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الجمهورية اليمنية
وزارة التعليم العالي والبحث العلمي
جامعة 21 سبتمبر للعلوم الطبية والتطبيقية

GIT DISTURBANCE

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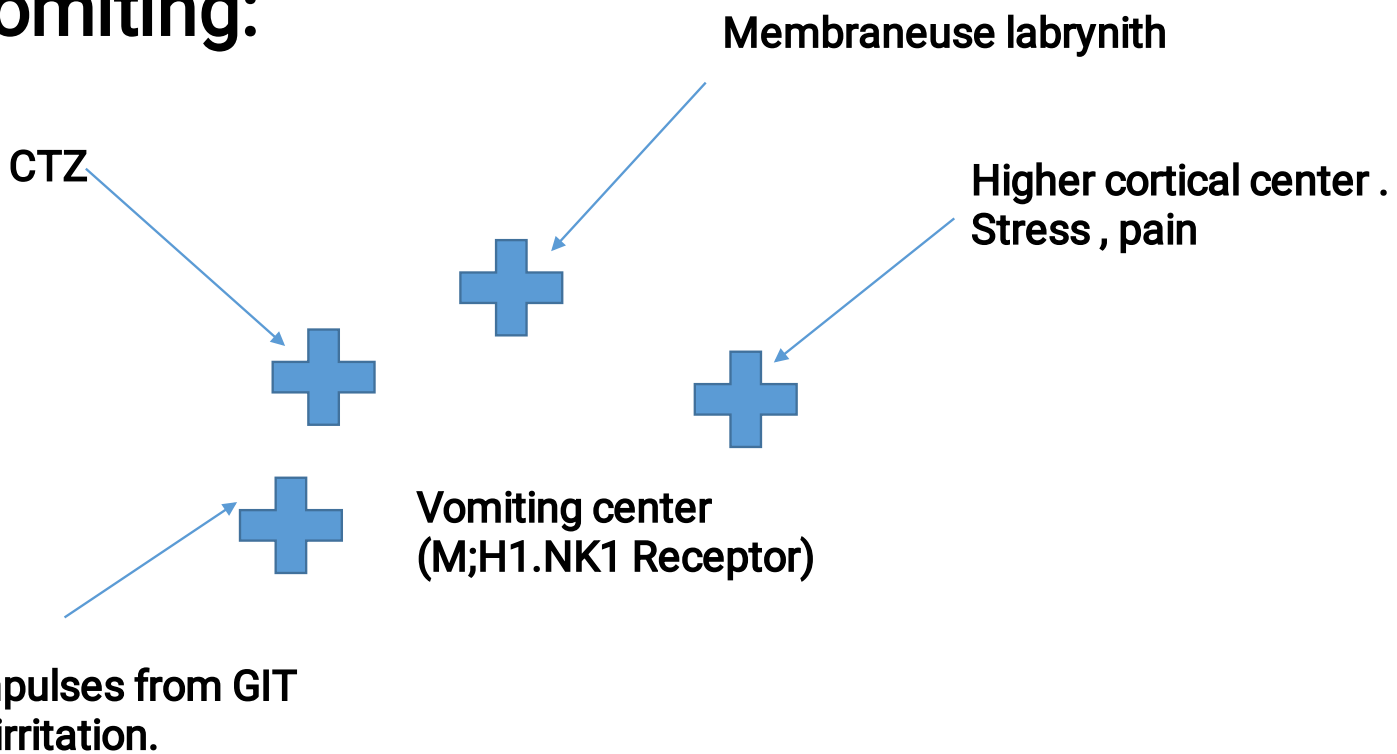
Vomiting

Mechanism of vomiting:



Emetics:

- Drugs that induce vomiting.
- Useful to evacuate the stomach in case of oral poisoning.
- Used only in conscious patients.

1- Central emetics:

As: Apomorphine

- Stimulate dopamine and opioid receptors in Chemoreceptor Trigger Zone
(CTZ)
- Used parenterally (S.C.)

2- Peripheral emetics:

- Used orally.
- As saturated solution of NaCl or mustard.
- Ipecacuanha (emetine) and ammonium carbonate are also used for slow
action.

Anti-Emetic drugs:

▯ Anti-muscarinic drugs:

As: Hyoscine

▯ Block muscarinic receptors in vomiting center.
▯ Short acting. (used for short journeys)
▯ Dose: 300 µg orally ½ hour before journey.
▯ Useful in motion sickness.

- Side effects:

▯ Dry mouth.
▯ Urinary retention.
▯ Constipation.
▯ Blurred vision.

Antihistaminic drugs:

- Block H1 receptors in vomiting center.
- Long acting. (used for long journeys)

- Examples:

- Cyclizine

- Meclizine

- Promethazine.

- Diphenhydramine - Dimenhydrinate

- Cyclizine & meclizine may combine with pyridoxine or caffeine. (Synergism and less side effects)
- Used in all types of vomiting.

- The common side effects:

 Sedation.

Anticholinergic effects.

Dopamine antagonists:

Block D2-receptors in CTZ.

Not effective in motion sickness.

- Examples:

- **Chlorpromazine (Largactil)®**
- **Prochlorperazine (Compazine)®**
- **Haloperidol (Haldol)®**

They are used mainly as anti-psychotic drugs.

Haloperidol has stronger anti-emetic effect than chlorpromazine.

Chlorpromazine avoided in pregnancy → teratogenic effect.

They are used orally and parenterally in chemotherapy-induced vomiting.

Side effects:

- Refer to antipsychotics.

▪ 5-HT3 receptor antagonists:

As: Ondansetron (Zofran)®

dose: 4-8mg bid or tid.

Granisetron (Kytril)®

dose: 1mg bid.

Dolasetron (Anzemet)

dose: 100mg orally or 12.5mg IV.

- Selective blockage of 5-HT3 receptors centrally (CTZ).
- They also act peripherally in GIT → ↓ visceral afferent impulses. (About 90% of serotonin released in GIT by enterochromaffin cells in intestine)
- Used orally and IV mainly in vomiting associated with surgery and cancer chemotherapy.

- Side effects:

▪ Headache.

▪ Minor Electrocardiographic changes. (↑ Q-T interval) with dolasetron.

▯ Metoclopramide: (plasil)®

- Dual anti-emetic.

▯ Act centrally by block D2 & 5-HT3 receptors in CTZ,

▯ Act peripherally by stimulation of 5-HT4 receptors in GIT and ↑cholinergic action → ↑ gastric motility → ↑ gastric emptying.

▯ The peripheral effects can be antagonized by atropine.

▯ Metoclopramide is effective in all types of vomiting except motion sickness.

▯ Used also in gastric ulcer, reflux esophagitis and hiccup.

- Dose:

10 mg 3-4 times/day before meals (t½ ≈ 4-6 hours)

- Side effects:

▯ Dizziness, sedation & nervousness.

▯ Extrapyramidal manifestations. (occur mainly in children and young patients)

▯ Diarrhea.

Domperidone: (Motilium)®

Similar to metoclopramide. (Dual anti-emetic)

Acting centrally by block D2 receptors in CTZ and peripherally by block α-receptors in stomach → ↑ motility. (Prokinetic agent)

Affects peripherally more than centrally.

Limited passage across BBB → less extrapyramidal side effects.

- Dose:

10-20 mg / 8 hours (orally and rectally)

Pyridoxine: (Vit. B6)

- The first choice in vomiting during pregnancy. (Weak effect)

- Dose:

25-40 mg tid orally

Cannabinoids:

Ex: Nabilone and dronabinol.

- They are derivatives of marijuana plant. (Cannabis Sativa)
- The exact action is not known but may be due to stimulation of cannabinoid receptors around vomiting center.
- Used mainly in patients receiving cancer chemotherapy.
- Used if no response to other antiemetics due to serious side effects:
- CNS toxicity → sedation, hallucination, vertigo & disorientation.
- Sympathomimetic effect.

Benzodiazepines:

Ex: Lorazepam & alprazolam.

- Their action may be due to sedative and anxiolytic properties.
- Cause sedation, hypnosis, dependence and addiction

Substance P receptor antagonists:

As: Aprepitant

 New class of drugs.

 Acting by block the neurokinin-1 (NK1) receptors for substance P in the brain.

 Given orally to prevent delayed emesis after cancer chemotherapy (2-5 days) where 5-HT3 antagonists are not effective.

 May used in combination with 5-HT3 antagonists and corticosteroids.

Side effects:

 Fatigue and constipation.

 Hepatic microsomal enzyme inducer.

Laxatives

• About 25% of population complains of constipation.
• Most of them are women & elderly people.
• Constipation and diarrhea result from the imbalance between the absorption and secretion of water and electrolytes by the gastrointestinal epithelium.
• Laxatives accelerate the movement of food through GIT.

Photo

- **Some causes of constipation:**

 Lack of dietary fibers.
 Dehydration or ↑sweating.
 Lack of physical exercises.
 Drugs. (as opioids, anticholinergics, diuretics, tricyclic antidepressants & iron preparations)
 GIT diseases. (as irritable bowel syndrome)
 Hormonal disturbances. (as hypothyroidism)
 Neurogenic disturbances. (as stress, parkinsonism & depression) Pregnancy.
 Increase drinking tea & coffee.

Non-pharmacological therapy:

- Increasing fluid intake.
- Increase of dietary fibers.
- Regular exercise.
- Appropriate bowel habits.

- Laxatives are used when non-pharmacological measures are not effective.

Classification of laxatives:

1- Stimulants and irritants:

- These agents probably induce a limited low-grade inflammation in the small
and large intestine to promote accumulation of water and electrolytes and
stimulate intestinal motility.

Examples:

a- Anthraquinone derivatives:

- Present in cascara, senna & aloe

 Contain emodin which stimulate colonic activity (onset of action 6-12 hours because emodine liberated after absorption).
 Produce colonic contractions and induce water & electrolytes secretion.
 Should not be recommended for chronic or long-term use.
 Melanotic pigmentation of the colonic mucosa may occur after months

b- Castor oil:

- Hydrolized in intestine by lipase and bile to ricinoleic acid which is very irritant → ↑ peristalsis.
- Produces laxative effect in about 1-3 hours.

c- Bisacodyl: (Dulcolax)®

- Potent stimulant of the colon.
- Effective orally & rectally (suppositories).
- The action need about 6 hours, so it taken at bedtime.
- **Oral dose: 10-15 mg/day.**
- Bisacodyl can damage the mucosa and initiate an inflammatory response

in intestine, so it should not be used for more than 10 consecutive days.

2- Bulking agents:

- ↑ Bulk of intestinal content → water retention & intestinal distension → ↑peristalsis
- Onset of action 1-3 hours.
- Taken in the morning.

- Examples:

a- Hydrophilic colloids: (indigestible foods)

- As agar, methyl cellulose & bran.
- Suitable & safe in chronic constipation of elderly patients.

b- Saline cathartics:

- Non absorbable salts have osmotic effect.
- As magnesium sulfate, magnesium hydroxide & sodium phosphate.
- Producing defecation in about one hour.
- They must be used with caution in patients with renal insufficiency or cardiac diseases.

c- Lactulose: (Duphalac)®

- Semisynthetic disacchride (fructose & galactose) → degraded in colon by bacterial flora to lactic acid and acetic acid.
- Not digested or absorbed → osmotic effect → ↑ peristalsis.
- **Dose:10-20 g 3-4 times daily**
- Safe and used for all ages.
- Used also in hepatic encephalopathy and liver diseases. (↓ ammonia)

d- Sorbitol and mannitol:

- Hydrolyzed in colon to short-chain fatty acids → fluid retention by osmotic effect → stimulates colonic motility.
- Given orally.

3- Stool softeners:

- Surface active agents → lower the surface tension of the stool to allow mixing of aqueous and fatty substances → softening the stool and permitting easier defecation.
- Taken at night. (onset of action 8-10 hours)
- Drug of choice in chronic constipation.

- Examples:

a- Liquid paraffin. (Mineral oil)

- Disadvantages:

 Bad taste.
 Prevent the absorption of fat soluble vitamins (A, D, E & K)
 Anal pruritus. (with long term use)
 ↓ Absorption of oral contraceptives.

b- Glycerin suppositories.

• Given rectally. (Absorbed from GIT)

• Rapid action in about one hour.

• Suitable for children and elderly people.

c- Docusate sodium. (Dicotyl sodium sulphosuccinate)

- Anionic surfactant.

- Dose: 200 mg/day.

- **Therapeutic uses of laxatives:**

 Constipation. (Acute & chronic)

 Oral food & drug poisoning.

 Before operations and abdominal X-ray. (Orally and by enema)

 After some anthelmintic drugs as niclosemide.

 Before labor. (Lactulose or liquid paraffin)

Antidiarrheals

• Drugs that decrease motility of GIT and increase reabsorption of fluids from intestine.

- Some causes of diarrhea:

 Bacterial gastroenteritis. (as E. Coli, Closteridium, Salmonella, Shigella & Cholera)
 Protozoal gastroenteritis. (as Entamoeba or Giardia)
 Viral infections. (as Rotavirus & HIV)
 Inflammatory bowel disease.
 Drugs (as some broad spectrum antibiotics, magnesium salts and mefenamic acid)
 Endocrine and metabolic diseases (as hyperthyroidism or diabetes)

- In therapy, we treat the specific cause firstly. (i.e. in cases of microbial infections, use antimicrobials.

➢ Non-specific Treatment (symptomatic):

1- Anti-motility drugs:

- The most effective antidiarrheal drugs.

a- Opioid derivatives:

Diphenoxylate (Lomotil)®

Loperamide (Imodium)®

- Stimulate presynaptic opioid receptors (μ and delta receptors) in enteric nervous system → ↓ acetylcholine release → ↓ intestinal motility and secretions.

- Side effects:

- Dizziness and narcosis.
- Constipation, urinary retention & dry mouth.
- Tolerance. (not used for long time).

- **Loperamide** has little side effects on CNS (weak BBB penetration).
- **Diphenoxylate** combined with atropine (synergism and less side effects).
- **Codeine phosphate** may be used from this group. (limited use due to dependence and addiction)

- This group is not recommended for young children.

b- Parasympatholytics:

- **As Atropine & propantheline**.

 Inhibit muscarinic receptors.

 Propantheline (Quaternary ammonium compound) is more selective action on GIT and less penetration for CNS comparing to atropine. (more polar)

 Dose of propantheline: 5 mg qid orally

 Side effects include anticholinergic effects.

2- Adsorbents:

▯ Kaolin & pectin (Kapect)®

▯ Act by adsorbing intestinal toxins or micro-organisms and by coating & protecting the intestinal mucosa.
▯ Decrease stool softness.
▯ Have weak antidiarrheal effect.
▯ Interfere with the absorption of other drugs.

▯ Cholestyramine: (Questran)®

▯ Binds with bile acids and some bacterial toxins. (cationic exchange resin)
▯ Cholestyramine mainly used in the treatment of bile acids-induced diarrhea (i.e. ↑ bile acids → ↑ osmosis in intestine).
▯ Used also as anti-hyperlipidemic drug →↓ cholestrol & LDL.
▯ Given orally with meals (as powder) tid or qid.
▯ ↓ Absorption of many drugs as digoxin, warfarin, aspirin, thyroxin and thiazides. (binding with them)

3- Agents that modify fluids & electrolyte transport:

- **As: Oral Rehydration Therapy. (ORT)**

 Correct dehydration, acid/base & electrolyte imbalance.

 Used in children for mild to moderate cases.

 Formulated as a powder containing:

o NaCl (2.6g)

o KCl (1.5g) dissolved in 1L of water to form solution

o Trisodium citrate (2.9g) **(New WHO formula)**

o Glucose (13.5g)

245mOsm/L

 This solution should not be stored for more than 24 hours.

 In severe cases use Parenteral Rehydration Therapy. (I.V. infusion of Nacl, glucose, ringer lactate,… etc)

Inflammatory Bowel Disease (IBD)

 Chronic inflammatory condition may lead to ulceration of the gut characterized by periods of remission and relapse over many years. (consider as autoimmune disease)

➢ **Symptoms:**

 Fever, lassitude.
 General malnutrition, anemia & weight loss. (due to poor absorption)
 Abdominal pain, nausea, diarrhea & anorexia.

➢ **Causes:**

 Genetic factors.
 Environmental factors (diet, stress, smoking, …… etc)
 Infective agents (bacteria, viruses)
 Drugs (as oral contraceptives)

- **Types of IBD:**

 Ulcerative colitis. (affect colonic & rectal mucosa)
 Crohn`s disease. (affect any pat of GIT)

- **The goals of treatment:**

 Correct dehydration, anemia & electrolytes.

- **Drug therapy.**

 Relief of symptoms.
 Maintaining remission and prevention of relapse.
 Preventing complications such as fistulas.
 Surgery.

Drugs used for therapy:

1- Corticosteroids:

- Broad anti-inflammatory effect.
- As:

✓**Prednisolone (40-60 mg/day orally)**

✓**Hydrocortisone**

✓**Budesonide**

- Given orally and rectally (as retention enema) and used parenterally in emergency situations.
- Dangerous side effects occur with long use. (Refer to Hormones)

2- Aminosalicylates:

- Active anti-inflammatory agents in IBD.
- The action may be related to inhibition of the production of IL-1 and TNF-α and inhibition of the lipoxygenase pathway.
- Taken orally and rectally. (Suppositories or enemas)

➢ **Sulfasalazine (salazopyrine)®**

 Consists of sulfapyridine plus 5-aminosalicylic acid linked by an azo bond.

 The azo-bond breaks by bacterial flora in colon to release 5-aminosalicylic acid (local anti-inflammatory action).

 The azo linkage prevents drug absorption in the stomach and small intestine.

 The usual dose 4-8 g/day in divided doses.

➢ **Side effects:** (due to sulfapyridine absorption)

 Nausea.

 Headache.

 Abdominal discomfort.

3- Immunosuppressive agents:

Ex: - Azathioprine
- Cyclosporine
- Infliximab (anti TNF-α)
- Used when the patients not respond to steroids and aminosalicylates.
- Given orally and parenterally.
- The serious side effects:
- Fever and rash
- Bone marrow depression.
- ↑ The risk of infection.
- Nephrotoxicity and hyperglycemia.

4- Antibiotics:

As:Metronidazole, ciprofloxacin and clarithromycin.

 Certain bacterial strains (e.g., Bacteroides or Lactobacillus) acting to manipulate the colonic flora in patients with IBD.

 The antibiotics used as adjunctive treatment with other medications or for prophylaxis from recurrence in postoperative IBD.

- Analgesics, anticholinergic and antidiarrheal agents play supportive roles
in reducing symptoms of IBD and improving quality of life.

Anti-spasmodic drugs

- Anticholinergic agents:

As: Atropine, propantheline, dicyclomine & hyoscine-N-butyl bromide (Buscopan)®

- Given orally or parenterally at onset of pain or used before meals in irritable
bowel syndrome (IBS).

-Mebaverine: (Duspataline)®

 Direct spasmolytic agent.

 Given orally in abdominal pain, cramps and in irritable bowel syndrome.

- **Chlorodiazepoxide** (from benzodiazepine group) 5 mg + Clidinium bromide (anti muscarinic) 2.5 mg = (Librax)®

 Cause rapid stabilization of visceral motor function → relief the symptoms of anxiety and tension in GIT & genitourinary tract.

 Given orally 2-3 times daily in chronic abdominal spasms and IBS.
 Drowsiness, anticholinergic effects and dependence are the main side effects.

- **Irritable bowel syndrome: (IBS)**

 Affects colon and characterized by chronic abdominal pain, discomfort, spasm, constipation or diarrhea.
 IBS may be caused by stress, infections, neurotransmitters imbalance or
hormonal changes.
 Common in women more than men.
 The treatment includes antispasmodics, selective serotonin reuptake inhibitors, relaxation therapy and prophylaxis from any irritant foods.