Drugs For Constipation (Purgatives)

✓ Too infrequent passage of stool that may be due to decreased motility in colon or due to difficulty in evacuation.

Causes:

1. Diet: decrease in water & fibers.
2. Local painful condition: anal fissures, piles.
3. Lack of muscular exercise.
4. Drugs: musclr relaxants, anticholinergics ,Ca++ blockers.

Treatment of constipation:

①General:

1.increase fluids.

2.increase fibers.

3.treat local causes.

4.regulation of bowel habit.

5.avoid drugs causing constipation.

②Drugs: (laxatives –purgatives) drugs that hasten the transit of food through the intestine by several methods

Classification of Laxative & Purgatives:

1) Bulk purgatives: increase volume of non absorbable solid residue.
2) Osmotic purgatives: increase water content in large intestine.
3) Stimulant purgatives: increase motility & secretion.
4) Fecal softeners (lubricants): alter the consistency of feces >>easier to pass.

❶Bulk purgatives:

- Dietary fibers: undigested polysaccaride, vegetables , fruits , grains, bran, pectin.
- Natural & semi synthetic hydrophilic colloids: psyllium seed, methyl cellulose, carboxymeythyl cellulose (CMC).
- Synthetic non absorbed resins: polycarbophil.

Mechanism of Action:

Non absorbed materials>>increase bulk of intestine content by water absorption>>increase mechanical pressure on the walls of intestine>>stimulate the stretch receptor >>increase peristalsis.

Side effects:

1) Delayed onset of action (several days).
2) Intestinal obstruction→so we have to take enough water.
3) Malabsorption syndrome, abdominal distention.
4) Interfere with other drug absorption ,e.g.iron , cardiac glycosides.
5) May affect other drug absorption cellulose>>>decrease absorption of salicylates, glucosides.
6) Ca carbopil >> decrease absorption of tetracycline.

❷Osmotic purgatives:

- soluble but not absorbed.
- increase water content in large intestine .

➲e.g:

- ✓ lactulose: semisynthetic disaccharide of fructose &galactose.
- ✓ saline purgatives: magnesium salts (most one to cause diarrhea), sodium of potassium salts.

Lactulose:

- Metabolized by bacterial flora in the colon into fructose& galactose.
- these sugar are fermented into lactic acid & acetic acid that function as osmotic laxatives.

Side effects:

- delayed onset (2-3)days.
- abdominal cramps& diarrhea.
- electrolyte disturbance.

Saline puragatives:

- Are poorly absorbed salts. They remain in the bowel & retain water by osmosis thereby ↑ the volume of faeces → ↑ distension → ↑ peristalsis → evacuation of watery stool.
- Rapid effect within 1 – 3 hr
  - × Magnesium sulphate (Epson`s salt)
  - × Magnesium hydroxide (milk of magnesia)
  - × Sodium phosphate.

Side effects:

1) Intravascular volume depletion
2) Electrolyte fluctuation : severe in children.
3) Isotonic or hypotonic soln should be used
4) Systemic effects.

Contraindication:

- Elderly patients, renal insufficiency or cardiac patients.
- Sodium salts →in CHF.
- Magnesium salt in:
  - × CNS depression
  - × neuromuscular block
  - × renal failure
  - × heart block

❸ stimulant purgatives :

🛠Mechanism of action :

- These are drugs stimulate gut mucosa through enteric nerves stimulation . these impulses arising from mucosa are transmitted smooth muscles of the gut → peristalsis & purgation.

Members:

1) Bisacodyl
2) Anthraquinone derivative .
3) Castor oil.

①Bisacodyl

- Act on large intestine (weak)
- Onset time 6 – 10 hr, take at night .

②Castor oil

- Fixed oil degraded by lipase → ricinoleic acid + glycerine.
- ricinoleic acid irritate mucosa.
- Acts on small intestine (strong) .
- 5-20 ml on empty stomach in the morning
- O.T = 4 hr

③Anthraquinone derivatives:

- Senna
- cascara
- aloes
- Glycosides (emodin morety + sugar)

- In colon, glycosides are hydrolyzed bacteria into emodrin
- Emodrin is absorbed , has direct stimulant action on myenteric plexuss → ↑ smooth muscle contraction → defaecation.
- Bowel movment in 12 hr orally or 2 hr rectally
- Given at night .

💀Side effects:

- Abdominal cramps may occur
- Atonic colon due to prolonged use

☠Contraindication

- Senna in lactation
- Castor oil in pregnancy → reflex contraction of uterus → abortion.

❹fecal softeners (lubricants)

- Are non absorbed drugs that soften the faeces thus promoting defaecation .

1) Surfactants :

Docusatae (sodium dioctyl sulfosuccinate)

↓ surface tension of faeces

2) Mineral oil (liquid paraffin) .
3) Glycerine (suppository)
4) Evacuant enema

Side effect of liquid paraffin:

1) ↓absorbtion of fat soluble vitamin
2) Delay wound healing in piles
3) ↑ activity of oral anticoagulant

Diarrhoea

✓ Frequent passage of liquid faeces.

Causes:

1) Infection (bacterial or protozoal)
2) Toxin (contaminated food)
3) Drug as :
   - cholinergics
   - adrenergic blockers
   - prostaglandins
   - bile acids
   - broad spectrum antimicrobial drugs.

Treatment :

➲ 3 approaches for acute diarrhea.

1) Maintenance of fluid & electrolyte balance.
2) Use of anti-infective agents.
3) Use of non antimicrobial ant diarrheal agent.

❶Maintenance of fluid & electrolyte balance:

1) Oral rehydration salts

- Na,K, glucose , amino acids.
- Diarrhea due to viral infection in infants.

2) Intravenous fluid therapy .
3) NSAIDs as aspirin & indomethacin.

❷ Anti infective agents

Are used to treat the infection responsible for diarrhea.

1) Anti- amebic drugs:
   Metronidazole
2) Anti-salmonella drugs:
   (typhoid-paratypoid fever):
   Chloramphenicol- Amoxicillin
3) Anti-shigella drugs (dysentery):
   Chloramphenicol
4) Cholera :
   Tetracyclines and Quinolones
5) Anti-fungal:
   Ketoconazole
6) Campylobacter pylori:
   Clarithromycin or metronidazole

❸Non-antimicrobial antidiarrheal agents:

a) Adsorbents:
   - Pectin "موجود بقشر التفاح" (indigestible carbohydrate), Kaolin (natural magnesium, Al silicate)
   - Adsorbe toxins, bacteria, fluids
   - Form protective coat over inflamed bowel
   - Used in acute diarrhea
   - E.g. kaopectate

b) Colloidal Bismuth: (traveler diarrhea)
   - Bismuth subsalicylate
   - Bismuth binds enterotoxines (antimicrobial)
   - Subsalicylate inhibit prostaglandin & chloride secretion
     " PG→ ↑ cl secretion → diarrhea"

Antimotility drugs:

1. Muscarinic receptor antagonist:
   - Atropine, hyoscine
   - Dicyclomine, propantheline
2. Opioid drugs:
   - Codeine, diphenoxylate, loperamide

Side effects:

- constipation
- abdominal cramps
- Drowsiness
- dependence

- Codeine (morphine congener)
- Diphenoxylate, loperamide (pethidine congener)

a) Loperamide:

- Don't cross BBB → no analgesic activity
- No potential for addiction

b) Diphenoxylate:

- Can cross BBB → potential for addiction (in high dose)
- Combine with atropine because if patient take high dose to give euphoria or sedation → side effects of atropine will appear → the patient will not take it more

Smooth muscle relaxants (antispasmodic):

Mebeverine:

- Reserpine derivatives
- Direct relaxant action on GI smooth muscle
- Antispasmodic agents in IBS

Irritable bowel syndrome: (IBS)

- ✓ Chronic bowel disorder characterized by abnormal GI motility, abdominal discomfort but no structural abnormalities

Treatment:

- Antispasmodics
- TCA (anticholinergis action, decrease visceral afferent sensation)
- Diarrhea (alosetron)
- Constipation (tegaseroid)

Alosetron:

- Selective $5HT_3$ receptor antagonist
- On enteric cholinergic neurons, thus inhibit colon motility
- Blocks central response to visceral stimulation
- Used in severe IBS with diarrhea (I mg/bid) only in females.
- Side effects: constipation & ischemic colitis

Tegaserod:

- Partial mucosal $5HT_4$ agonist
- IBS-associated with constipation
- 6 mg bid for 8 weeks
- Side effects: diarrhea, headache(due to crossing BBB)

Chronic inflammatory bowel disease

Comprises:

ulcerative colitis
ulceration of colon.

chron's disease
granulomatous lesions affecting ileum & colon

Causes:

- Not known.
- Abnormal activation of the immune system due to unknown invader.
- The susceptibility is genetically inherited.

→ treated by anti-inflammatory & immunosuppressant drugs.

Symptoms:

- Abdominal pain.
- Diarrhea.
- Bleeding.

Complication:

- anemia.
- megacolon(fever, abdominal pain, dehydration).
- colon cancer.

Anti-inflammatory drugs

✓ Needs direct contact with inflammed tissues.

1) 5 aminosalicylic acid compound (5-ASA).
2) corticosteroids.

- Treat→ Moderate – Severe ulcerative colitis. (*not mild cases*)
- Less effective as prophylactic (maintaining remission)(as treatment only)
- Orally :prednisone , prednisolone.
  - ➲ Budesonide as controlled release oral formulation (low bioavailability).
- Budesonide is subjected to rapid 1st pass hepatic metabolism resulting in low oral bioavailability which is wanted to ↓ systemic adverse effects that's resulting from the oral & rectal preparations & the budesonide has controlled release preparation will releases the drug in distal ileum & colon where it acts.
- Hydrocortisone enema or suppository.

3) immunomodulators:
   - Azathioprine
   - Methotrexate
   - Cyclosporine
   - 6-mercaptopurine
   - In Severe condition. resistanceSteroid dependent or steroid resistant patients.

4) biologial therapy (infliximab).
5) antibiotics:metronidazole – ciprofloxacine.
6) surgery: removal of entire colon & rectum (megacolon).

① 5 aminosalicylic acid compound (5-ASA)

- Topical anti-inflammatory effect.
  - Azostructure (N=N)
- Reduces absorption in small intestine.
- it's poorly absorbed orally
- Release 5-ASA at site of action.
  - Olsalazine: 2 molecules of 5-ASA (dipentum).
  - Balsalazine:5-ASA + inert carrier (colozal)
  - Sulfasalazine:5-ASA + sulphapyridine.

Mesalamines

✓ Controlled release spheres of 5-ASA.

✓ Released into small intestines & colon.

- Given orally (absorption occurs at site of action) & rectally.

➲ Treat & maintain remission in mild to moderate ulcerative colitis.

- Well tolerated, less side effects (sulfa free).
- Eg: pentasa (orally)

➲Used in :
Rx & maintain remission in (mild to moderate UC)

Sulfasalazine (Azulfidine)

- Prodrug.
- Broken by flora (azoreductase) in the colon into:
  - 5 aminosalicylic acid (not absorbed , active moiety).
  - Sulphapyridine (absorbed, not active, side effects).

Mechanism of action:

- 5ASA has anti-inflammatory due to:
- Inhibition of prostaglandine & leukotrienes.
- Decrease neutrophil chemotaxis.
- Decrease free radical production.

Side effects:

1) Crystalluria.
2) Megaloblastic anemia.
3) Bone marrow depression.
4) Impairment of male infertility.
5) Folic acid deficiency (should be provided).
6) Interstitial nephritis.

➲ all AEs are attributed to sulphapyridine except interstitial nephritis which is caused by 5-ASA.

Uses:

- Orally & rectally for treatment of :
  - Mild-moderate ulcerative colitis.
  - chron's disease.
  - Rheumatoid arthritis.
- Should be taken after meals.
- Dose should be reduced in renal failure.
- Can be used in pregnant women.

➲Used in :

- Orally &rectally
  1) (mild-moderate UC)
  2) Chron's Diz
  3) Rheumatoid Arthritis

Infliximab

- ✓ Is a monoclonal IgG antibodies.
    - 25% murine – 75% human.
- ✓ Anti TNF α.
- ✓ Given as infusion (5-10 mg/kg).
- ✓ 2 weeks to give response.

Uses:

- Severe Chrone disease
- Patients not responding to immunomodulators or glucocorticoids.

Side effects:

- Adverse infusion reaction.
- Infection complication (TB , sepsis).

➲Used in :

1) Sever CD
2) Pnts not responding to Immunomodulators or glucocorticoids

Drugs therapy of reflux esophegitis

Definition:

Inflammation of ! lower pat of ! esophagus due to regurgitation of Hcl

Causes:

- Delayed evacuation of ! stomach
- Increased intra-abdominal pressure e.g. during pregnancy
- Smooth muscle relaxant (Ca+ channel blockers)
- Caffeine
- Nicotine (smocking)

Treatment:

- Diet rich in ptn
- Avoid spicy food
- Weight reduction in obese pts
- Elevation of head during sleep
- Drug therapy:
    - Mild :antacids
    - Moderate: H2 receptor blockers ,prokinetics
    - Severe:PPIs

Prokinetics

- Drugs that increases gastric motility, emptying, & lower esophageal sphincter pressure (LESP)

Classification:

1. Cholinomimitics (bethanecol)
2. Dopamine antagonists (metocloprimide,domperadone)
3. 5HT4 receptoragonist(cisapride)

Uses:

1. Reflux esophegitis
2. Post operative atony
3. Decreased gastric motility due to diabetetic neuropathy
4. As antiemitics (D2 agonists)

Domperadone:

- Peripheral D2 agonist
- Does not penetrate well into CNS
- Has antiemetic (b/c CTZ located outside ! CNS) & prokinetic actions
- Its antiemetic action is less than metocloprimide
- Hyperprolactinemia: due to blockade of D2 receptors in posterior pituitary

Pharmacokinetics:

- Taken orally
- It undergoes 1st pass metabolism
- Excreted by in ! feces

Side Effects:

- Headache
- No interference with Parkinson's disease (b/c of its less CNS effect)
- Hyperprolactinemia: galactorrhea, breast enlargement, tenderness, & amenorrhea

◎Metoclopramide

- D2 antagonist (centrally & peripherally),it can blocke 5HT3 in high dose

Central actions:

1. Blocks D2 receptor in CTZ (chemical trigger zone)
2. Blocks D2 receptor in basal ganglia →pakinsonian symptoms & dystonia
3. Hyperprolactinemia (post pituitary)

Peripheral actions:

1. Blocks D2 receptor in stomach→increase motility
2. Cholinergic effect: by increasing ! release of Ach from cholinergic neurons →increase gastric motility & increase LESP (blocked by atropine)

Pharmacokinetics:

- Taken orally
- It undergoes 1st pass metabolism
- Excreted by ! kidney & bile
- T1/2 is 4-6 hs (24 hs in renal failure)
- Crosses BBB & placenta
- Dosage:10 mgs tdo oral, IV , supp
- No increase in gastric secretion
- No increase in colon motility >> no diarrhea

Uses:

- Prokinetic →increase motility in reflux esophegitis
- Antiemetic in vomiting due to toxic drugs, uremia, gastroenteritis, & postoperative pts

Adverse Effects:

- Extrapyramidal signs (parkinsonism):tardive dyskinesia, sedation,& dystonic reactions
- Endocrinological changes: galactorrhea, gynecomastia, menstrual irregulations
- CNS effect: drowsiness, dizziness

Anti-emetics

- Nausea and vomiting may be manifestations of many conditions. A useful mnemonic for remembering causes of vomiting is VOMIT
  - **V**estibular
  - **O**bstruction (opiates)
  - **M**ind (dysmotility)
  - **I**nfection (irritation of gut)
  - **T**oxins (taste and other)

Control of Vomiting:

1. Vomiting Center: Responds to inputs from
   - Vestibular System
   - Periphery (pharynx, GIT)
   - Higher brain stem & cortical structures
   - CTZ stimulation
   - Muscarinic, histaminergic, serotoninergic receptors

2. Chemoreceptor trigger zone (CTZ):
   - CTZ includes nucleus ambiguous, nucleus of solitary tract & nucleus of ! vague
   - CTZ is physiologically outside BBB (chemical stimuli in blood, CSF)
   - D2, 5HT3 receptors

Causes of Vommiting:

1. CTZ stimulation:
   - Drugs: Morphine, Apomorphine, Digitalis, L-dopa, Bromocryptine, Estrogen, Emetine
   - Chemicals
   - Radiation
   - Uremia
2. ! periphery via sensory nerves : GIT irritation, MI, renal or biliary stones
3. Disturbance of vestibular system
4. Higher cortical centers stimulation:
   - Emotional factors
   - Nauseating smells or sights

◎Classification of antiemetic dugs:

1) Muscarinic receptor antagonists:
   - **Hyoscine & Atropin**
   - Motion sickness
   - Not in chemotherapy induced vomiting

2) H1 receptor antagonists:
   - Promathazine & Diphenhydramine
   - Motion sickness
   - Not in chemotherapy induced vomiting

3) Dopamine antagonists:
   - **Prokinetics:**
     - **Metclopromide & Domperidon**
     - Effective against vomiting due to gastroenteritis, medications, surgery, toxins, & uremia
     - S/Es: dystonic reactions, sedation, & postural hypotension
   - **Neuroliptics:**
     - **Chlorpromazine**
     - A/Es: Hypotension, restlessness, extrapyramidal symptoms

4) 5HT3 Receptors:
   - **Ondansetron**
   - Long duration of action
   - Very effective in vomiting due to chemotherapy, post-operative vomiting, & after radiotherapy

5) Cannaboids:
   - **Nabilone**, Dronabinol
   - S/Es: sedation, hallucination, & dystonia

6) Glucocorticoids:
   - **Dexamethason & Methyl prednisolon**
   - Highly effective in acute emiss
   - Mechanism is not known
   - S/Es: hyperglycemia & insomnia

7) Vit B6 (Pyridoxine) → for pregnant

Therapeutic choice of antiemetics

Motion sickness :

- Hyoscine for short journey.
- Diphenhydramine for long journey.

Vomiting with pregnancy:

a) Avoid all drugs in the 1st trimester.
b) Pyridoxine (B6).
c) Promethazine (late pregnancy).

Drug-induced vomiting (CTZ):

- Domperidone and metoclopramide.

Vomiting due to cytotoxic drugs:

- Ondansetron, dopamine antagonists.
- Dexamethazone, nabilone.

Post operative vomiting:

- Dopamine antagonists

شكرا خاص للي ساعدوني في تكملة الناقص من المحاضرة :
- الجوهرة
- سامية
- حنان شنقيطي

N.B: It is ! Last pharma lecture in our l!fe

En shallah

So → be happyyyyyyyyyy 

425 Pharma Girls

أشجان الحجي بدور الشلوي

حنان الشنقيطي دانة العيسى

نرمين العثيمين الدانة آل سعد