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Lactulose

DESCRIPTION

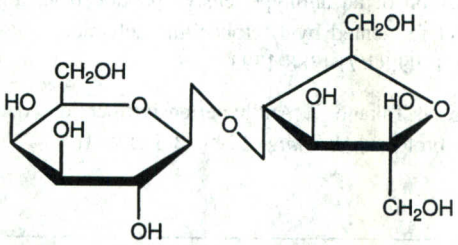
Lactulose is a semisynthetic disaccharide comprised of the sugars D-lactose and D-fructose. It is not found naturally. The sugars are joined by a beta glycosidic linkage making it resistant to hydrolysis by human digestive enzymes. There is no disaccharidase in the microvillus membrane of small intestine enterocytes that can hydrolyze lactulose; nor is the disaccharide absorbed from the small intestine. Lactulose is, however, fermented by a limited number of colonic bacteria. This can lead to changes in the colonic ecosystem in favor of some bacteria, such as lactobacilli and bifidobacteria, which may confer some health benefits.

Lactulose is used in the treatment of constipation and hepatic encephalopathy. The efficacy of lactulose in these conditions is based on its fermentation in the colon by certain bacteria and the increase of the biomass of these bacteria in the colon. The products of fermentation are mainly organic acids, such as lactic acid and small-chain fatty acids, which, by exerting a local osmotic effect in the colon, result in increased fecal bulk and stimulation of peristalsis. The higher doses used for hepatic encephalopathy lower the colonic pH, and ammonia, in the form of ammonium ions, is used by the bacteria for amino acid and protein synthesis. This lowers the serum ammonia levels and improves mental function.

The stimulation of the growth of bacteria, such as bifidobacteria, may have other health benefits, such as protection against cancer of the colon. Lactulose is referred to as a bifidogenic factor. Substances such as lactulose that promote the growth of beneficial bacteria in the colon are called prebiotics. Prebiotics are typically nondigestible oligosaccharides. In addition to its uses in treatment of hepatic encephalopathy and constipation, lactulose is used in Japan in functional foods and as a nutritional supplement. These

uses of lactulose are being explored in the United States, as well.

Lactulose is a solid substance that is very soluble in water and has a sweet taste. It is sweeter than lactose but not as sweet as fructose. Lactulose is also known as 4-O-beta-D-galactopyranosyl-D-fructofuranose. Its molecular formula is $C_{12}H_{22}O_{11}$, and its molecular weight is 342.30 daltons. The structural formula is:



Lactulose

ACTIONS AND PHARMACOLOGY

ACTIONS

Therapeutically, lactulose has laxative and ammonia-detoxifying actions.

Supplemental lactulose may have antitumor, antimicrobial, hypolipidemic and hypoglycemic actions in some. It may also help improve mineral absorption and balance, and may have antiosteoporotic activity.

MECHANISM OF ACTION

The possible antitumor activity of lactulose might be accounted for, in part, by the possible antitumor action of butyrate. Butyrate, along with other short-chain fatty acids, is produced by bacterial fermentation of lactulose in the colon. Some studies suggest that butyrate may induce growth arrest and cell differentiation and may also upregulate apoptosis, three activities that could be significant for possible antitumor activity. Lactulose may also aid in increasing the concentrations of calcium and magnesium in the colon. High concentrations of these cations in the colon may help control the rate of cell turnover. High concentrations of calcium in the colon may also lead to the formation of insoluble bile or salts of fatty acids. This might reduce the potential damaging effects of bile or fatty acids on colonocytes.

Lactulose may promote the growth of favorable bacterial populations, such as bifidobacteria, in the colon. Bifidobacteria may inhibit the growth of pathogenic bacteria, such as *Clostridium perfringens* and diarrheogenic *Escherichia coli*.

Lactulose may aid in lowering serum triglycerides in some. The mechanism of this possible effect is unclear. Decreased hepatocyte *de novo* synthesis of triglycerides is one hypothetical possibility. Lactulose may also lower total cholesterol and LDL-cholesterol levels in some. Again, the mechanism of this possible effect is unclear. Propionate, a product of lactulose fermentation in the colon, may inhibit HMG-CoA reductase, the rate-limiting step in cholesterol synthesis.

The possible effects of lactulose on blood glucose may be explained in a few ways. Lactulose may delay gastric emptying and/or shorten small-intestinal tract transit time. This may be via the short-chain fatty acids produced from lactulose in the colon. Short-chain fatty acids may be involved in the so-called "ileocolonic brake," which refers to the inhibition of gastric emptying by nutrients reaching the ileo-colonic junction. Short-chain fatty acids may also stimulate contractions of the ileum and shorten ileal emptying. In addition, propionate may inhibit gluconeogenesis by its metabolic conversion to methylmalonyl-CoA and succinyl-CoA. These metabolites could inhibit pyruvate carboxylase. Propionate may also reduce plasma levels of free fatty acids. High levels of free fatty acids lower glucose utilization and induce insulin resistance. Finally, propionate may enhance glycolysis via depletion of citrate in hepatocytes. Citrate is an allosteric inhibitor of phosphofructokinase.

Lactulose may bind/sequester such minerals as calcium and magnesium in the small intestine. The short-chain fatty acids formed from the bacterial fermentation of lactulose may facilitate the colonic absorption of calcium and, possibly, also magnesium ions. This could be beneficial in preventing osteoporosis and osteopenia.

PHARMACOKINETICS

Following ingestion, lactulose reaches the colon with very little digestion or absorption taking place in the stomach or small intestine. Lactulose is fermented by bifidobacteria, lactobacilli and some other bacteria in the colon to produce the short-chain fatty acids acetate, propionate and butyrate; the gases hydrogen, hydrogen sulfide, carbon dioxide and methane; and lactate, pyruvate, succinate and formate. Acetate, propionate and butyrate that are not metabolized in colonocyes are absorbed from the colon and transported via the portal circulation to the liver. These short-chain fatty acids are extensively metabolized in hepatocytes. Acetate, propionate and butyrate that are not metabolized in hepatocytes are transported by the circulation to various tissues, where they undergo further metabolism. Butyrate is an important respiratory fuel for the colonocytes. Lactulose is completely metabolized in the colon, and no lactulose is excreted in the feces.

Those with ileostomies may have a microbial flora colonizing their ileums. In those cases, lactulose could be fermented by some of the bacteria in a fashion similar to their fermentation in the colon.

INDICATIONS AND USAGE

Lactulose is used to treat constipation and hepatic encephalopathy. Preliminary research suggests that it might protect against a number of intestinal pathogens, that it might be helpful in the treatment of some inflammatory bowel diseases and that it could help prevent colorectal cancers. There is additional preliminary evidence suggesting that it could be of benefit in osteoporosis, diabetes mellitus and renal failure.

RESEARCH SUMMARY

Lactulose has proved effective in the treatment of some with chronic constipation, helping to restore normal peristalsis and defecation rhythm, softening stools and diminishing pain and other symptoms of dyspeptic disorders.

Lactulose is used with good results in some with compensated liver disease; lactulose has been shown in various studies to increase protein tolerance and help prevent hepatic encephalopathy.

Lactulose has helped protect against *Salmonella* infection and has shown activity against a number of other intestinal pathogens. It has reduced the incidence of bacterial translocation from the gut to mesenteric lymph nodes in rats with obstructive jaundice. It has also prevented bacterial translocation in animal models of surgical trauma. Other experiments suggest that lactulose might be helpful in idiopathic, as well as infectious inflammatory bowel diseases.

Lactulose has suppressed experimentally induced colonic aberrant crypt foci in rats and has helped protect colonic mucosa against a known colon carcinogen.

There is some early but promising clinical work. In one controlled study, patients who had undergone endoscopic removal of colorectal polyps were given antioxidant vitamins or lactulose to see if these substances could reduce the recurrence rate of adenomatous polyps. Over the course of this five-year study, polyps recurred in 5.7% of those taking the vitamins (A, C and E) and in 14.7% of those taking lactulose, compared with a recurrence rate of 35.9% in untreated controls. There were 209 subjects in the study.

Lactulose has also been shown to significantly stimulate calcium absorption in postmenopausal women, though the research has not yet been done to see whether it slows the rate of bone loss in aging subjects. There is, in addition, preliminary research suggesting that lactulose might improve glucose tolerance and have other effects on carbohydrate metabolism that could be of benefit in those with diabetes mellitus.

Finally, there is the suggestion in other preliminary research that lactulose might be helpful in the treatment of chronic renal failure. Lactulose has been shown to promote fecal excretion of water, sodium, potassium, amonium, urea, creatine and hydronium ions.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Some lactulose preparations contain galactose. Therefore, lactulose is contraindicated in those who require a low galactose diet. Lactulose is also contraindicated in those who are hypersensitive to any component of a lactulose-containing preparation.

PRECAUTIONS

In the United States, lactulose is a prescription drug. Its use requires medical supervision. Its use as a dietary supplement is considered experimental.

Those who develop gastrointestinal symptoms (flatus, bloating, diarrhea) with the use of dietary fiber should exercise caution in the use of lactulose.

Those with lactose intolerance should exercise caution in the use of lactulose.

One of the metabolites of lactulose is hydrogen gas. Hypothetically, this represents a potential hazard for those using lactulose who may be required to undergo electrocautery procedures during proctoscopy or colonoscopy. Accumulation of hydrogen gas in significant amounts in the presence of an electric spark may result in an explosion. Therefore, those undergoing these procedures should stop lactulose intake at least a week before the procedure.

Pregnant women and nursing mothers should avoid lactulose.

ADVERSE REACTIONS

Laxative doses are typically 20 to 40 grams daily. Doses up to 10 grams daily are usually well tolerated. Some may be more sensitive to the possible gastrointestinal side effects of lactulose. The adverse reactions are mainly gastrointestinal and include flatus and abdominal cramps. Doses of greater than 13 grams daily can cause diarrhea. Also, nausea and vomiting have been reported following the higher doses. Some find the taste of lactulose to be disagreeable.

INTERACTIONS

DRUGS

Concomitant use of nonabsorbable antacids with lactulose may inhibit the desired lactulose-induced drop in colonic pH which might affect laxative activity and activity in the treatment of hepatic encephalopathy.

NUTRITIONAL SUPPLEMENTS

The concomitant use of such probiotics as *Bifidobacterium longum* and lactulose may enhance the possible health benefits of lactulose.

Lactulose may enhance the colonic absorption of calcium and magnesium supplements if used concomitantly.

FOODS

Lactulose may enhance the colonic absorption of calcium and magnesium in foods.

OVERDOSAGE

There have been no reports of overdosage.

DOSAGE AND ADMINISTRATION

Lactulose is available in some functional foods and nutritional supplements in Japan. Its use in the U.S. for supplemental purposes is still experimental. Supplemental doses used in Japan are about 2 to 5 grams daily. Doses higher than 10 grams daily are likely to cause gastrointestinal side effects (flatus, abdominal cramping, diarrhea). Doses of 10 to 20 grams daily and up to 40 grams daily are used to treat constipation. Doses from 60 to 120 grams daily are used to treat hepatic encephalopathy. Pharmaceutical lactulose is available in solutions and in the form of a crystalline powder. Lactulose is a prescription drug in the U.S. for pharmaceutical uses.

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Larch Arabinogalactan

DESCRIPTION

Larch arabinogalactan refers to a polysaccharide derived from wood of the Western larch or *Larix occidentalis.* Arabinogalactans occur in other types of larch, but that which is marketed for supplemental usage comes from the Western larch. Larch arabinogalactan is not one substance but a mixture of several different arabinogalactans with molecular weights as low as 3,000 daltons and as high as 100,000 daltons.

Arabinogalactans are water-soluble polysaccharides widely found in plants, fungi and bacteria. They are comprised of D-galactose and L-arabinose residues in the form of a beta-D-(1-3)-galactan main chain with side chains made up of galactose and arabinose units of various lengths. Galactan itself is a polymer of galactose.

In plants, arabinogalactans occur as arabinogalactan proteins. These proteins are proteoglycans involved in plant growth and development; they may also be involved in signal transduction in plants.

Dietary intake of arabinogalactans comes from carrots, radishes, tomatoes, pears and wheat, among other plant foods. Gum arabic, a commonly used food additive, is composed of highly branched arabinogalactan. Arabinogalactans are also found in such herbs as *Echinacea* spp. and such edible mushrooms as *Ganoderma lucidum.* Arabinogalactans are thought to contribute to the possible immune-enhancing activities of echinacea and ganoderma.

Larch arabinogalactan is considered a nondigestible soluble dietary fiber. It is also thought to stimulate the colonic growth of such bacteria as bifidobacteria and lactobacilli. These bacteria may confer certain health benefits. Substances that stimulate the growth of bifidobacteria are called bifidogenic factors. Substances that promote the colonic growth of beneficial bacteria are called prebiotics.