42.1. Antidiarrheals

Diarrhea may be caused by various factors.

- Osmotic diarrheas are caused by insufficient absorption of compounds with osmotic activity from the intestines.
- Secretory diarrheas are observed when increased secretion of electrolytes and water to the intestinal lumen occurs.
- There are also diarrheas caused by the increased permeability of the intestinal mucosa.
- Diarrheas resulting from the disturbance of intestinal motility are also known.

The cause of osmotic diarrheas may be the maldigestion or malabsorption syndromes or consumption of food that is absorbed with difficulty.

Secretory diarrheas are caused by bacterial toxins, which by reacting with protein G activate adenylate cyclase in mucosa cells, which leads to an increased production of cAMP.

Endogenic substances such as cholic acids and VIP (vasoactive intestinal peptide) may also be responsible for secretive diarrheas.

Diarrheas caused by the increased permeability of the intestinal mucosa can appear in enteritis and in colon carcinoma.

Diarrheas resulting from the disturbance of intestinal motility can be observed in hyperthyroidism.

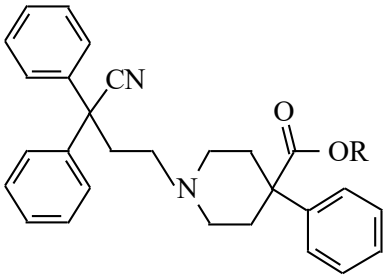
The causes of diarrheas should be taken into account when therapy is administered.

The following agents are used:

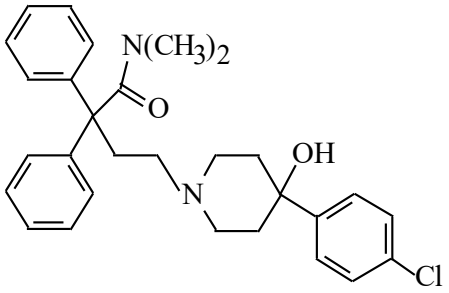
- astringent agents (tannins and bismuth compounds)
- adsorptive agents (medicinal charcoal and pectins)
- agents increasing the tone of the intestinal smooth muscles (opioids – diphenoxin, diphenoxylate, loperamide)
- antibacterial agents (nystatin, furazolidon, nifuroxazide).

Some diphenylpropane derivatives with peripheral activity are used as antidiarrheals.

Diphenoxin, diphenoxylate and loperamide are used for this purpose. These derivatives show a similar chemical structure to phenylpropanamine derivatives with central activity, which are used as opioid analgesics.



Diphenoxylate, R = -CH_2-CH_3; REASEC
Diphenoxin, R = H; LYSPAFEN



Loperamide, IMODIUM, LOPERAMID

Diphenoxylate is a prodrug. Its ester group hydrolyses in the body to an acid derivative – diphenoxin, whose action is 5 times stronger than that of diphenoxylate. Loperamide, in contrast to diphenoxylate, contains an amide group. It acts 3 times more strongly than diphenoxylate and 50 times than codeine. These drugs are indicated in the treatment of diarrheas of different origin.

42.2. Laxatives

The laxatives are commonly used to accelerate the movement of food through the gastrointestinal tract.

Based on their mechanism of action these drugs can be classified as:

- bulking agents (magnesium sulfate, lactulose, lactitol, macrogol)
- stool softeners (docusate sodium, mineral oil, glycerin suppositories)
- irritants and stimulants (bisacodyl, sennosides)
- motility agents that block peripheral dopaminergic receptors (metoclopramide, cisapride, domperidone).

42.2.1. Bulking agents (osmotic laxatives)

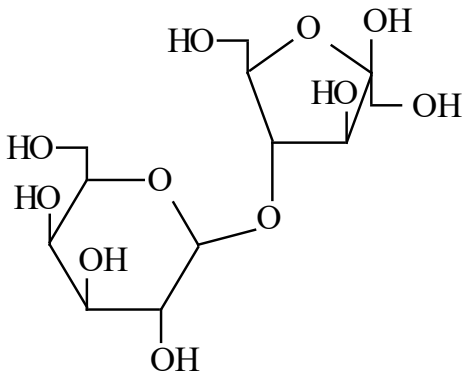
The bulk laxatives include hydrophilic colloids (from indigestible parts of fruits and vegetables). They form gels in the large intestine, causing water retention and intestinal distension, thereby increasing peristaltic activity. Similar actions are produced by macrogol and bran.

Saline cathartics such as magnesium sulfate and magnesium hydroxide are nonabsorbable salts that hold water in the intestine by osmosis and distend the bowel, increasing intestinal activity and producing defecation in about one hour.

Macrogol pharmaceuticals (FORLAX, FORTRANS, PROLAXATAN) are used in the symptomatic treatment of the constipation in adults.

Isosmotic electrolyte solutions containing polyethylene glycol are also used as colonic lavage solutions to prepare the gut for radiologic and endoscopic procedures.

Lactulose and lactitol are semisynthetic disaccharides that also act as osmotic laxatives.

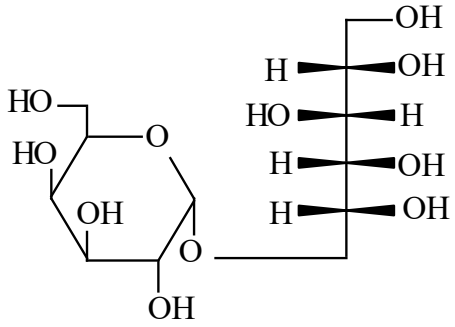


Lactulose, DUPHALAC, LACTULOSUM, NORMALAC, NORMASE

4-*O*-*D*-Galactopyranosil-*D*-fructose

Lactulose is composed of fructose and galactose.

Lactitol, in contrast to lactulose contains sorbitol instead of fructose.



Lactitol, LACTITOL

4-*O*-*D*-Galactopyranosil-*D*-glucitol

These disaccharides are nonabsorbable from the gastrointestinal tract. They are not metabolized in the small intestine, whereas in the colon they are metabolised by intestinal bacteria to organic acids, mainly acetic, propionic and butyric acids that change the pH of the colon environment from 6.5 to 5.6.

At this pH value, the proteolytic activity of bacteria using ammonia to synthesise their own proteins is decreased. That decreases the absorption of ammonium ions from the colon into the blood circulation (Figure 42.1).

The degradation of disaccharides to small-molecule organic acids increases osmotic pressure and, as a result, increases the amount of water in the colon and softens the stool.

The laxatives are used in habitual and chronic constipations caused by excessive dehydration and in liver encephalopathy.

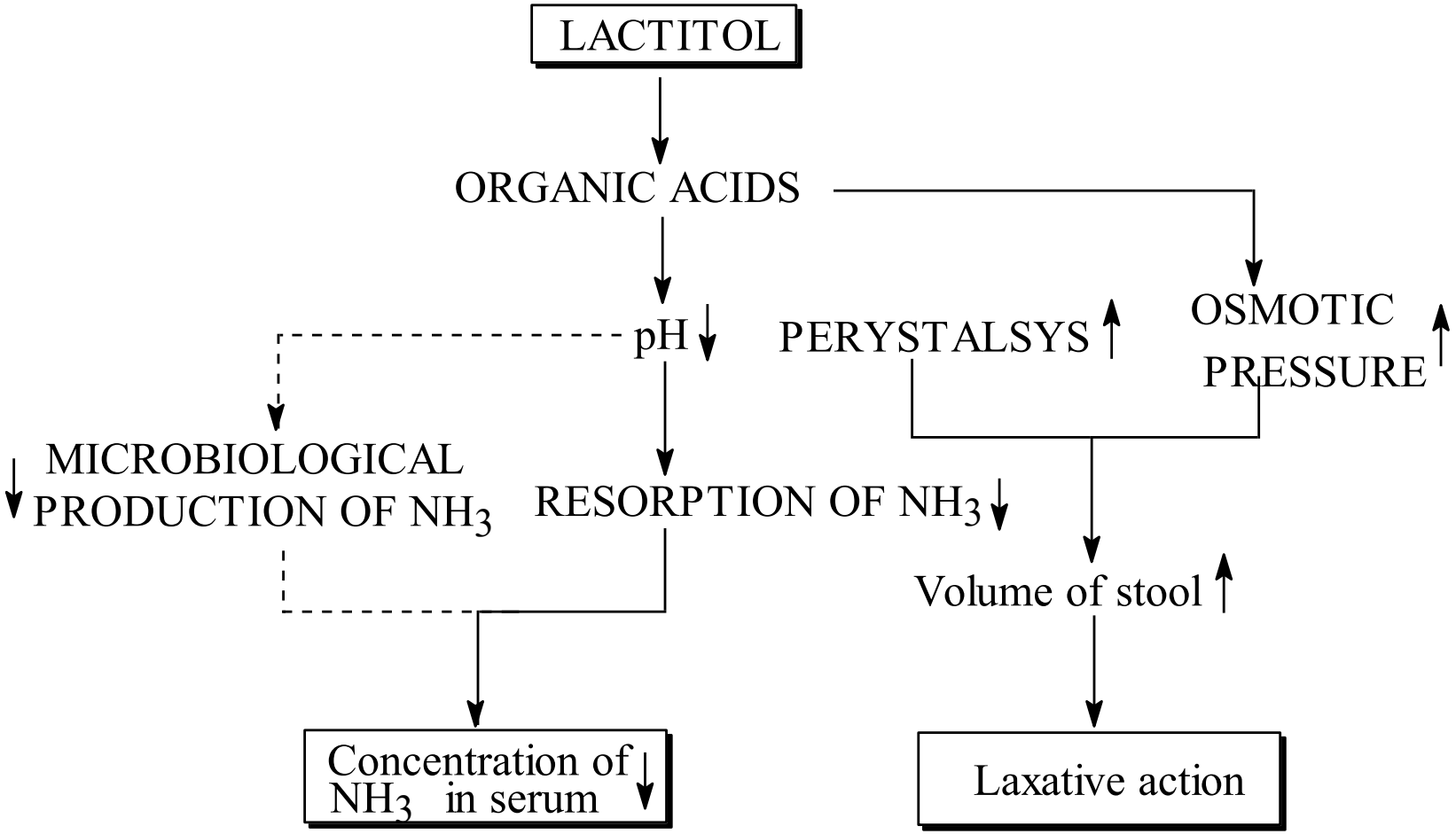
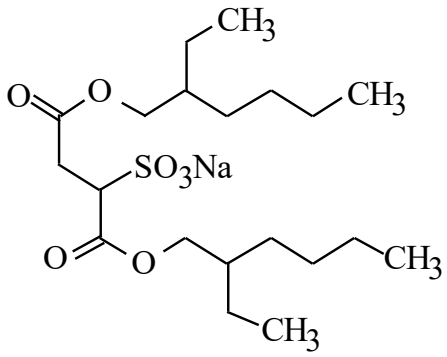


Figure 42.1. The action of lactitol.

42.2.2. Stool softeners



Docusate sodium, LAXOL, LAXOPOL

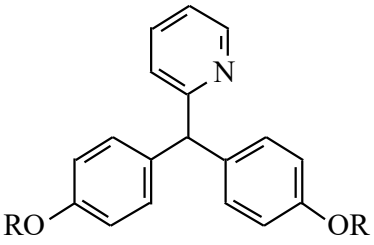
1,4-Bis(2-ethylohexyl)sulfosuccinate sodium

Docusate sodium is an anion detergent. It decreases the surface tension of the colon contents, which facilitates the penetration of water and fats to the colon contents and its softening and excretion.

Liquid paraffin pharmaceuticals (MENTHO-PARAFFINOL) act similarly to docusate sodium**.**

42.2.3. Motility agents

Phenolphtalein, used previously as a laxative, was the prototype for this group of drugs. At present, bisacodyl and sodium picosulfate, structural analogues of phenolphtalein are used as laxatives.



Bisacodyl, R = -CO-CH_3
ABILAXINE, BISACODYL, X-PREP

Sodium picosulfate, *Natrii picosulfas*, R = -SO_3Na
LAXIDOGOL

These agents are not absorbed from the gastrointestinal tract.
They act laxatively and carminatively. This action is the effect of the increased secretion of mucus in the colon and its increased motility.
These drugs are indicated in habitual and chronic constipations in severe illness, in habitual constipations in the elderly and in constipations after surgical procedures.

Pharmaceuticals containing sennosides (REGULAX, SE-NALAX, SENEFOL, XENNA) demonstrate mild laxative action.

They are indicated in constipation, in postoperative intestinal atony, before surgical procedures and as adjuvants in the treatment of hemoroids.

42.2.4. Peripheral dopaminergic receptor antagonists

The stimulation of the D_2 dopaminergic receptors in the gastrointestinal tract decreases its motility.

Some benzamide derivatives block peripheral dopaminergic receptors and do not demonstrate central action because they do not permeate the blood-brain barrier.

Metoclopramide, cascapride, cisapride and domperidon demonstrate this action. They increase the gastrointestinal motility, especially of the stomach, duodenum and small intestine by affecting the hypothalamus. These drugs also act antiemetically.

The peripheral dopaminergic receptor antagonists are also used in the symptomatic treatment of gastroesophageal reflux, stomach atony and functional dispersion.