

UNIT - I

* Pharmacology of drugs acting on Respiratory System

ANTI-ASTHMATIC DRUGS :-

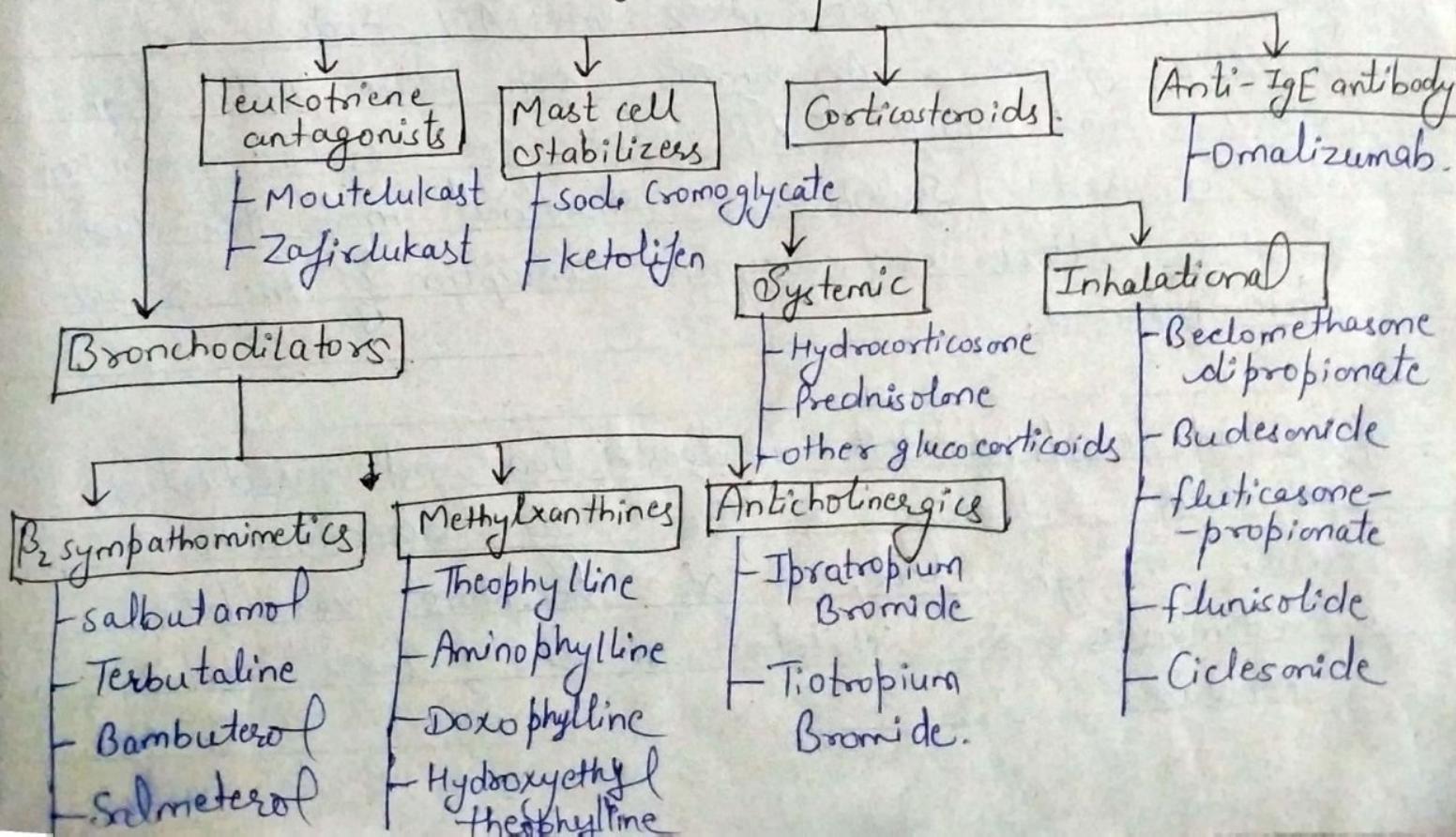
It is characterized by hyperresponsiveness of tracheobronchial smooth muscle to a variety of stimuli narrowing of air tubes, mucosal edema & mucus plugging.

Two principal varieties are recognised :-

- Extrinsic Asthma : Mostly episodic, less prone to status asthmaticus.
- Intrinsic Asthma : It tends to be perennial, status asthmaticus is more common.

The inflammation in bronchial asthma is initiated by mast cells (present in lungs) & infiltrate is dominated by eosinophils, lymphocytes and mast cells.

Drugs for Bronchial Asthma



Pharmacological Action:-

1.) Salbutamol :- Highly selective β_2 agonist, cardiac side effects are less prominent. Inhaled salbutamol delivered mostly from pressurized metered dose inhaler produces bronchodilation within 5 minutes and the action lasts for 2-4 hours.

Palpitation, restlessness, nervousness, throat irritation and ankle edema can also occur. Oral salbutamol undergoes presystemic metabolism in the gut wall, bioavailability is 50%. It acts as 4-6 hrs.

2.) Sympathomimetic Drug Action

i) Heart :- Adrenaline increases heart rate by enhancing the pacemaker activity of SA node. Adrenaline also activates latent pacemakers in A.V node and Purkinje fibres. Arrhythmias can occur with high doses that raise B.P. force of cardiac contraction is increased. Systole is shortened more than diastole. Cardiac output and oxygen consumption of the heart are enhanced.

ii) Blood vessels :- Both vasoconstriction and vasodilation can occur depending on the drug. Vasoconstriction occurs through α_1 & α_2 receptors. Vasodilation predominates in skeletal muscles, liver and coronary.

iii) BP :- The effect depends on the amine, its dose and rate of administration: Adrenaline given by slow i.v. infusion or s.c injection causes rise in systolic but fall in diastolic BP. Rapid i.v. injection of Adrenaline produces a marked increase in both systolic as well as diastolic B.P.

iv) Respiration :- Adrenaline and isoprenaline are potent bronchodilators. Adrenaline can directly stimulate respiratory centre.

v) Eye :- Mydriasis occurs due to contraction of radial muscle of iris, but this is minimal after topical application, because adrenaline penetrates cornea poorly.

vi) GIT :- In isolated preparations of gut, activation of both α & β receptors produces relaxation.

vii) Bladder :- Detrusor is relaxed (β_2 & β_1) and trigone is constricted (α_1) both actions tend to oppose bladder voiding.

viii) Uterus :- Adrenaline can both contract and relax uterine muscle, both α & β receptors.

ix) Metabolism :- Adrenaline causes glycogenolysis \rightarrow hyperglycemia as well as lipolysis \rightarrow rise in plasma free fatty acid.

x) CNS:- Adrenaline in clinically used doses, does not produce any marked CNS effects because of poor penetration in brain, but restlessness & tremor may occur.

3.) Methylxanthines Action:-

i) CNS:- Caffeine and theophylline are CNS stimulants primarily affect the higher centres. Caffeine 150-250 mg produces a sense of alertness, fatigue thinking becomes clear. Vomiting at high doses is due to both gastric irritation and CTZ stimulation.

ii) CVS:- It direct stimulates the heart and increase force of myocardial contractions. They tend to increase heart rate by cardiac action, but decrease it by causing vagal stimulation.

iii) Smooth muscles:- All smooth muscles are relaxed most prominent effect is exerted on bronchi in asthmatics. Theophylline is more potent bronchodilator than caffeine.

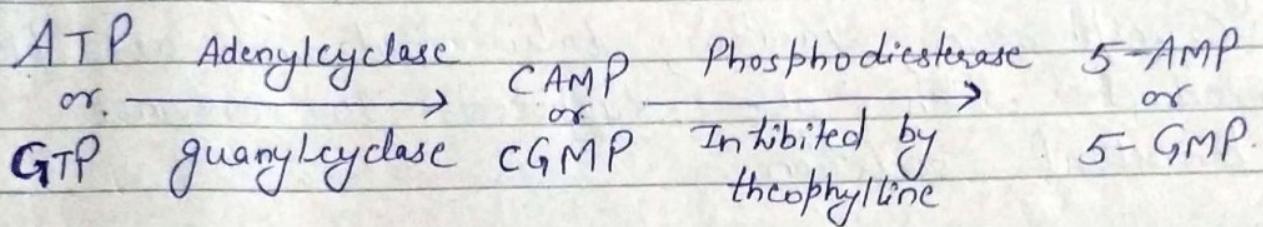
iv) Kidney:- Mild diuretics. They act by inhibiting tubular reabsorption of Na^+ and water as well as increased renal blood flow.

v) Skeletal muscles:- Caffeine enhances contractile power of skeletal muscles.

vi) stomach :- Methylxanthines enhance secretion of acid and pepsin in stomach even on parenteral injection.

vii) Mast cells & inflammatory cells :- Theophylline decreases release of histamine, other mediators and cytokines from mast cells and activated inflammatory cells.

Mechanism of Action :-



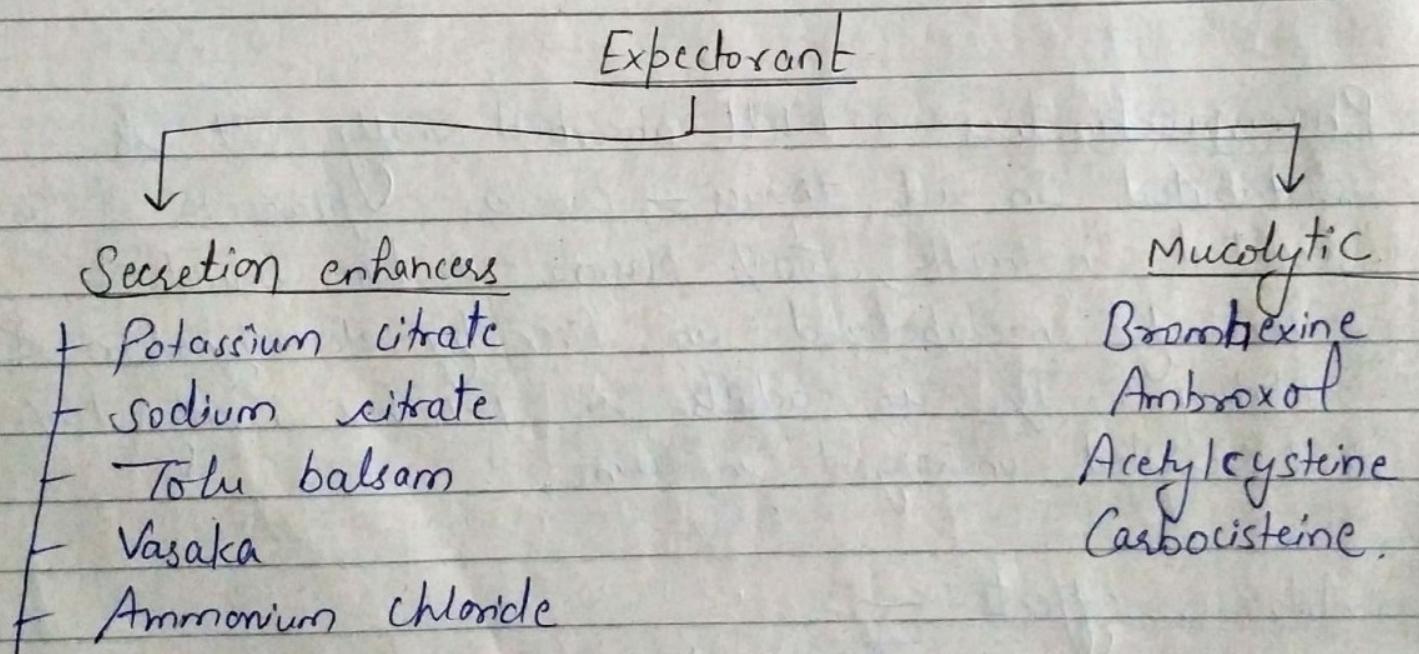
Pharmacokinetics :- Well absorbed orally. It is distributed in all tissues - crosses placenta & is secreted in milk, 50% plasma protein bound & extensively metabolized in liver by demethylation & oxidation. $T_{1/2}$ in adults is 7-12 hrs. Only 10% is excreted unchanged in urine.

Adverse effects :-

Theophylline has a narrow margin of safety. Headache, Nervousness and nausea are early symptoms, the irritant property of theophylline is reflected in gastric pain, rectal inflammation & pain at site of i.m. injection.

* EXPECTORANT & ANTITUSSIVE *

- Expectorant — are the drugs used to increase bronchial secretion or reduce its viscosity, facilitating its removal by coughing. Sodium and potassium citrate are considered to increase bronchial secretion by salt action. Potassium iodide is secreted by bronchial gland and can irritate the airway mucosa. Guaiphenesin vasaka, tolu balsam are plant product which are supposed to enhance bronchial secretion.



Mucolytics :-

Bromhexine :- A derivative of the alkaloid vasicine obtained from Adhatoda vasica (vasaka) is a mucolytic & mucokinetic, capable of inducing thin copious bronchial

Side effect :- Lacrimation, nausea, gastric irritation, hypersensitivity.

Ambroxol :- Ambroxol is a metabolite of bromhexine having similar mucolytic action.

Acetylcysteine :- It opens disulphide bonds in mucoprotein present in sputum & makes it less viscid.

It can be administered orally (200-600mg TDS) as well as by inhalation of 10-20% nebulized solution.

- Antitussive :-

These are the drugs which suppress the cough production.

These are the drugs that act in the CNS to raise the threshold of cough centre or act peripherally in the respiratory tract to reduce tussal impulse or both these actions:

Antitussive

Antitussive

Peripherally acting drug

i) Narcotic/opioid antitussive
→ codeine, hydro

i) Mucosal anaesthetic
→ Benzo

Antitussive

Peripherally acting drugs

ii) Non-narcotic / non-opioid antitussive

→ Dextromethorphan,
Diphenhydramine.

ii) Hydrating agent
→ steam, Aerosol.

iii) Miscellaneous
→ Bromhexine,

~~Imp.~~

* ANTIULCER DRUGS / PEPTIC ULCER :-

→ Peptic ulcer occurs in that part of the gastrointestinal tract (g.i.t) which is exposed to gastric acid & pepsin, i.e. the stomach and duodenum.

→ It probably due to an imbalance between the aggressive (acid, pepsin, bile & H. pylori) and the defensive (gastric mucus, nitric oxide, bicarbonate secretion, prostaglandins etc.) factors.

Duodenum ulcer - high production of acid

Classifications :

1.) Reduction of gastric acid secretion :

a) H_2 anti-histamines :- Cimetidine, Ranitidine, Famotidine, Roxatidine, Lafutidine

b) Proton pump inhibitors :- Omeprazole, Pantoprazole, Rabeprazole, Esomeprazole, Lansoprazole.

c) Anticholinergics :- Pirenzepine, Propantheline, oxyphenonium.

d) PG (Prostaglandin) analogue :- Misoprostol.

2.) Neutralization of gastric acid (Antacids)

a) Systemic :- Sodium bicarbonate, sodium citrate.

b) Non-systemic :- Magnesium hydroxide, magnesium trisilicate, Aluminium hydroxide, Magaldrate, calcium carbonate.

3.) Ulcer protectives :- Sucralfate, colloidal bismuth subcitrate (CBS)

4.) Anti H. Pylori drugs :- Amoxicillin, clarithromycin, Metronidazole, Tinidazole, tetracycline, CBS.

• H₂ receptor antagonist :- e.g :- Cimetidine

Acid is generated by the carbonic anhydrase mediated catalysis of CO₂ & H₂O to form H⁺ & HCO₃.

H^+ ions are then exchanged for K^+ by $H^+ K^+$ ATPase pump & later coupled with Cl^- ions entering the parietal cell from the blood in exchange for HCO_3^- .

These are 3 regulatory molecules that stimulate acid secretion (Ach., histamine & gastrin)

- Anticholinergic drugs :-

e.g.:- Piperazine which is a anti-cholinergic drugs inhibit acetylcholine action on muscarinic receptors decrease HCl secretion.

- Prostaglandins analogue :-

e.g.:- Misoprostol which increase mucus & bicarbonate secretion show cytoprotective action by increase mucosal blood supply increase healing by increase blood supply and decrease HCl secretion.

Pharmacological Action :-

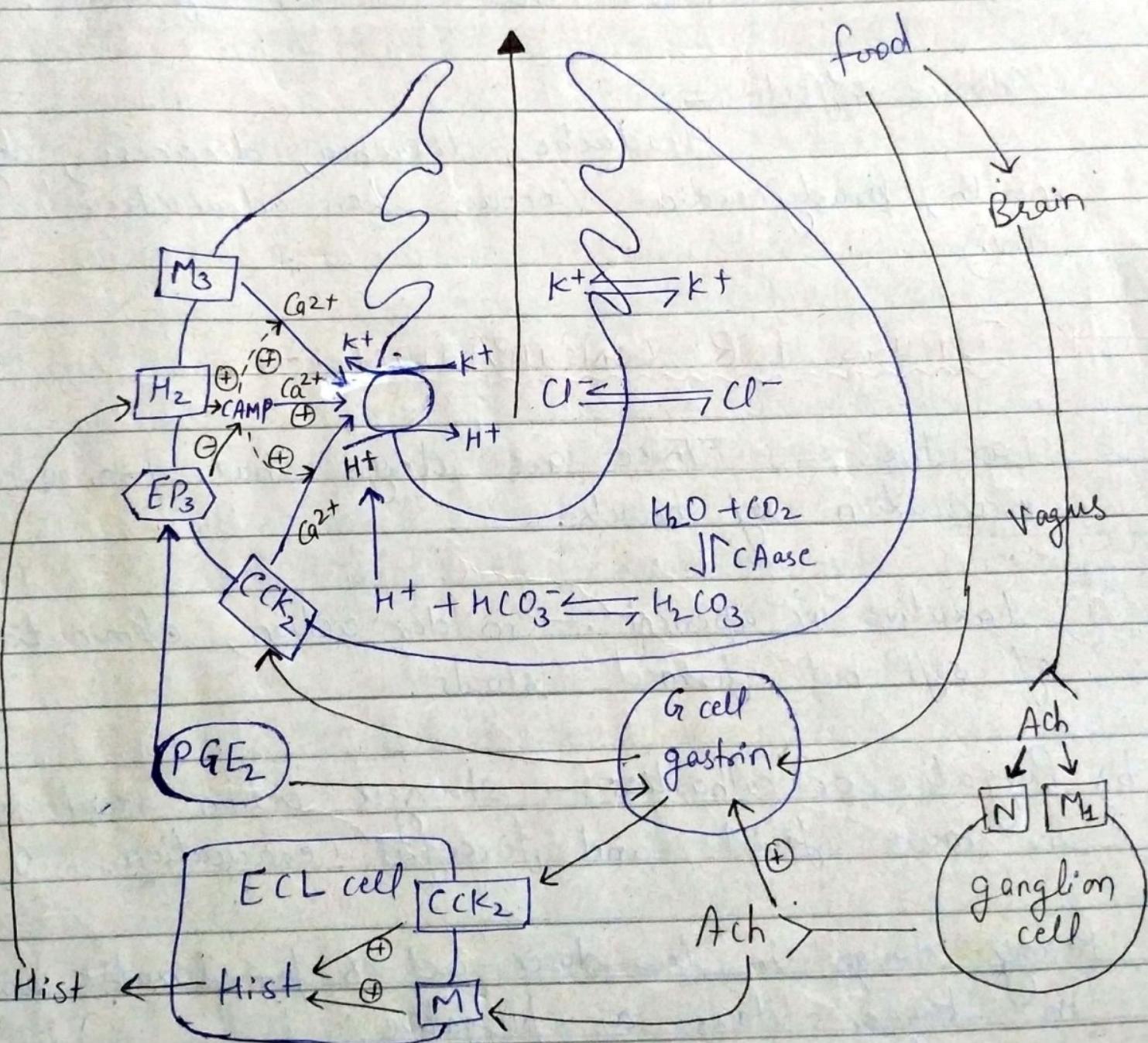
1.) H_2 Blockade :- These drugs block histamine induced gastric secretion, cardiac stimulation, uterine relaxation.

→ No effect on H_1 responses because they are selective.

2.) Gastric secretion :- The only significant in vivo action of H_2 blockers is marked inhibition of gastric secretion.

- All phases are suppressed dose dependently.
- H₂ blockers have no direct effect on gastric or oesophageal motility or on lower oesophageal sphincter tone.

Mechanism of Action:-



Pharmacokinetic :-

Absorbed orally, bioavailability - 60-80%. undergoes first pass metabolism.
About 2/3 of dose is excreted unchanged in urine / bile.
Elimination t_{1/2} is 2-3 hrs.
Dose reduction is needed in renal failure.

Adverse effects :-

Headache, diarrhea, dizziness, dry mouth, bradycardia (occur when administered as i.v.).

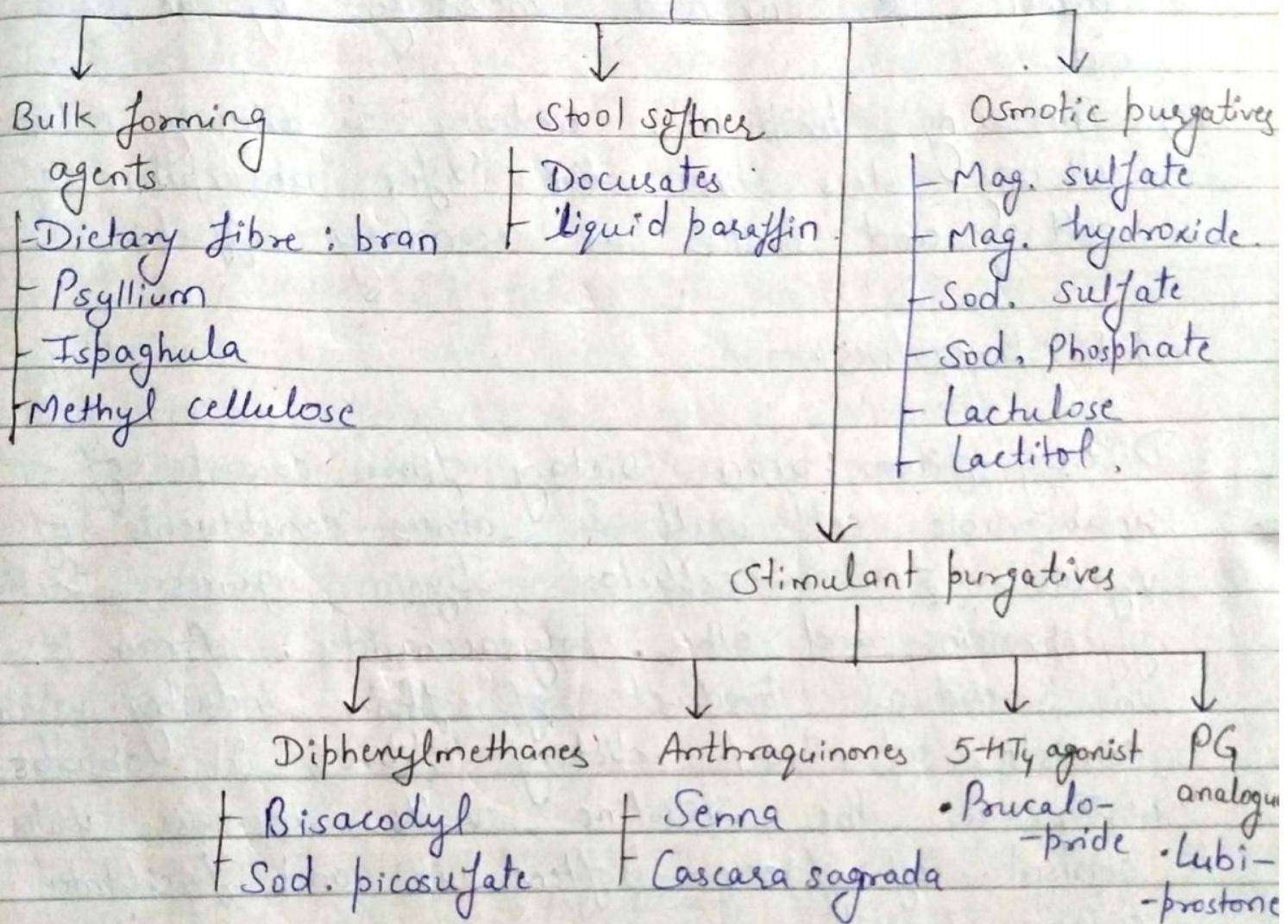
—* DRUGS FOR CONSTIPATION :-

Laxatives :- These are drugs that promote evacuation of bowels.

- a) Laxative or aperient :- milder action, elimination of soft but formed stools.
- b) Purgative or cathartics :- stronger action resulting in more fluid and forceful evacuation.

Many drugs in low doses act as laxative and in larger doses as purgative.

Classification of drugs for constipation



Mechanism of Action :-

All purgatives increase the water content of the faeces by :-

- A hydrophilic or osmotic action, retaining water and electrolytes in the intestinal lumen — increase volume of colonic content and make it easily propelled.

- b) Acting on intestinal mucosa, decrease net absorption of water and electrolyte; intestinal transit is enhanced indirectly by the fluid bulk.
- c) Increasing propulsive activity as primary action - allowing less time for absorption of salt and water as secondary effect.

Bulk purgatives:-

Dietary fibre: bran Dietary fibre consists of unabsorbable cell wall & other constituents of vegetable food — cellulose, lignins, gums, pectins, glycoproteins and other polysaccharides. Bran is the residual product of flour industry which consists of ~40% dietary fibre. It absorbs water in the intestine, swells, increases water content of faeces — softens it and facilitates colonic transit.

Increased intake of dietary fibres is the most appropriate method for prevention of functional constipation, particularly if the diet is deficient in fibre.

Drawbacks:- Bran is generally safe, but it is unpalatable, large quantity (20-40 g/day) needs to be ingested. Full effect requires daily intake for at least 3-4 days. As such, bran is useful for prevention of constipation.

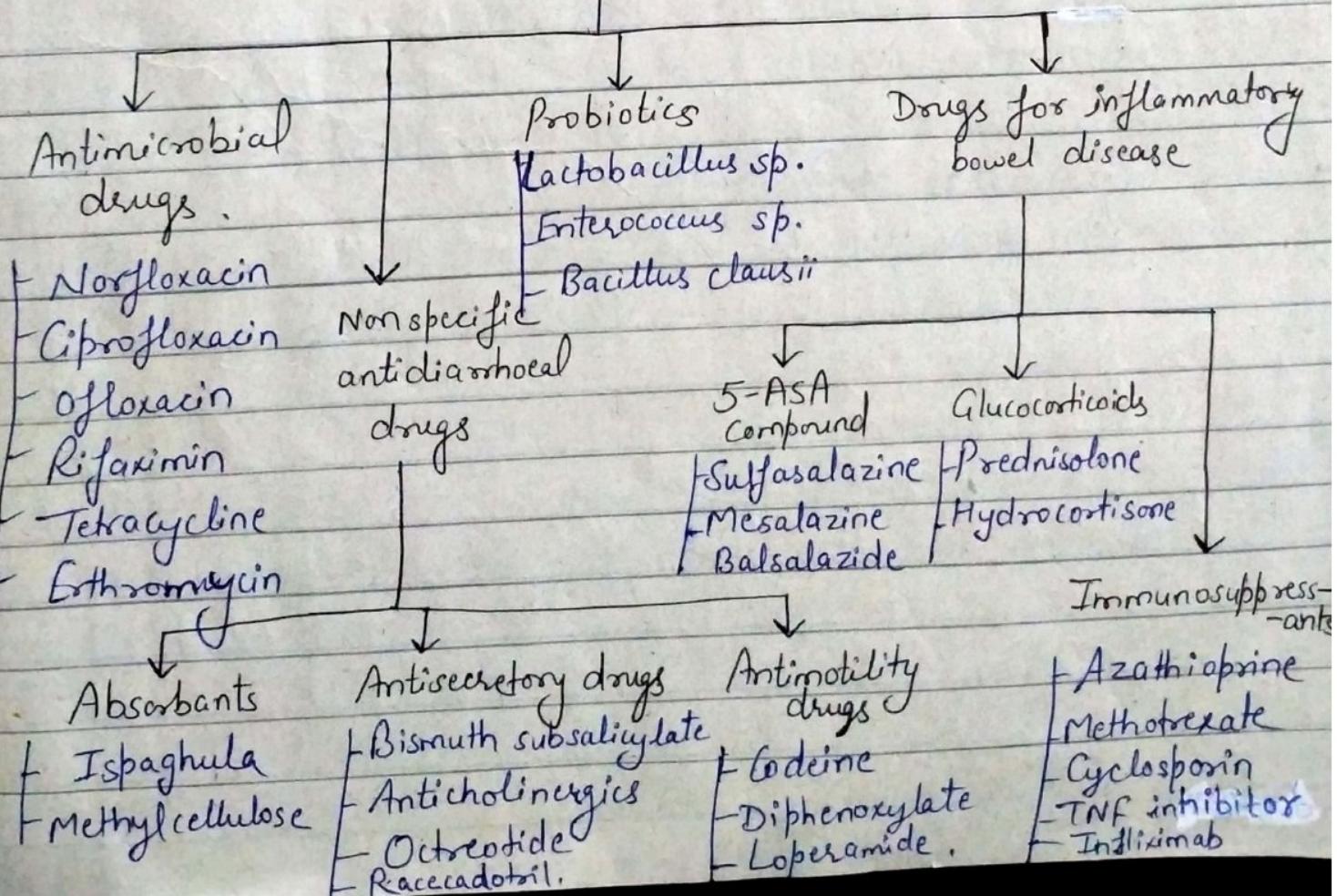
DRUGS FOR DIARRHOEA :-

Diarrhoea :— Diarrhoea is too frequent, often too precipitate passage of poorly formed stools. Diarrhoea is defined by WHO as three or more loose or watery stools in a 24 hrs period.

In pathological terms, it occurs due to passage of excess water in faeces. This may be due to:

- Decrease electrolyte and water absorption.
- Increase secretion by intestinal mucosa.
- Increase luminal osmotic load.
- Inflammation of mucosa & exudation into lumen.

Classifications :-



- * EMETICS & ANTIEMETICS :-

- Emetics :- These are the drugs used to evoke vomiting.

- i) Act on CTZ : Apomorphine
- ii) Act reflexly & on CTZ : Ipecacuanha.
(not Ipecac)

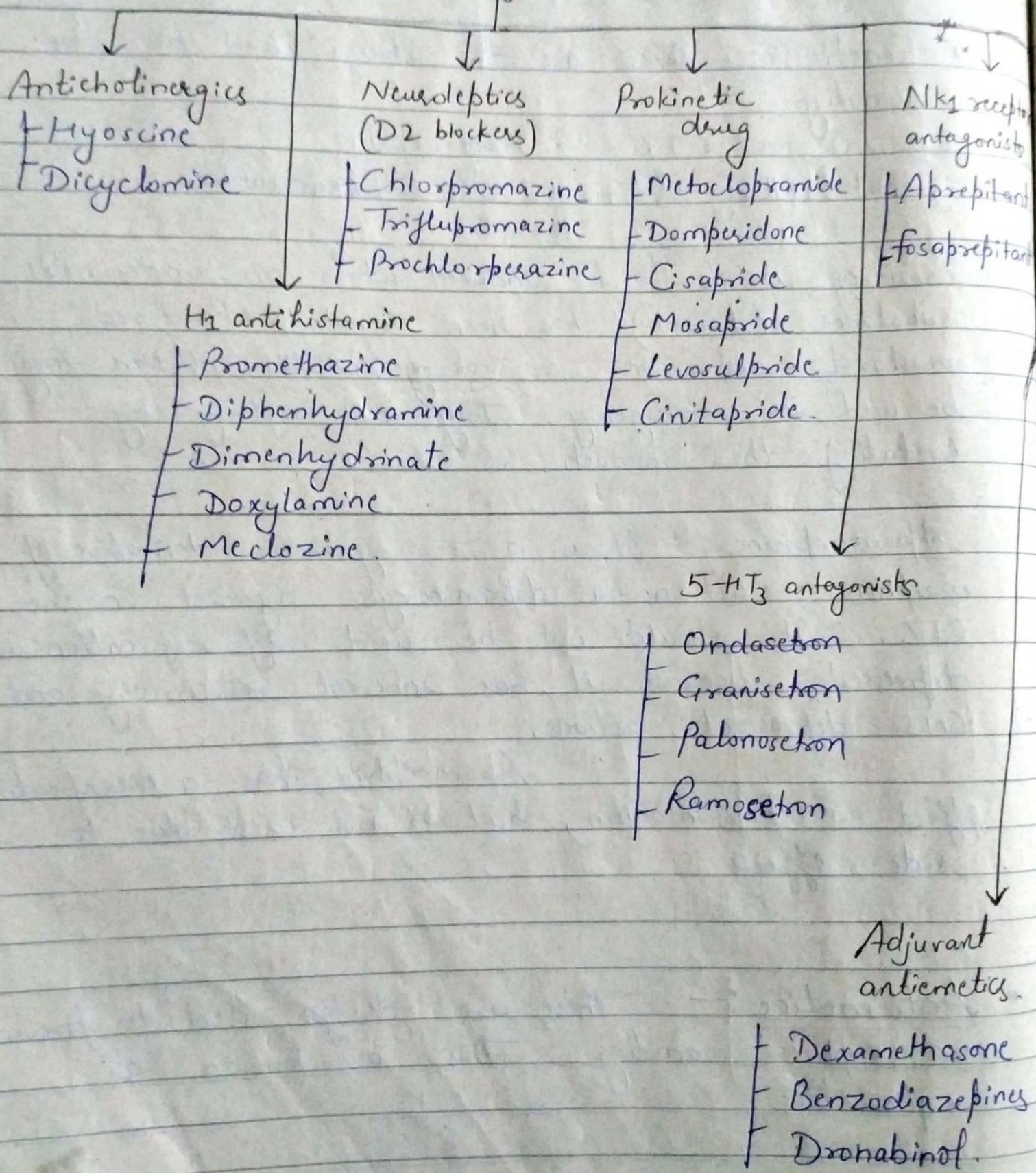
Vomiting needs to be induced when an undesirable substance (poison) has been ingested. Powdered mustard suspension or strong salts solution may be used in emergency. They act reflexly by irritating the stomach.

Apomorphine :- It is a semisynthetic derivative of morphine; act as a dopaminergic agonist on the CTZ. It should not be used if respiration is depressed, because it has inherent respiratory and CNS depressant actions.

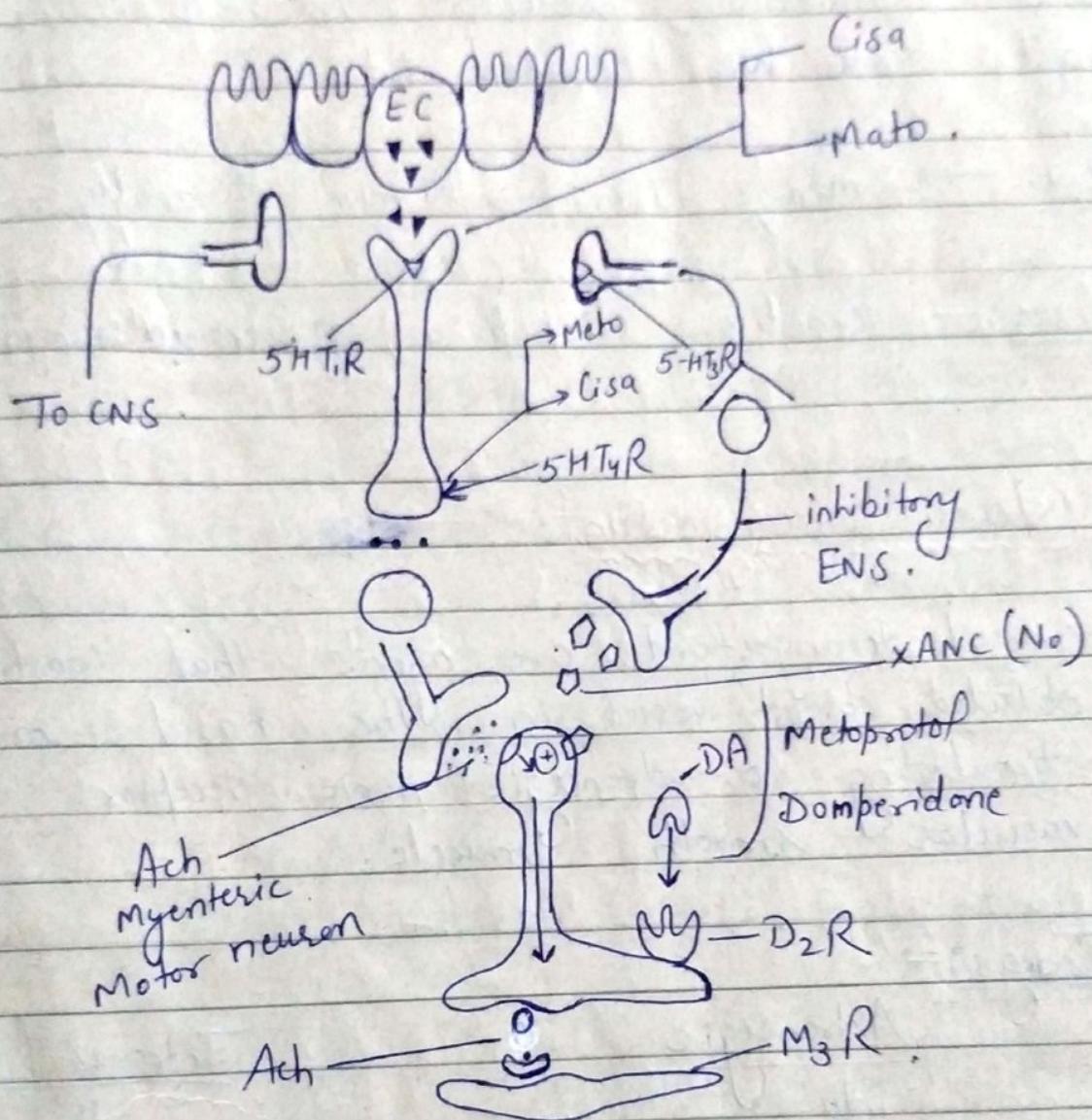
Apomorphine has a therapeutic effect in parkinsonism, but is not used due to side effects.

- Antiemetics :- These are drugs used to prevent or suppress vomiting. This is known as antiemetics.

Classifications of antiemetics :-



Mechanism of action:



Pharmacokinetic / - / well absorbed orally / enter/in

Distension & other stimuli trigger 5-HT release from the enterochromaffin cells located in the enteric mucosa stimulates intrinsic & extrinsic primary afferent neurons of the enteric nervous system through peripheral variant of 5-HT₁ receptor & 5-HT₃ receptor.

Pharmacokinetic :— well absorbed orally. enters in blood, placenta, secreted in milk. $t_{1/2} = 3-6 \text{ hrs}$. after 24 hrs excreted out.

i.v. \rightarrow 2 min, i.m \rightarrow 10 min & orally \rightarrow $\frac{1}{2}$ hr.

Uses :— emetics, dyspepsia, gastro-oesophageal reflux

* Nasal decongestant :-

Nasal decongestants are agents that constrict dilated blood vessels in the nasal mucosa by stimulating α -adrenergic nerve receptors in vascular smooth muscle.

Drugs :-

Adrenergic

- ↓
Topical & oral route
→ Ephedrine
→ Naphazoline
→ Oxymetazoline
→ Phenylephrine.
→ Pseudoephedrine.

Intranasal steroids

- ↓
Topical route
→ Beclomethasone.
→ fluticasone.
→ Mometasone.

(Analeptics)

- * Respiratory stimulant :-

are those which stimulate respiration & have resuscitative value in coma or fainting.

Situations in which analeptics are used :-

- Respiratory depression due to hypnotic drug poisoning.
- Suffocating on drowning
- failure to ventilate spontaneously after general anesthesia.

Drugs :-

Doxapram

Pethcarnide

Modafinil

Reflex stimulant :- Ammonia & alcohol vapours.

Doxapram :— 1.5-4 mg/min iv. is given as

respiratory stimulant along with assisted mechanical ventilation.

* Appetite stimulant & suppressants :-

- Appetite stimulant :- These are substances intended to promote digestion of food.
- A no. of proteolytic, amylolytic and lipolytic enzyme are marketed in combination formulation.
- Vigorously promoted for dyspeptic symptom & as appetite stimulant or health tonics.
- They are occasionally beneficial, only when elaboration of enzymes in gut is deficient.
- Their routine use in tonic & appetite improving mixtures is irrational.

e.g :- Megesterol acetate :-

- Appears to act via CNS to enhance appetite, mechanism of action is not fully known.
- Stabilizes or increase body weight.
- Any weight gain = fat accumulation (drug enhance expression and activity of lipogenic enzyme)
- Possible side effect (edema).

- Appetite suppressants :-

An anorectic or anorexic is a drug which reduces appetite resulting in lower food consumption leading to weight loss.

Drugs used in appetite suppressants :-

- Benzphetamine
- Mazindol.
- Diethylpropion
- Phentermine.

— * Carminative :-

Carminative is a preparation intended to either prevent formation of a gas in the GIT or facilitate the expulsion of ~~gas~~ ^{caused by} gas, thereby combatting flatulence.

Drugs used in carminative:

Sodium bicarbonate

0.6-1.5 g

Peppermint oil

0.06-0.1ml

Tincture cardamom

1-2ml

Oil of oil

0.06-0.2ml

Tincture ginger

0.6-1ml

Uses :- • flatulent dyspepsia.

• To prevent regurgitation of milk in infants.

* Digestants :-

These are the substances intended to promote digestion of food. A no. of proteolytic, amylolytic and lipolytic enzymes are marked in combination formulation and promoted for dyspeptic symptom & as appetite stimulant.

- i) Pepsin :— may be used along with HCl in gastric achylia due to Atrophic gastritis carcinoma etc.
- ii) Pepain :— It is proteolytic enzyme obtained from raw papaya.
- iii) Pancreatin :— It is mixture of pancreatic enzymes obtained from ~~dog~~ hog & pig pancreas. It contains amylase, trypsin & lipase and is indicated in chronic pancreatitis fat and nitrogen content of stools may be reduced and diarrhoea may be prevented.
- iv) Diastase :— These are amylolytic enzyme obtained from the fungus Aspergillus oryzae.