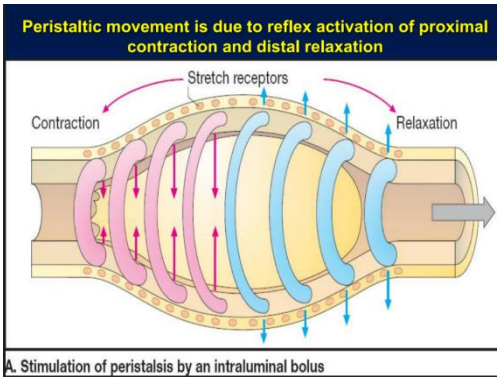
Drugs Affecting GI Motility

A. Drugs Stimulating GI Motility "Prokinetic Agents"
B. Laxative Agents.
C. Antidiarrheal Agents.



Remember the structure of the gastrointestinal tract





As we know, Peristatic contractions are responsible for forward movement of food which is due to reflex activation of proximal contraction and distal relaxation.

Drugs Stimulating GI Motility "Prokinetic Agents"

Potential Uses:

1. Lower esophageal sphincter: GERD (gastroesophageal reflux disease) and heart burn.
2. Stomach: gastroparesis and postsurgical gastric emptying delay.
3. Small intestine: Postoperative ileus.
4. Colon: constipation.

- Gastroparesis: also called delayed gastric emptying, is a disorder that slows or stops the movement of food from your stomach to your small intestine.

- Postsurgical gastric emptying delay: intestinal laziness after surgeries under general anaesthesia.
- Postoperative ileus: prolonged absence of bowel function after surgical procedure.
- Every single part of GIT must be targeted by certain drugs.(e.g: GERD is treated by drugs work on upper GIT while constipation is treated by drugs need CNS stimulation (vagal stimulation) for ENS.

A.Cholinomimetic Agents:

- they mimic the acetylcholine (ACh) effect (so it is a Cholinergic Agonists) or **parasympathetic** nervous system accordingly stimulates GIS (motility and secretion) which is found in the upper part of gastrointestinal part.

*Remember some of Ach effects:
-contraction of smooth muscles
-dilation of blood vessels
-increases body secretion

- They are directly acting by binding to and stimulate cholinergic receptors, and Indirect-acting as cholinesterase inhibitors.

**Remember that Ach has short half time so we can use Cholinomimetic agents instead of it.

1. Bethanecol

- Stimulates **M3** receptors on smooth muscle cells and myenteric plexus synapses.
- It was used in GERD and gastroparesis, but now there are better choices.

- Used to treat bladderotmy.

2. Neostigmine

AChase inhibitor (cholinesterase inhibitors), can be:

1. Reversible: insecticide
2. Irreversible: used in medicine.

- "Acute Colonic Pseudo-obstruction": IV can result in rapid evacuation of flatus and feces post-surgical.

- also we can give it orally

- Can cause cholinergic effects.

-Acute Colonic Pseudo-obstruction: postsurgical condition characterized by abdominal pain, nausea, vomiting with failure to pass flatus and failure of evacuation (consequence of acute dilatation of the colon in the absence of an anatomic lesion that obstructs the flow of intestinal contents.)

B. Dopamine Receptor Antagonists:

**Remember that we have 5 types of dopamine recepotors, and dopamine is a central neurotransmitter (precursors for NE).
*Dopamine receptor antagonists stimulate **sympathetic** nervous system.

1. Metoclopramide

- Dopamine (D2) antagonists.

*It is an old drug but still used, rather than it causes some side effects and sometimes it can be serious.

2. Domperidone

- Both are D2 antagonists.
- Dopamine inhibits cholinergic action of smooth muscle (the cholinergic receptors are modified by the dopamine receptors and by dopamine)
- Have actions on esophagus and stomach (upper GI), but not the small or large intestine so they will localize the action to diseases like nausea and vomiting not diarrhea and constipation.
- Also inhibit the chemoreceptor trigger zone (Area Postrema).

**Remember that: Parkinson disease due to deficiency of dopamine in substantia nigra.

Vomiting centre divided into 2 parts (this part follow the CNS):

1. Chemoreceptor trigger zone which is affected by chemicals like drugs and fluids and causing nausea and vomiting, how?! It receives inputs from blood-borne drugs or hormones and communicate with other structures in vomiting centres to initiate vomiting.
2. Actual vomiting centre which is affected by mechanical stimulation, like when you swallow a strange thing or something that tastes strange.

These centers are beside each others, and come out of them efferent neurons to stomach and esophagus causing vomiting and nausea.

Uses of Dopamine Receptor Antagonists:

1. GERD

- Not effective with erosive esophagitis.

*GERD not affected by drugs that affect the motility, they are mostly

treated with Antiacid or PPIs or H2 antagonists, however that the disease itself due to something involving the motility

- Not superior to antisecretory agents (like PPIs).
- Used in combination with antisecretory drugs (if the case is very severe).

2. Gastroparesis:

- Postsurgical: vagotomy and antrectomy

*these surgical interventions are used to reduce HCl secretion by:

1.Cutting parts of vagus, thus decreasing vagal stimulation so decreasing HCl.

2. Antrum resection: where the gastric peptic ulcer take place.

However, these surgical interventions aren't used anymore, because so the presence of better choices with minimal side effects e.g: H_1/H_2 antagonist (e.g: cimetidine) and PPIs.

- Diabetic.
- Advancement of feeding nasoenteric tubes (by inserting a tube from the nose to the duodenum in case of esophagus resection and esophageal tumours, we give them partial digested food like amino acids).

Other Uses of Dopamine Receptor Antagonists:

3.Nonulcer dyspepsia (heart burn, if we do endoscopy and we didn't find any thing, we give dopamine receptor antagonists).

4. Antiemetic agents.

5. Postpartum lactation stimulation. (dopamine inhibits lactation)

Adverse Effects of Dopamine Receptor Antagonists:

-Metoclopramide **crosses BBB** so can cause CNS symptoms: Restlessness, drowsiness, insomnia, anxiety, agitation, extrapyramidal

symptoms (dystonia, akathisia, parkinsonian like features) and tardive dyskinesia.

-Domperidone **does not cross the BBB**, so doesn't cause CNS effects and works peripherally.

- Both drugs can elevate serum prolactin levels causing galactorrhea, gynecomastia, impotence and menstrual disorders (Endocrine dysfunction).

C. Macrolide Antibiotics (Erythromycin)

- Directly stimulates motilin receptors in the GIT (also they have antibacterial effect).
- Used in Gastroparesis: given IV, but tolerance develops rapidly.
- Used in Acute Emergency Upper GIT Bleeding: to promote emptying of blood before endoscopy.

D. Chloride Channel Activator:

-prostone indicates prostaglandin.

–Lubiprostone:

- PG analog (PGE_1).
- Can be used in chronic constipation.
- Stimulates chloride channel opening in GIT.
- This increases liquid secretion in the intestine (It will draw water).
- Delays gastric emptying leading to nausea.

Antiemetic Agents

Affects afferent Inputs to the Vomiting Center:

- Chemoreceptor trigger zone, which is stimulated by certain receptors such as: DA2(dopamine 2 receptor), **5-HT3** receptor, NK1 receptor (Neurokinin), and opioid receptors, that's why people who take opioids vomits when taking the first dose or when increasing the dose, but after the first dose, tolerance develops.
  (بس بالجرعة الأولى الثانية غير تكيف 😆)
- Vestibular system involved with motion sickness through cranial nerve VIII. Rich in Muscarinic and H1 receptors, so to treat motion sickness, we use Muscarinic and H1 receptor antagonists.
- Pharyngeal irritation through the vagus (mechanical).
- GIT afferents through the vagus and spinal afferent nerves, rich in **5-HT3** receptors

- Central mechanisms due to psychiatric disorders, stress (vomiting due to stress), and anticipatory vomiting of cancer chemotherapy (**5-HT3**). (For example, when they tell a cancer patient that he needs to take chemotherapy on a weekly basis (on Saturday for example), on Friday, he develops vomiting and nausea due to anticipation).

**5-HT3 receptor antagonists are very effective antiemetic agents.

A. Serotonin 5-HT3 - Receptor Antagonists(setron):

1. **Ondansetron** (very effective and famous)
2. **Granisetron.**
3. **Dolasetron.**
4. **Palonosetron.**

- 5-HT3 receptors are involved in three out of the five inputs involved with vomiting.
- Activity restricted to vomiting due to vagal stimulation and chemotherapy.
- Motion sickness is poorly controlled (it is controlled by H1(histamine) & M1 receptor antagonist).
- Used before chemotherapy to avoid nausea and vomiting ic cancer patients, their activity enhanced by dexamethasone (short acting cortisone given by injection IM or IV) and NK1 antagonist.
- Can also be used in postoperative and post radiation vomiting.
- Safe drugs but can cause headache, dizziness and constipation.
- Also prolong QT interval (one of the ECG recoding, if it increases, it enhances cardiac arrythmias which can turn into ventricular tachycardia or fibrillation, which is big problem (i.e. proarrhythmic), according to that any drug must undergo clinical trials on sick and healthy individuals to ensure that these drugs don't increase QT interval, which has a serious side effects on CVS as explained above.

B. Neurokinin Receptor (NK1) Antagonists:

– Apripetant:

• Causes Central blockade in the area postrema (such as D antagonists)
• Used in combination with 5-HT3 antagonists.
• Can cause fatigue, dizziness and diarrhea.

**However, it is useful in treatment of chemotherapy induced vomiting.

C. Antipsychotic drugs (schizophrenia drugs):

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

- Inhibit dopamine and muscarinic receptors (both dopamine and ACh are involved in the vomiting center)
- Can cause extrapyramidal effects (parkinsonism), hypotension and prolong QT interval.

*Parkinson drugs elevate dopamine levels but schizophrenia drugs inhibits dopamine mechanisms by blocking dopamine and muscarinic receptors thus decreasing dopamine levels, so if we give the patient extra dopamine, it can cause schizophrenia. And if we give him extra schizophrenia drugs it can cause parkinsonism.

D. Antihistamines and anticholinergic Drugs:

*These drugs are non-specific smooth muscle relaxant, so they are simple and primitive drugs used to treat allergies and abdominal colic and renal colic.

1. **Diphenhydramine** such as Alerfin
2. **Meclizine.**
3. **Hyoscine (scoplamine)** (like atropine but long acting)

**Diphenhydramine and Meclizine are pure antihistamine which can cause some blockade to alpha receptors.

- Particularly useful in motion sickness.
- Can cause dizziness, sedation, confusion, dry mouth (anticholinergic), cycloplegia (antimuscarinic activity), and urinary retention & constipation.
- Hyoscine can be used as a transdermal patch (this is a benefit for it because when the patient vomits, we can't give him a drug orally. So to cause continuous release of the drug, we give him a transdermal patch).

E. Benzodiazepines (CNS drugs):

1. **Lorazepam.**
2. **Diazepam (Valium).**

- Antianxiety-hypnotic drugs
- Reduce anticipatory vomiting caused by anxiety.

F. Cannabinoids (marijuana):

1. Dronabinol.
2. Nabilone.

- Delta-9- tetrahydrocannabinol from marijuana is useful for chemotherapy-induced vomiting (like ondansetron maybe better).
- Mechanism not understood.
- Can cause euphoria, dysphoria, sedation, hallucinations, dry mouth, and increased appetite (the munchies).
- Also, hypotension, tachycardia, and conjunctival injection.

Test your knowledge

Which one of the following drugs is a neurokinin receptor antagonist:
a. Nabilone.
b. Diphenhydramine.
c. Apripetant.
d. Ondansetron.
e. Aldosterone. Ans: C

**The 3 following questions aren't from test banks.

1. 5-HT3 antagonists do not inhibit DA or M receptors:
a. True
b. false Ans: A

2._____ antagonists have antiemetic properties that are mediated through central blockade in the area postrema.
Ans: NK1 (Neurokinin)

3.Antidopaminergic drugs are useful to treat not only nausea and vomiting but also what other conditions?
A. Seizures
B. Bone marrow suppression
C. Anxiety
D. Schizophrenia
E. C&D Ans: E

Do not forget us in your prayers