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Lactulose

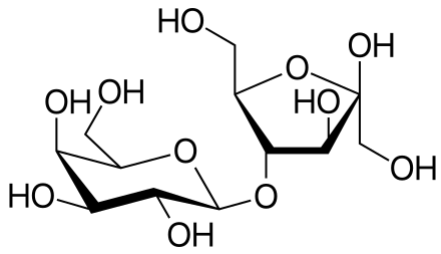
Lactulose is a non-absorbable sugar used in the treatment of constipation and hepatic encephalopathy.[1][4] It is used by mouth for constipation and either by mouth or in the rectum for hepatic encephalopathy.[1] It generally begins working after 8–12 hours, but may take up to 2 days to improve constipation.[2][3]

Common side effects include abdominal bloating and cramps.[1] A potential exists for electrolyte problems as a result of the diarrhea it produces.[1] No evidence of harm to the baby has been found when used during pregnancy.[1] It is generally regarded as safe during breastfeeding.[5] It is classified as an osmotic laxative.[6]

Lactulose was first made in 1929, and has been used medically since the 1950s.[7][8] It is on the World Health Organization's List of Essential Medicines.[9] It is available as a generic and brand-name product.[4] Lactulose is made from the milk sugar lactose, which is composed of two simple sugars, galactose and glucose.[10][1]

Contents

Lactulose



Clinical data	
Pronunciation	/ˈlæktjʊloʊs/
Trade names	Cholac, Generlac, Consulose, Duphalac, others
Other names	4-O-β-D-Galactosyl-D-fructose
AHFS/Drugs.com	Monograph (https://www.drugs.com/monograph/lactulose.html)
MedlinePlus	a682338 (https://medlineplus.gov/druginfo/meds/a682338.html)
Routes of administration	By mouth (oral solution)
ATC code	A06AD11 (WHO (https://www.whocc.no/atc_ddd_index/?code=A06AD11))
Legal status	
Legal status	UK: General sales list (GSL, OTC) US: Prescription required[1]

History

In 1957, Peitele discovered that lactulose is a *bifidobacterium* proliferation factor. In 1964, Hoffman found that only *bifidobacteria*, *Lactobacillus* and *Streptococcus* could metabolise lactulose into lactic acid and acetic acid. In 1966, Baicier found that lactulose can promote the growth of basophilic gram-positive bacteria lacking urease (e.g. *Escherichia coli*) and reduce ammonia production. It has been proven that lactulose reduces blood ammonia, and it has been successfully used in the treatment of hepatic encephalopathy. In 1979, Nianmoleyou treated viral hepatitis with lactulose and he found that lactulose has the effect of reducing plasma endotoxin. From 1980 to 1981, Leicier found that the limulus test agglutination reaction of lactulose inhibits endotoxin in vitro, alleviating the liver injury of rats induced by D-amino galactose. He believed that lactulose had anti-endotoxin activity, meaning that and it can be used in the treatment of liver and kidney syndrome.

Medical uses

Constipation

Lactulose is used in the treatment of chronic constipation in patients of all ages as a long-term treatment.[11] The dosage of lactulose for chronic idiopathic constipation is adjusted depending on the constipation severity and desired effect, from a mild stool softener to causing diarrhea. Lactulose is contraindicated in case of galactosemia, as most preparations contain the monosaccharide galactose due to its synthesis process.[12][13]

Lactulose may be used to counter the constipating effects of opioids, and in the symptomatic treatment of hemorrhoids as a stool softener.

Lactulose is commonly prescribed for children who develop fear of their bowel movements and are withholders. This is because lactulose, when dosed in the proper amount, causes a bowel movement that is impossible to retain for very long. Lactulose is also used for the elderly because of its gentle and consistent results.

Hyperammonemia

Lactulose is useful in treating hyperammonemia (high blood ammonia), which can lead to hepatic encephalopathy. Lactulose helps trap the ammonia (NH_3) in the colon and bind to it.[14] It

	In general: Over-the-counter (OTC)
Pharmacokinetic data	
Bioavailability	Poorly absorbed
Metabolism	100% in colon by enteric bacteria
Onset of action	8 to 48 hours[2][3]
Elimination half-life	1.7–2 hours
Excretion	Fecal
Identifiers	
IUPAC name	4-*O*-β-D-Galactopyranosyl-β-D-fructofuranose OR (2*S*,3*R*,4*S*,5*R*,6*R*)-2-((2*R*,3*S*,4*S*,5*R*)-4,5-Dihydroxy-2,5-bis(hydroxymethyl)tetrahydrofuran-3-yloxy)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol
CAS Number	4618-18-2 (https://commonchemistry.cas.org/detail?cas_rn=4618-18-2) ✓
PubChem CID	11333 (https://pubchem.ncbi.nlm.nih.gov/compound/11333)
DrugBank	DB00581 (https://www.drugbank.ca/drugs/DB00581) ✓
ChemSpider	10856 (https://www.chemspider.com/Chemical-Structure.10856.html) ✓
UNII	9U7D5QH5AE

does this by using gut flora to acidify the colon, transforming the freely diffusible ammonia into ammonium ions (NH_4^+), which can no longer diffuse back into the blood.[15] It is also useful for preventing hyperammonemia caused as a side effect of administration of valproic acid.[16]

Small intestine bacterial overgrowth

Lactulose is used as a test of small intestine bacterial overgrowth (SIBO). Recently, the reliability of it for diagnosing SIBO has been seriously questioned.[17][18][19][20] A large amount of it is given with subsequent testing of molecular hydrogen gas in the breath. The test is positive if an increase in exhaled hydrogen occurs before that which would be expected by normal digestion by the normal gut flora in the colon. An earlier result has been hypothesized to indicate digestion occurring within the small intestine. An alternate explanation for differences in results is the variance in small bowel transit time among tested subjects.[20]

Pregnancy

No evidence of harm to the baby has been found when used during pregnancy.[1] It is generally regarded as safe during breastfeeding.[5]

Side effects

Common side effects of lactulose are abdominal cramping, borborygmus, and flatulence. In normal individuals, overdose is considered uncomfortable, but not life-threatening.[21] Uncommon side effects are nausea and vomiting. In sensitive individuals, such as the elderly or people with reduced kidney function, excess lactulose dosage can result in dehydration and electrolyte disturbances such as low magnesium levels. Ingestion of lactulose does not cause a weight gain because it is not digestible, with no nutritional value. Although lactulose is less likely to cause dental caries than sucrose, as a sugar, a potential for this exists. This should be taken into consideration when taken by people with a high susceptibility to this condition.

Mechanism of action

It is a disaccharide formed from one molecule each of the simple sugars (monosaccharides) fructose and galactose. Lactulose is not normally present in raw milk, but is a product of heat processes:[22] the greater the heat, the greater amount of this

	(https://precision.fda.gov/uniisearch/srs/unii/9U7D5QH5AE)
KEGG	D00352 (https://www.kegg.jp/entry/D00352) ✓
ChEBI	CHEBI:6359 (https://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:6359) ✓
ChEMBL	ChEMBL296306 (https://www.ebi.ac.uk/chembldb/index.php/compound/inspect/ChEMBL296306) ✓
CompTox Dashboard (EPA)	DTXSID5045833 (https://comptox.epa.gov/dashboard/chemical/details/DTXSID5045833)
ECHA InfoCard	100.022.752 (https://echa.europa.eu/substance-information/-/substanceinfo/100.022.752)
Chemical and physical data	
Formula	$C_{12}H_{22}O_{11}$
Molar mass	342.297 g·mol^{-1}
3D model (JSmol)	Interactive image (https://chemapps.stolaf.edu/jmol/jmol.php?model=O%5BC%40H%5D2%5BC%40H%5D%28O%5BC%40%40H%5D1O%5BC%40H%

substance (from 3.5 mg/l in low-temperature pasteurized milk to 744 mg/l in in-container sterilized milk).[23] It is produced commercially by isomerization of lactose.

Lactulose is not absorbed in the small intestine nor broken down by human enzymes, thus stays in the digestive bolus through most of its course, causing retention of water through osmosis leading to softer, easier-to-pass stool. It has a secondary laxative effect in the colon, where it is fermented by the gut flora, producing metabolites which have osmotic powers and peristalsis-stimulating effects (such as acetate), but also methane associated with flatulence.

Lactulose is metabolized in the colon by bacterial flora to short-chain fatty acids, including lactic acid and acetic acid. These partially dissociate, acidifying the colonic contents (increasing the H^+ concentration in the gut).[15] This favors the formation of the nonabsorbable NH_4^+ from NH_3, trapping NH_3 in the colon and effectively reducing plasma NH_3 concentrations. Lactulose is therefore effective in treating hepatic encephalopathy.[24] Specifically, it is effective as secondary prevention of hepatic encephalopathy in people with cirrhosis.[25] Moreover, research showed improved cognitive functions and health-related quality of life in people with cirrhosis with minimal hepatic encephalopathy treated with lactulose.[26]

	5D%28CO%29%5BC%40H%5D%28O%29%5BC%40H%5D%28O%29%5BC%40H%5D1O%29%5BC%40H%5D%28O%5BC%40%5D2%28O%29CO%29CO)
SMILES	
O[C@H]2[C@H](O[C@@H]1O[C@H](CO)[C@H](O)[C@H](O)[C@H]1O)[C@H](O[C@]2(O)CO)CO	
InChI	
InChI=1S/C12H22O11/c13-1-4-6(16)7(17)8(18)11(21-4)22-9-5(2-14)23-12(20,3-15)10(9)19/h4-11,13-20H,1-3H2/t4-,5-,6+,7+,8-,9-,10+,11+,12-/m1/s1 ✓	
Key:JCQLYHFGKNRPGE-FCVZTGTOSA-N ✓	
(verify)	

Society and culture

Name

Lactulose is its international nonproprietary name (INN).[27] It is sold under various brand names.

Availability

Lactulose is available as a generic medication.[4] It is available without prescription in most countries, but a prescription is required in the United States and Austria.

Food additive

In some countries where lactulose may be obtained without a prescription, lactulose is commonly used as a food additive to improve taste and promote intestinal transit.

Veterinary use

Lactulose is used in veterinary medicine.[28]

References

1. "Lactulose" (https://www.drugs.com/monograph/lactulose.html). The American Society of Health-System Pharmacists. Archived (https://web.archive.org/web/20170904152058/https://www.drugs.com/monograph/lactulose.html) from the original on 2017-09-04. Retrieved Aug 11, 2015.
2. Goldman eb, Hain R, Liben S (2006). *Oxford textbook of palliative care for children* (https://books.google.com/books?id=f1fTsoA4wDMC&pg=PA352) (2 ed.). Oxford: Oxford University Press. p. 352. ISBN 9780198526537. Archived (https://web.archive.org/web/20170908140003/https://books.google.com/books?id=f1fTsoA4wDMC&pg=PA352) from the original on 2017-09-08. {{cite book}}: |first1= has generic name (help)
3. Helms, Richard A. (2006). *Textbook of therapeutics : drug and disease management* (https://books.google.com/books?id=aVmRWrknaWgC&pg=PA1310) (8 ed.). Philadelphia, Pa. [u.a.]: Lippincott Williams & Wilkins. p. 1310. ISBN 9780781757348. Archived (https://web.archive.org/web/20170908140003/https://books.google.com/books?id=aVmRWrknaWgC&pg=PA1310) from the original on 2017-09-08.
4. Hamilton, Richard J. (2013). *Tarascon pocket pharmacopoeia : 2013 classic shirt-pocket edition* (https://books.google.com/books?id=lwueJ4IAl4oC&pg=PA111) (27 ed.). Burlington, Ma.: Jones & Bartlett Learning. p. 111. ISBN 9781449665869. Archived (https://web.archive.org/web/20170908140003/https://books.google.com/books?id=lwueJ4IAl4oC&pg=PA111) from the original on 2017-09-08.
5. Jones, Wendy (2013). *Breastfeeding and Medication* (https://books.google.com/books?id=0Y8lbCnF1mgC&pg=PA127). Routledge. p. 127. ISBN 9781136178153. Archived (https://web.archive.org/web/20170908140003/https://books.google.com/books?id=0Y8lbCnF1mgC&pg=PA127) from the original on 2017-09-08.
6. Whitlow, Charles (2009). *Improved Outcomes in Colon and Rectal Surgery* (https://books.google.com/books?id=9FfvBQAAQBAJ&pg=PT378). New York: Informa Healthcare. p. 366. ISBN 9781420071535. Archived (https://web.archive.org/web/20170908140003/https://books.google.com/books?id=9FfvBQAAQBAJ&pg=PT378) from the original on 2017-09-08.
7. McSweeney, Paul L.H.; Fox, Patrick F. (2009). *Advanced dairy chemistry* (https://books.google.com/books?id=hz9U9nzy-rQC&pg=PA236) (3rd ed.). New York: Springer-Verlag. p. 236. ISBN 9780387848655. Archived (https://web.archive.org/web/20170908140003/https://books.google.com/books?id=hz9U9nzy-rQC&pg=PA236) from the original on 2017-09-08.
8. Schumann C (November 2002). "Medical, nutritional and technological properties of lactulose. An update". *European Journal of Nutrition*. 41 Suppl 1: I17-25. doi:10.1007/s00394-002-1103-6 (https://doi.org/10.1007%2Fs00394-002-1103-6). PMID 12420112 (https://pubmed.ncbi.nlm.nih.gov/12420112). S2CID 20487660 (https://api.semanticscholar.org/CorpusID:20487660).
9. World Health Organization (2019). *World Health Organization model list of essential medicines: 21st list 2019*. Geneva: World Health Organization. hdl:10665/325771 (https://hdl.handle.net/10665%2F325771). WHO/MVP/EMP/IAU/2019.06. License: CC BY-NC-SA 3.0 IGO.
10. Kuntz, Hans-Dieter (2008). *Hepatology textbook and atlas : history, morphology, biochemistry, diagnostics, clinic, therapy* (https://books.google.com/books?id=oL6d9KuVqLQC&pg=PA887) (3 ed.). Heidelberg: Springer. p. 887. ISBN 9783540768395. Archived (https://web.archive.org/web/20170908140003/https://books.google.com/books?id=oL6d9KuVqLQC&pg=PA887) from the original on 2017-09-08.
11. "Lactulose" (https://www.nlm.nih.gov/medlineplus/druginfo/meds/a682338.html). *nih.gov*. Archived (https://web.archive.org/web/20150905124827/https://www.nlm.nih.gov/medlineplus/druginfo/meds/a682338.html) from the original on 5 September 2015. Retrieved 25 August 2015.

12. Panesar, Parmjit S.; Kumari, Shweta (2011-11-01). "Lactulose: Production, purification and potential applications" (https://www.sciencedirect.com/science/article/pii/S0734975011001406). *Biotechnology Advances*. **29** (6): 940–948. doi:10.1016/j.biotechadv.2011.08.008 (https://doi.org/10.1016%2Fj.biotechadv.2011.08.008). ISSN 0734-9750 (https://www.worldcat.org/issn/0734-9750). PMID 21856402 (https://pubmed.ncbi.nlm.nih.gov/21856402).
13. Bae, Sun Hwan (July 2010). "Long-term safety of PEG 4000 in children with chronic functional constipation: A biochemical perspective" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3004485). *Korean Journal of Pediatrics*. **53** (7): 741–744. doi:10.3345/kjp.2010.53.7.741 (https://doi.org/10.3345%2Fkjp.2010.53.7.741). ISSN 1738-1061 (https://www.worldcat.org/issn/1738-1061). PMC 3004485 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3004485). PMID 21189949 (https://pubmed.ncbi.nlm.nih.gov/21189949).
14. Shukla S, Shukla A, Mehboob S, Guha S (March 2011). "Meta-analysis: the effects of gut flora modulation using prebiotics, probiotics and synbiotics on minimal hepatic encephalopathy" (https://doi.org/10.1111%2Fj.1365-2036.2010.04574.x). *Alimentary Pharmacology & Therapeutics*. **33** (6): 662–71. doi:10.1111/j.1365-2036.2010.04574.x (https://doi.org/10.1111%2Fj.1365-2036.2010.04574.x). PMID 21251030 (https://pubmed.ncbi.nlm.nih.gov/21251030). S2CID 37455679 (https://api.semanticscholar.org/CorpusID:37455679).
15. Patil DH, Westaby D, Mahida YR, Palmer KR, Rees R, Clark ML, Dawson AM, Silk DB (March 1987). "Comparative modes of action of lactitol and lactulose in the treatment of hepatic encephalopathy" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1432706). *Gut*. **28** (3): 255–9. doi:10.1136/gut.28.3.255 (https://doi.org/10.1136%2Fgut.28.3.255). PMC 1432706 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1432706). PMID 3570029 (https://pubmed.ncbi.nlm.nih.gov/3570029).
16. Gerstner T, Buesing D, Longin E, Bendl C, Wenzel D, Scheid B, Goetze G, Macke A, Lippert G, Klostermann W, Mayer G, Augspach-Hofmann R, Fitzek S, Haensch CA, Reuland M, Koenig SA (September 2006). "Valproic acid induced encephalopathy--19 new cases in Germany from 1994 to 2003--a side effect associated to VPA-therapy not only in young children" (https://doi.org/10.1016%2Fj.seizure.2006.05.007). *Seizure*. **15** (6): 443–8. doi:10.1016/j.seizure.2006.05.007 (https://doi.org/10.1016%2Fj.seizure.2006.05.007). PMID 16787750 (https://pubmed.ncbi.nlm.nih.gov/16787750).
17. Vanner S (April 2008). "The lactulose breath test for diagnosing SIBO in IBS patients: another nail in the coffin". *The American Journal of Gastroenterology*. **103** (4): 964–5. PMID 18371132 (https://pubmed.ncbi.nlm.nih.gov/18371132).
18. Barrett JS, Irving PM, Shepherd SJ, Muir JG, Gibson PR (July 2009). "Comparison of the prevalence of fructose and lactose malabsorption across chronic intestinal disorders" (https://doi.org/10.1111%2Fj.1365-2036.2009.04018.x). *Alimentary Pharmacology & Therapeutics*. **30** (2): 165–74. doi:10.1111/j.1365-2036.2009.04018.x (https://doi.org/10.1111%2Fj.1365-2036.2009.04018.x). PMID 19392860 (https://pubmed.ncbi.nlm.nih.gov/19392860). S2CID 31378290 (https://api.semanticscholar.org/CorpusID:31378290).
19. Grover M, Kanazawa M, Palsson OS, Chitkara DK, Gangarosa LM, Drossman DA, Whitehead WE (September 2008). "Small intestinal bacterial overgrowth in irritable bowel syndrome: association with colon motility, bowel symptoms, and psychological distress" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3856223). *Neurogastroenterology and Motility*. **20** (9): 998–1008. doi:10.1111/j.1365-2982.2008.01142.x (https://doi.org/10.1111%2Fj.1365-2982.2008.01142.x). PMC 3856223 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3856223). PMID 18482250 (https://pubmed.ncbi.nlm.nih.gov/18482250).

20. Yu D, Cheeseman F, Vanner S (March 2011). "Combined oro-caecal scintigraphy and lactulose hydrogen breath testing demonstrate that breath testing detects oro-caecal transit, not small intestinal bacterial overgrowth in patients with IBS". *Gut*. **60** (3): 334–40. doi:10.1136/gut.2009.205476 (https://doi.org/10.1136%2Fgut.2009.205476). PMID 21112950 (https://pubmed.ncbi.nlm.nih.gov/21112950). S2CID 6749287 (https://api.semanticscholar.org/CorpusID:6749287).
21. "Safety Data Sheet Lactulose" (http://static.usp.org/pdf/EN/referenceStandards/msds/1356803.pdf) (PDF). 2015. Retrieved 3 December 2016.
22. M. Luzzana; D. Agnellini; P. Cremonesi; G. Caramenti; S. De Vita (September–October 2003). "Milk lactose and lactulose determination by the differential pH technique" (http://lait.dairy-journal.org/articles/lait/pdf/2003/05/L3503.pdf) (PDF). *Le Lait*. **83** (5): 409–16. doi:10.1051/lait:2003022 (https://doi.org/10.1051%2Flait%3A2003022). Archived (https://web.archive.org/web/20140512221309/http://lait.dairy-journal.org/articles/lait/pdf/2003/05/L3503.pdf) (PDF) from the original on 2014-05-12.
23. E. Marconi; M. C. Messia; A. Amine; D. Moscone; F. Vernazza; F. Stocchi; G. Palleschi (2004). "Heat-treated milk differentiation by a sensitive lactulose assay" (https://web.archive.org/web/20130616102238/http://www.parmalat.it/documents/10157/29233/upload_00001438_Heat-treated%20milk%20differentiation%20by%20a%20sensitive.pdf) (PDF). *Food Chemistry*. **84** (3): 447–50. doi:10.1016/S0308-8146(03)00268-1 (https://doi.org/10.1016%2FS0308-8146%2803%2900268-1). hdl:2108/12457 (https://hdl.handle.net/2108%2F12457). Archived from the original (http://www.parmalat.it/documents/10157/29233/upload_00001438_Heat-treated%20milk%20differentiation%20by%20a%20sensitive.pdf) (PDF) on 2013-06-16.
24. Gluud, Lise Lotte; Vilstrup, Hendrik; Morgan, Marsha Y. (2016-05-06). "Non-absorbable disaccharides versus placebo/no intervention and lactulose versus lactitol for the prevention and treatment of hepatic encephalopathy in people with cirrhosis" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7004252). *The Cochrane Database of Systematic Reviews* (5): CD003044. doi:10.1002/14651858.CD003044.pub4 (https://doi.org/10.1002%2F14651858.CD003044.pub4). ISSN 1469-493X (https://www.worldcat.org/issn/1469-493X). PMC 7004252 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7004252). PMID 27153247 (https://pubmed.ncbi.nlm.nih.gov/27153247).
25. Sharma BC, Sharma P, Agrawal A, Sarin SK (September 2009). "Secondary prophylaxis of hepatic encephalopathy: an open-label randomized controlled trial of lactulose versus placebo". *Gastroenterology*. **137** (3): 885–91, 891.e1. doi:10.1053/j.gastro.2009.05.056 (https://doi.org/10.1053%2Fj.gastro.2009.05.056). PMID 19501587 (https://pubmed.ncbi.nlm.nih.gov/19501587).
26. Prasad S, Dhiman RK, Duseja A, Chawla YK, Sharma A, Agarwal R (March 2007). "Lactulose improves cognitive functions and health-related quality of life in patients with cirrhosis who have minimal hepatic encephalopathy" (https://doi.org/10.1002%2Fhep.21533). *Hepatology*. **45** (3): 549–59. doi:10.1002/hep.21533 (https://doi.org/10.1002%2Fhep.21533). PMID 17326150 (https://pubmed.ncbi.nlm.nih.gov/17326150). S2CID 22686421 (https://api.semanticscholar.org/CorpusID:22686421).
27. "International Nonproprietary Names for Pharmaceutical Preparations. Recommended International Non-Proprietary Names (Rec. I.N.N.): List 7" (https://www.who.int/medicines/publications/druginformation/innlists/RL07.pdf) (PDF). World Health Organization. 1967. p. 8. Archived (https://web.archive.org/web/20160518192653/http://www.who.int/medicines/publications/druginformation/innlists/RL07.pdf) (PDF) from the original on 18 May 2016. Retrieved 9 November 2016.
28. "Constipation and Obstipation in Small Animals - Digestive System" (https://www.msdvetmanual.com/digestive-system/diseases-of-the-stomach-and-intestines-in-small-animals/constipation-and-obstipation-in-small-animals). *Veterinary Manual*. Retrieved 22 June 2019.

External links

- "Lactulose" (https://druginfo.nlm.nih.gov/drugportal/name/lactulose). *Drug Information Portal*. U.S. National Library of Medicine.