

Date
8/4/21

Day - Thursday

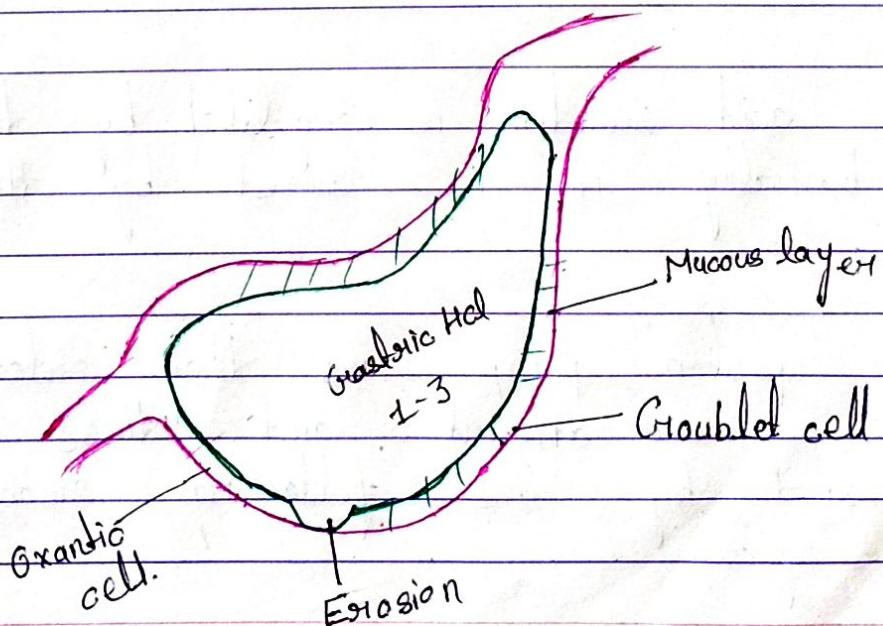
Pharmacology of Drugs acting on the Gastrointestinal Tract

CHAPTER - 1st

Antulcer Agents

Peptic Ulcer - In our stomach and Intestine area there is mucous layer is present which protect the gastric HCl to touch the stomach wall.

But at any condition when there is erosion of mucous layer or disintegration of mucous layer at any place then the gastric HCl directly touch the stomach wall and it causes the severe kind of pain, this is called peptic ulcer.



Cause - There are 2 factors -

[1] Aggressive factor

[2] Protecting factor.

Aggressive factor release the HCl and protecting factor release the mucus, both should be balanced for healthy body.

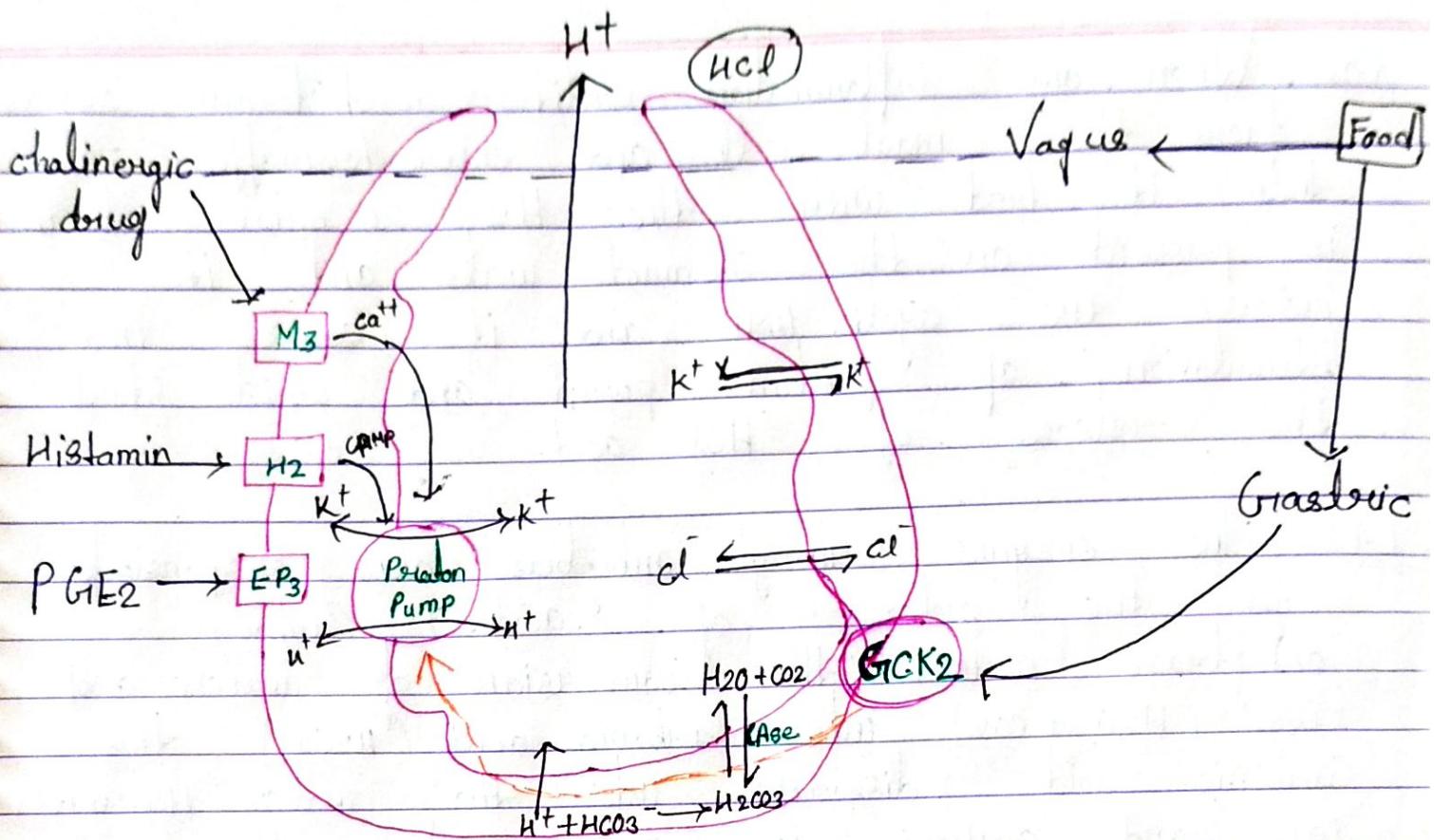
But any reason like cyclosporin, Aggression, depression and very poor / bad life style when the imbalance b/w the protective and releasing factor occurs then it causes the peptic ulcer.

The 2nd cause of the peptic ulcer is Bacterium Helicobacter pylori / H. Pylori it causes 65% - 70% of peptic ulcer.

V.V Time Regulation of Gastric Acid Secretion

The gastric acid secretion is regulated by the various factors basically it is caused by the proton pump.

When the proton pump runs they release the gastric HCl more amount, and these proton pumps are regulated by the following receptors and following types -



[1] When we imagine about the food then the gastric is release, and this gastric is bind with the GCK2 receptor (gastric catecholamine receptor) and this GCK2 activate the proton pump and the release of HCl started.

[2] When a human imagine about the food then the vagus nerve become activated and it release the cholinergic drugs / Acetylcholine and this acetylcholine bind with the M₃ (muscimanic) receptor which is present in the stomach wall and it causes the influx / release of Calcium ion and this activate the proton pump so gastric HCl started release.

[3] When any inflammation condition, histamine release from the mast cell and enterochromaffin cells then it bind with the H₂ receptor, which is present on the stomach wall and it release the cyclic AMP and it causes the stimulation of proton pump and which start the release of HCl acid.

[4] The enzyme carbonyl anhydride also responsible for the release of acid. Carbonyl anhydride causes the conversion of water and CO₂ (H₂O + CO₂) into carbonic acid (H₂CO₃). This carbonic acid dissociate into the water Hydrogen ion and carbonic ion (H⁺ + HCO₃⁻). This proton ion causes the release of HCl.

Classification of Antiulcer Drugs

[1] H₂ & Gastric Acid Secretion Inhibitors-

[A] H₂ Antihistaminics-

Cimetidine, Ranitidine, Fometidine, Rosatetidine, Lafutidine.

[B] Proton Pump Inhibitors-

Omeprazole, Esomeprazole, Pantoprazole, Lansoprazole, Rabeprozole, Ilaprazole.

[C] Anticholinergics -

Piperazine, Propantheline, Oxyphenonium

[D] Prostaglandin Analogue -

Mesoprostol.

[E] Gastric Acid Neutralizer -

[A] Systemic -

Sodium bicarbonate, Sodium Citrate.

[B] Non systemic -

Magnesium hydroxide ($Mg(OH)_2$), Magnesium trisilicate,
Alcohol hydroxide ($Al(OH)_3$), Calcium carbonate ($CaCO_3$)

[3] Ulcer Prospective -

Sucralfate syrup, Colloidal bismuth sub citrate.

[4] Antibiotic -

Amoxicillin, clavethromycin, Metronidazole,

Tinidazole, Tetracycline.

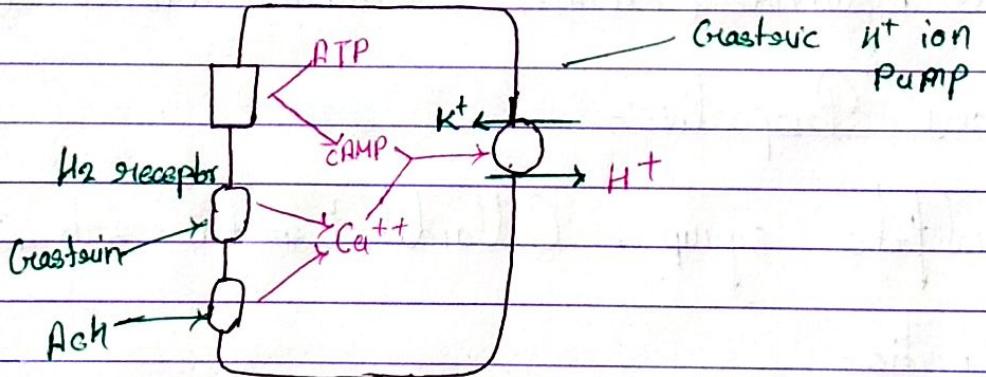
Pharmacology of Antiulcer drugs

[1] H₂ Antagonists

These are 1st class of highly effective drugs, but have been super surpassed (less potent) by PPIs.

Cimetidine was first H₂ blocker introduced clinically and is described as prototype, though other H₂ blockers are more commonly used.

Mode of Action - Blocks the H₂ (histamine) receptor of parietal cells to prevent transport of H⁺ ions out of the cell into the stomach (acid formation).



Adverse effect-

- Headache
- Dizziness
- Bowel upset

Pharmacokinetics -

- Absorbed rapidly.
- Food and antacids may reduce absorption.
- Distributed widely throughout the body.
- Metabolized by the liver.
- Excreted primarily in the urine.

Therapeutic Use -

- Promote healing of duodenal and gastric ulcers.
- Provide long term treatment of pathological GI hyper secretory conditions.
- Reduce gastric acid production and prevent stress ulcers.

[2] Proton Pump Inhibitors

They are prodrugs that activate in acid environment.

After absorption, the active metabolite diffuses into the parietal cells.

Uses - Clinically used PPIs are - omeprazole, Lansoprazole, esomeprazole, pantoprazole, rabeprazole.

Mode of Action -

Act. histamine, gastrin the acid production with the activity of proton pump.

PPIs block the final step of acid production.

OR

When the PPI drug are given they stop the histamine , gastrin the acid production by inhibit the proton pump. , and when proton pump inhibited the production of acid reduces , and it help in the gastrin ulcer.

Therapeutic Uses -

- Peptic ulcer
- Bleeding peptic ulcer.
- Stress ulcers
- Zollinger- Ellison syndrome. (Tumors cause the fundus stomach to produce too much acid, resulting peptic ulcer).

Adverse effect -

- Headache
- Diarrhoea
- Constipation
- Rash

53] Prostaglandin Analogs

Prostaglandin analog are produce in gastric mucosa and appear to serve a protective role by inhibiting acid secretion and promoting mucus and bicarbonate secretion.

MRA- Misoprostol acts upon gastric parietal cell, inhibiting the secretion of gastric acid via GPCR mediated inhibition of adenylate cyclase, which lead to decreased intracellular cyclic AMP levels and decreased pump activity at the surface of parietal cell.

Pharmacokinetic - After oral administration it is rapidly absorbed and metabolized, the half life is 30 min. and is excreted in urine.

[47] ANTACID

MRA- Neutralize gastric acid.

It should not be given with enteric coated tablet otherwise it will dissolve in stomach because antacid increase the stomach pH.

During acid neutralization foam formation occurs.

↓

It will cause esophagus burn.

So anti foaming agent (insoluble oils, Polydimethylsiloxanes and other silicones) or dispersing agent (waxes, glycerin G) must be add.

Adverse effect -

- Nausea
- Constipation
- Diarrhoea
- Headache
- Loss of appetite

- Black or tarry stool
- Deep sleep.

[5] Non Systemic Antacid

These are in soluble and poorly absorbed basic compound.

React in stomach with acid to form respective chloride salts.

This again react bicarbonate is not allow for absorption, hence no acid base disturbance.

[6] Aluminium hydroxide gel

They relaxes smooth muscle leads to delay in gastric emptying.

This causes constipation.

Mucosal astringent reaction also leads to constipation.

[6] Ulcer Protective

[6] Sucralfate - Aluminium salt of sulfated sucrose.

MOA - In acidic environment ($\text{pH} < 4$) it polymerises by cross linking molecules to form sticky viscous gel that adheres to ulcer crater act as acid resistant physical barrier.

Dietary proteins another coat.

May stimulate PG-E₂ synthesis and HCO₃⁻ secretion.

Bind epithelial and fibroblast growth factors which promote mucosal repair.

Uses -

- Prophylaxis of stress ulcer.
- Bile reflux gastritis.
- Topically - burn, bedsore ulcers.

[B] Colloidal Bismuth Subcitrate [CBS]

CBS are the most commonly used oral preparations.

Their mode of action is not clear.

They Probably -

- Precipitate proteins and protect ulcer base.
- Stimulate the secretion of PG-E, mucus and bicarbonate.
- Have antimicrobial effect against H. pylori.

Adverse effect -

- Blackening of tongue.
- Stools.
- Diarrhoea.
- Headache
- Dizziness.

Date
10/5/21

CHAPTER - 2nd

Day - Monday

Antidiarrhoeal Agents

Diarrhoea

- Generally, the term 'diarrhoea' denotes passage of unusually loose or watery stools at least three times or more in 24 hour period.
- Based on the pattern of onset, there are two types of diarrhoeas -
 - Acute diarrhoea.
 - Chronic diarrhoea.
- In acute diarrhoeas are caused by infectious agents.

In acute diarrhoeas, irrespective of the aetiology, emphasis is given to prevent dehydration, which is responsible for most of mortalities.

- In chronic diarrhoeas when it persists for more than two weeks.

In chronic diarrhoea, finding out the cause is important for effective management.

Antidiarrhoeal Drugs

[1] Non-specific therapy.

(a) Oral and parenteral rehydration.

(b) Antimotility and antisecretory agents.

(i) Opioids - Codeine, diphenoxylate, Loperamide.

(ii) α adrenergic receptor agonist - clonidine.

(iii) Octreotide

(iv) Racecadotril.

[2] Specific therapy - Antimicrobial agents.

[1] Non-Specific Therapy

(a) Oral Rehydration Solution (ORS)

- In acute diarrhoea, it is important to maintain water and electrolyte balance with proper fluid replacement (rehydration).
- Oral rehydration seems to be the simplest, safest and least expensive method of choice for acute diarrhoea.
- WHO- ORS contains sodium chloride 2.6 gm, Potassium chloride 1.5 gm sodium citrate 2.9 gm and glucose 13.5 gm.
- If dissolved in 1 l of water, promotes better absorption of water from the solution.

- ORS decreases stool volume and vomiting, it also useful in heart stroke and maintenance of hydration in burn patients.
- It is also effective in cholera.
- In case of severe diarrhoea with dehydration, IV fluids are indicated.
- WHO recommends the use of zinc (10-14 days) with ORS in acute diarrhoea in children, it decreases intestinal secretions, promotes regeneration of intestinal epithelium and reduces duration and severity of diarrhoea.

[B] Antimotility and Antisecretory Agents

i) Codeine It is a natural opium alkaloid, it decreases GI motility and produces constipation, it has abuse potential.

ii) Diphenoxylate- It is related to pethidine. In high doses, it has abuse liability, hence is usually available in combination with small dose of atropine to discourage abuse or overdose.

The side effects are - constipation, paralytic ileus and drug addiction.

This drug has been banned in many countries.

iii) Loperamide - It is an opiate analogue and has more potent antidiarrhoeal effect than morphine.

- By interacting with μ -opiod receptors in gut, loperamide reduce GI motility and increases the anal sphincter tone.
- It is orally effective and has rapid onset of action.
- It poorly penetrates BBB and has no abuse potential.
- The usual dose of loperamide is 4 mg stale and then 2 mg after each loose stool but the maximum dose should not exceed 16 mg in 24 hours.
- It has been used in both acute and chronic diarrhoea.
- The toxic effects are skin rashes, headache and paralytic ileus, it should not be used in children less than 4 years of age.
- These drugs also increase intraluminal pressure, hence they should be avoided in inflammatory bowel disease (IBD).

FCI Clonidine

It has an antisecretory as well as antimotility effects.

It has been used to control diarrhoea due to opioid withdrawal and in diabetics with autonomic neuropathy.

The side effects are depression and hypotension.

ivii Octreotide

It is an analogue of somatostatin which is useful in secretory diarrhoea due to hormone secreting tumors of the GIT and pancreas.

It inhibits secretion of 5-hydroxytryptamine (5-HT), vasoactive intestinal peptide (VIP), gastrin, insulin etc.

It is administered either intravenously or subcutaneously.

It can be used to treat diarrhoea in patients with NIDs.

viii Racecadotril

Racecadotril (Prodrug) \rightarrow active metabolite \rightarrow enkephalinase inhibitor \rightarrow Inhibits degradation of enkephalins in intestinal mucosa \rightarrow decrease in intestinal secretion.

It is used in acute secretory diarrhoea.

It can be used in children.

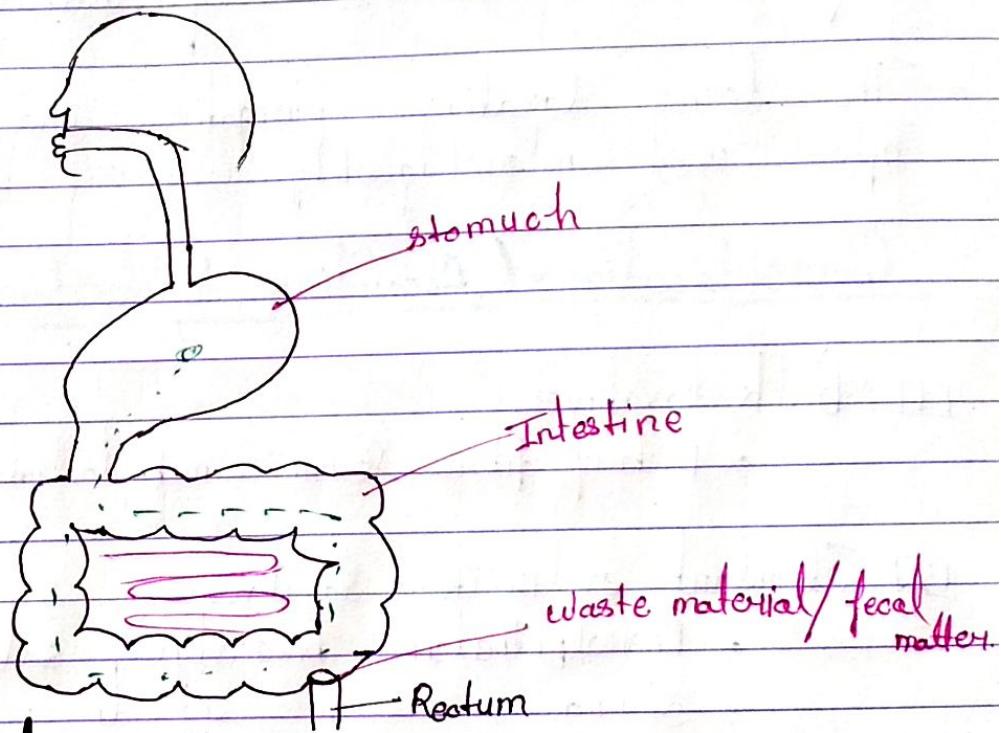
Side effects are nausea, vomiting and drowsiness.

Date
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Day - Wednesday

Constipation

When the colon and caecum absorb maximum amount of water from our waste material, then fecal matter becomes hard and tough and the movement (evacuation movement) becomes slow, and the painful evacuation movement of hard fecal matter occurs, that condition is called constipation.



Cause of Constipation -

- Drug Induced
- Pregnancy
- Travelling
- Fibreless diet
- Lack of physical activity.
- Dehydration
- Metabolic disorder.

Classification of Drugs -

- Any kind of supplement which is used for the treatment of constipation, they are called laxative.

Basically they increase the water concentration in the stool and softening the stool.

- Purgatives cause evacuation of watery stools.
- The terms laxative, purgatives and cathartics are often used interchangeably.

Classification - (According to mechanism of Action)

[1] Bulk laxatives.

- Dietary fibre - Bran, methylcellulose, ispaghula (isabgol)

[2] Stimulant or irritant laxatives

- Phenolphthalein, bisacodyl, sodium picosulfate.
- Senna, Cascara sagrada.

[3] Osmotic laxatives.

- Magnesium sulphate, magnesium hydroxide, sodium phosphate, sodium sulphate, lactulose, polyethylene glycol.

[4] Stool Softeners.

- Docusates, liquid paraffin.

[5] 5-HT agonist

- Perucalopride.

(1) Bulk-forming Laxatives -

They are indigestible, hydrophilic substance like bran, methyl cellulose, agar etc. which absorb water, swell up and increase the bulk of stools.

They cause mechanical distension, so stimulate peristalsis and promote defaecation.

It takes 1-3 days for the evacuation of formed stool.

The side effects include abdominal discomfort and flatulence.

(2) Stool Softeners -

Docusates - They are anionic surfactants. They lower the surface tension of stool, thereby cause accumulation of fluid and fatty substance, thus softening the stools.

These agent act within 1-3 days, they administered orally.

Liquid Paraffin - Liquid paraffin is a mineral oil and is administered orally. It softens stools.

They also have a lubricant effect which helps in smooth defaecation.

It is useful in patients cardiac disease.

Adverse effect - 1. Lipid pneumonia may occur due to entry of drug into lungs, hence liquid paraffin

should not be given at bed time and in lying down position.

2. Long-term use may cause malabsorption of Vit A, D, E and K. (fat soluble vitamins).
3. Leakage of faecal matter through anal sphincter may lead to spoiling of clothes.

[3] Stimulant (irritant) laxatives -

This causes an increased secretion of water and electrolyte by mucosa thus stimulating peristalsis.

They cause evacuation of semifluid stools.

Large dose may cause loose of fluid and electrolyte.

They are contraindicated in pregnancy as they cause reflex stimulation in uterus.

or

Basically they are stimulant, they stimulate the colon, cecum layer to decrease the absorption of water so much amount of water aggregated with the stool and stool become soft and comes out easy.

[4] Osmotic purgatives -

They are salts of magnesium sodium or potassium, those having magnesium or phosphate are known as saline laxatives.

Osmotic purgatives are given orally, early morning on empty stomach with plenty of water.

Act on the small and large intestines (within 1-3 hr).

No absorbed in the gut.

Draw fluid into the lumen by osmotic activity.

Distend the bowel

stimulate peristalsis.

Evacuation of watery stool in 1-3 hours.

[5] 5-HT Agonist -

Prucalopride - Prucalopride, a prokinetic drug, is a 5-HT agonist.

It is useful in chronic constipation not responding to laxatives.

It increases chronic motility.

Date - 11/5/21

Day - Wednesday

Emetics and Anti-emetics

Vomiting

Vomiting is a phenomena of expulsion of the gastric fluid in opposite direction through the mouth / towards outside.

It is cause when the vomiting centre is stimulated which is situated in medulla oblongata.

Types of Vomiting

There are basically 3 types of Vomiting -

1. Morning sickness - Cause due early 3 month of pregnancy.
2. Motion sickness - Cause due to the travelling in passengers.
3. Gastric sickness - Caused by various disease, bad food, drug abuse.

Physiology of Vomiting

In the medulla oblongata vomiting centre is present, when vomiting centre is stimulated then vomiting occurs.

[Q1] The vomiting centre can be activated by different - different method -

- It can be activated by itself by the histaminic receptor.
- It can be activated by the CTZ (Chemo trigger zone) which is present in the cerebellum.
- It is also activated by NTS (Nucleus tractus solitarius) also present in the cerebellum.

[C1] In the CTZ basically there are 6 kinds of receptors are present they are basically H_1 receptor, D_2 (Dopamine) receptor, serotonin ($5HT_3$) receptor, cholinergic receptor, Neurokinin receptor, opioid receptor.

When these kinds of drugs are bind with the chemo tactic zone it stimulate the vomiting centre and causes the vomiting.

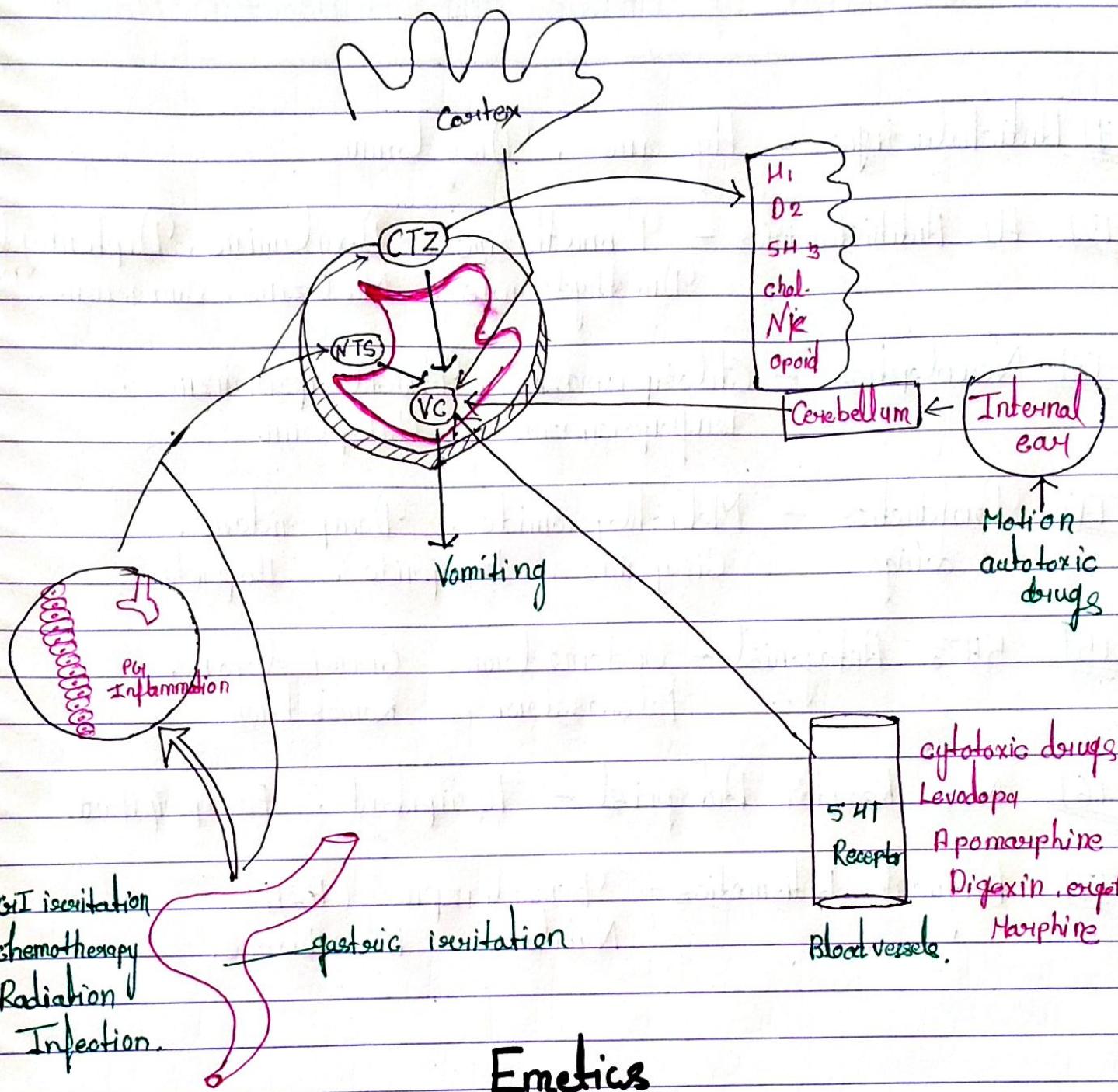
[Q2] There are 3 kinds of ear ossicles, Malleus, Incus and stapes are present in our internal ear and during the motion and effect of autotoxic drugs, when these ear ossicles are activated then they activate the cerebellum of the brain, and this cerebellum activate the Vomiting centre (VC) which causes the vomiting and this is called motion sickness.

[E1] The vomiting in human can be also affected by the Psychological and newtonal things due to the smell, pain, sight and psychological stimulation cortex is activated and then this activated

cooter stimulate the opening centre and which causes the vomiting.

[F] In intestine or stomach wall there are histamin and prostaglandins receptors are present and due to the different reasons like gastric irritation, chemotherapy, Radiation, Infection and other drugs, the histamines are release and causes the inflammation and the histamine bind with the histaminic receptor of the GTZ and it activate the vomiting centre and it causes the vomiting.

[G] In human blood and platelets basically histaminic receptor is present and due to some different different drugs like cytotoxic drugs, Levodopa, Apomorphine, Digoxin, Ergot and morphine these drugs release the histamine and this histamine bind with the receptor of the blood vessels and it causes the activation of vomiting centre and causes the vomiting.



Those drugs which induced the vomiting called emetics.

Ex- Morphine.

Classification of Emetic and Antiemetic Drugs

E1 Anticholinergic - Hyoscine, Dicyclomine.

E2 H₁ Antihistaminics - Promethazine, Doxylamine, Diphenhydramine, Meclozine, Cinnarizine.

E3 Neuroleptics - Chlorpromazine, Prochlorpromazine, Trifluoperazine, Haloperidol.

E4 Prokinetics - Metoclopramide, Domperidone, Cisapride, Mesoperide, Itopride.

E5 5HT₃ Antagonist - Ondansetron, Granisetron, Palonsetron, Riomosetron.

E6 NK₁ Receptor Antagonist - Aprepitant, Fasaprepitant.

E7 Adjacent Antiemetics - Benzodiazepine (BZD), Nabilone, Dronabinol.