

### Antidiarrheal Agents

Can be used in mild to moderate acute diarrhea.

Should not be used in the presence of infective diarrhea.

Can be used to control chronic diarrhea, like in irritable bowel syndrome or inflammatory bowel disease.

### Opioid Agonists:

Have significant constipating effects: Inhibit presynaptic cholinergic nerves, leading to increased colonic transit time and increased fecal water absorption. Decrease mass colonic movements and gastrocolic reflex. Can have CNS effects and addiction potential. Usually combined with atropine to reduce dependence.

### Loperamide:

Does not cross BBB. No analgesic or addiction potential.

### Diphenoxylate:

Can have CNS effects and dependence.

### Kaolin and Pectin:

Kaolin is a naturally occurring hydrated magnesium silicate. Pectin is an indigestible carbohydrate derived from apples. Both act to absorb bacteria, toxins and fluid. Usually combined, e.g. Kaopectate. Taken far from other medications.

### Bile salt-binding resins:

#### Cholestyramine

#### Colistipol.

Malabsorption of bile salts (e. g .after surgical resection), can cause diarrhea. The drugs can bind bile salts. Can cause bloating, flatulence, constipation and fecal impaction. Also, drug and fat malabsorption.

### Octreotide:

Is a synthetic octapeptide with actions similar to somatostatin.

Somatostatin is a 14 amino acid peptide released in the

GIT and pancreas as well as from the hypothalamus:

1. Inhibits release of many hormones.
2. Reduces intestinal fluid and pancreatic secretions.
3. Slows GIT motility and gallbladder contraction.
4. Contracts blood vessels.
5. Inhibits secretion of some anterior pituitary hormones.

Clinical Uses:

1. Inhibition of endocrine tumor effects: Carcinoid can cause secretory diarrhea and systemic symptoms like flushing and wheezing.
  2. Diarrhea due to vagotomy or dumping syndrome or and AIDS.
  3. In small doses can stimulate motility in small bowel bacterial overgrowth or intestinal pseudo-obstruction secondary to scleroderma.
  4. pituitary tumors and GI bleeding. vagotomy usually means cutting the branch of the vagus nerve that tells your stomach to secrete gastric acid
- Dumping syndrome is a condition in which food, especially food high in sugar, moves from your stomach into your small bowel too quickly after you eat
- Scleroderma is an uncommon condition that results in hard, thickened areas of skin

## Drugs Used in the Treatment of Irritable Bowel Syndrome :

IBS is an idiopathic chronic, relapsing disorder characterized by: Abdominal discomfort pain, bloating, distention, or cramps with alterations in bowel habits, diarrhea, constipation, or both. Pharmacologic therapies for IBS are directed at relieving abdominal pain and discomfort and improving bowel function.

### • Antispasmodic or Anticholinergic Agents:

- Dicyclomine
- Hyoscyamine.

• Spasm is not an important symptom in IBS.

• They inhibit muscarinic cholinergic receptors in the enteric plexus and on smooth muscle.

• At usual low doses, have minimal side effects.

### • Serotonin 5-HT<sub>3</sub>- Receptor Antagonists:

- Alosterone:

• 5-HT<sub>3</sub> receptors are present in the afferent pain fibers in the extrinsic sensory neurons. Also present on the terminals of the enteric cholinergic neurons. Centrally, 5-HT<sub>3</sub> is involved in the central response to visceral afferent stimulation.

- Selective antagonist of 5-HT<sub>3</sub> receptors.

- Has long duration of action.

- Approved for women with severe IBS in whom diarrhea is the prominent symptom.

- Efficacy in men is not established.

- Can cause ischemic colitis, severe constipation requiring hospitalization and surgery

Ischemic colitis occurs when blood flow to part of the large intestine is temporarily reduced

• Tagaserod:

- Approved for short term treatment of women with IBS who predominantly have constipation.

- Reduces pain, bloating and hardness of stool.

- Expensive.

## Antiemetic Agents

Nausea and vomiting may be manifestations of a wide variety of conditions, including:

Adverse effects of medications.  
systemic disorders or infections.

Pregnancy.

Vestibular dysfunction.

CNS infection or increased pressure.

Peritonitis.

Hepatobiliary disorders.

Radiation or chemotherapy.

GIT obstruction, dysmotility, or infections.

### Pathophysiology

The brainstem "vomiting center" coordinates vomiting through interactions with cranial nerves VIII and X and neural networks in the nucleus tractus solitarius that control respiratory, salivatory, and vasomotor Centers.

Vomiting center contains high concentrations of:

M1 receptors.

H1 receptors.

Neurokinin 1 (NK1) receptors.

5-HT<sub>3</sub> receptors.

### Serotonin 5-HT<sub>3</sub> Antagonists

Ondansetron

Granisetron

Block central 5-HT<sub>3</sub> and peripheral (main effect) 5-HT<sub>3</sub> receptors.

Prevent emesis due to vagal stimulation and chemotherapy.

Other emetic stimuli such as motion sickness are poorly controlled.

Uses

Prevention of acute chemotherapy-induced nausea and emesis and postoperative nausea and vomiting.

Their efficacy is enhanced by combination therapy with dexamethasone and NK1-receptor antagonist.

Adverse effects: Headache, dizziness, and constipation

### Neurokinin 1 Receptor (NK1) Antagonists

Block central NK1 receptors in the area postrema.

Aprepitant

Used in combination with 5-HT<sub>3</sub>-receptor antagonists and corticosteroids for the prevention of acute and delayed nausea and vomiting from chemotherapy.

Cannabinoids

Dronabinol, Nabilone

Psychoactive agents.

Used for chemotherapy-induced vomiting.

Mechanisms for these effects are not understood.

Adverse effects

Euphoria, dysphoria, sedation, hallucinations, dry mouth, and increased appetite.

### Antipsychotic drugs

Prochlorperazine

Promethazine

Droperidol

Antiemetics due to blocking dopamine and muscarinic receptors.

Sedative effects due to antihistamine activity.

### Benzodiazepines

Lorazepam

Diazepam

Reduce vomiting caused by anxiety.

## Antiprotozoal drugs

• Protozoal and helminthic infections are a major cause of disease in many parts of the world.

some of these diseases

• in migrant workers

• or individuals returning from an endemic area

### Selected PROTOZOAL DISEASES

#### Amebiasis

• The protozoan *Entamoeba histolytica* causes amebiasis, an infection that is endemic in parts of the United States

• The parasite can be present in the host as either an encysted or a trophozoite form.

■ Initial ingestion of the cyst may result either in no symptoms or in severe amebic dysentery characterized by the frequent passage of bloodstained stools.

• symptom occurs after invasion of the intestinal mucosa by the actively motile and phagocytic trophozoite form of the protozoan.

• Trophozoites may spread to the liver through the portal vein and produce acute amebic hepatitis

• Many patients continue to excrete cysts for several years after recovery from the acute disease and therefore are a hazard to themselves and other persons

*Entamoeba histolytica*.

This organism can cause:

Asymptomatic intestinal infection.

Mild to moderate colitis.

Severe intestinal infection (dysentery).

Ameboma (a tumor-like mass in the intestines in amebiasis which results in a large local lesion of the bowel).

Liver abscess and other extraintestinal infection

#### Treatment of Specific Forms of Amebiasis

##### Asymptomatic Intestinal Infection

Asymptomatic carriers are treated with a luminal amebicide.

Standard luminal amebicides are:

Diloxanide furoate, Iodoquinol, and Paromomycin.

Therapy with a luminal amebicide is also required in the treatment of all other forms of amebiasis.

##### Amebic Colitis

Metronidazole + a luminal amebicide is the treatment of choice.

Tetracyclines and erythromycin are alternative drugs for moderate colitis but are not effective against extraintestinal disease.

Dehydroemetine or emetine can also be used, but are best avoided because of toxicity.

## *Balantidium coli*

• the largest of the protozoans that infect humans

• trophozoite form is covered with cilia, which impart mobility

• Infection is acquired through the ingestion of cyst-contaminated soil, food, or water.

• The trophozoite causes superficial necrosis or deep ulceration in the mucosa and submucosa of the large intestine

• healthy persons commonly exhibit nausea, vomiting, abdominal pain, and diarrhea

• nutritionally stressed patients may develop severe dysentery.

81

### Classes of oral antiprotozoal drugs

Commonly used oral antiprotozoal drugs can be

generally classified into two main groups:

• antimalarial drugs

• miscellaneous antiprotozoals.

In addition to their use as antiprotozoals, some of them such as metronidazole and doxycycline

are also used for treating bacterial infections.

## antiprotozoals

Commonly used miscellaneous

antiprotozoals include

- metronidazole,
- tinidazole and
- nifuratel.

## Metronidazole

Drug of choice in the treatment of extraluminal amebiasis.

It kills trophozoites but not cysts of *E histolytica* and effectively eradicates intestinal & extraintestinal tissue infections.

- exerts activity against most anaerobic bacteria and several protozoa.

- The drug freely penetrates protozoal and bacterial cells but not mammalian cells.

- The enzyme, pyruvate-ferredoxin oxidoreductase, found only in anaerobic organisms, reduces metronidazole and thereby activates the drug.

- Reduced metronidazole disrupts replication and transcription and inhibits DNA repair.

## Clinical Uses

### Amebiasis

Metronidazole

The drug of choice in the treatment of all tissue infections with *E histolytica*. (hepatic abscess; intestinal wall/ extraintestinal infections)

- Not effective against luminal parasites and so must be used with a luminal amebicide to ensure eradication of the infection.

kills trophozoites but not cysts

### Giardiasis

Metronidazole is the treatment of choice

Efficacy after a single treatment is about 90%

Tinidazole is equally effective.

### Trichomoniasis

Metronidazole is the treatment of choice.

A single dose of 2 g is effective.

## Adverse Effects & Cautions

Common:

Nausea, headache, dry mouth, metallic taste.

Infrequent adverse effects:

vomiting, diarrhea, insomnia, weakness, dizziness,.

Rare:

Pancreatitis and severe central nervous system toxicity

Tinidazole is better tolerated.

Metronidazole is best avoided in pregnant or nursing

women, although congenital abnormalities have not

clearly been associated with use in humans.

## Tinidazole

Similar activity

& better toxicity profile than metronidazole.

Tinidazole works as well as metronidazole and has many of the same side effects, but it can be given in a single dose. Whereas, nifuratel can be used as an alternative to metronidazole or tinidazole in the treatment of trichomoniasis.

## Antimalarial Drugs

- Malaria is a mosquito-borne infectious disease of humans and other animals caused by parasitic protozoans (a group of single-celled microorganism) belonging to the genus *Plasmodium*.

### Life Cycle of Malaria Parasites

- Malaria transmitted by the bite of infected female *Anophelinosquitoes*.

- From the mosquito salivary glands enter the circulation

- localize in hepatocytes to multiply, and develop

- Asymptomatic for 5 to 15 days, depending on the *Plasmodium*

- Tissue schizonts rupture,

- releasing thousands of merozoites that enter the circulation, invade erythrocytes where mature schizonts form

- Schizont-containing erythrocytes rupture, each releasing 6 to 32 merozoites this process that produces febrile attacks.

## Antimalarial Drugs

- Chloroquine:

- Most useful agent to terminate an acute attack.

- Available as oral, IV, and IM preparation.

- Resistance develops.

- Causes N, headache, and is teratogenic.

- Quinine:

- Oldest drug, from *Cinchona* tree.

- Many actions

- Toxic

- Still used, no resistance to its action

- Artemisinin:

- New drug, from Sweet wormwood, الشيخ

- Doxycycline

- Pyrimethamine