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Lactose in drugs and lactose intolerance – realities and myths

Laktoza zawarta w lekach a nietolerancja laktozy – fakty i mity

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Abstract

Lactose intolerance is a set of clinical symptoms occurring after lactose intake, characterised by abdominal pain, bloating and diarrhoea. Adult-type hypolactasia is the most common cause of lactose intolerance and is associated with the physiological loss of lactase activity in adulthood. Hypolactasia occurs in 30% of the population of Polish adults. It should be noted that the presence of lactase deficiency does not mean that the patient will develop symptoms of lactose intolerance. Currently, many patients self-diagnose lactose intolerance based on the occurrence of various symptoms and begin to apply a restrictive diet, avoiding dairy products without consulting a doctor. Self-reported lactose intolerance is often not confirmed by objective tests. A restrictive diet can, however, lead to complications. Studies have shown that the occurrence of lactose intolerance symptoms depends on the dose of consumed disaccharide, and the dose of 12 g is considered to be well-tolerated in most patients. This means that, for many patients, it is not necessary to completely eliminate lactose from diet. Lactose is one of the most commonly used excipients in pharmaceutical industry. Some studies have shown that small amounts of lactose contained in medicines do not cause symptoms in patients; however, their role in inducing symptoms of lactose intolerance has not been confirmed so far. Moreover, the information on the exact content of lactose in drugs is often limited. This data could positively impact the quality of care for lactose intolerant patients and increase their medication compliance.

Keywords: lactose, lactose intolerance, excipients

Streszczenie

Nietolerancja laktozy to zespół objawów klinicznych występujący po spożyciu laktozy, w którym pojawiają się ból brzucha, biegunka i wzdęcia. Hipolaktazja typu dorosłych jest najczęstszą przyczyną nietolerancji laktozy i wiąże się z fizjologiczną utratą aktywności laktazy w życiu dorosłym. Szacuje się, że w Polsce hipolaktazja występuje u 30% populacji dorosłych. Należy zaznaczyć, że niedobór laktazy nie jest równoznaczny z tym, że u pacjenta wystąpią objawy nietolerancji laktozy. Obecnie wielu pacjentów samodzielnie rozpoznaje u siebie nietolerancję laktozy na podstawie występowania różnych objawów i zaczyna stosować restrykcyjną dietę z wykluczeniem nabiału bez konsultacji z lekarzem. Okazuje się jednak, że w ten sposób stwierdzona nietolerancja laktozy często nie znajduje potwierdzenia po przeprowadzeniu obiektywnych testów. Restrykcyjna dieta może prowadzić natomiast do wielu powikłań. Badania wykazały, że wystąpienie objawów nietolerancji laktozy zależy od dawki spożytego dwucukru, a za dawkę dobrze tolerowaną u większości pacjentów uznaje się 12 g laktozy. Oznacza to, że u wielu pacjentów nie jest konieczne całkowite wyeliminowanie laktozy z diety. Laktoza należy do najczęściej stosowanych substancji pomocniczych w przemyśle farmaceutycznym. Chociaż niektóre badania wykazały, że niewielkie ilości laktozy zawarte w lekach nie wywołują objawów u pacjentów, rola leków w wywoływaniu objawów nietolerancji laktozy nie została do tej pory potwierdzona. Ponadto informacje na temat dokładnej zawartości laktozy w lekach są często ograniczone. Dane te mogłyby jednak pozytywnie wpłynąć na poziom opieki lekarzy nad pacjentami z nietolerancją laktozy oraz zwiększyć przestrzeganie zaleceń lekarskich przez tę grupę pacjentów.

Słowa kluczowe: laktoza, nietolerancja laktozy, substancje pomocnicze

INTRODUCTION

Lactose is a disaccharide consisting of galactose and glucose, naturally present in the milk of most mammals. The greatest concentration of lactose occurs in human milk and amounts to about 7%. In comparison, cow's milk contains 4.4–5.2% of lactose[1,2].

In the human body, lactose is hydrolysed to monosaccharides – D-glucose and D-galactose, which are then absorbed into the blood. The lactase enzyme, located on the brush border of the small intestine, is responsible for the distribution of lactose. Its largest concentration is to be found in the central part of the jejunum[1,2].

Lactase activity changes during the ontogenetic development. The highest concentration of lactase occurs during the perinatal period, when the ability to digest lactose contained in breast milk is crucial for the survival of the newborn. However, after the very first few months of life, its concentrations begin to decrease. This is due to the physiological phenomenon of the silencing of the gene responsible for the synthesis of the enzyme. The time and speed with which the changes take place vary in individuals and ethnic groups[3].

Only 30% of the world's adult population retain the ability to digest lactose effectively. Most people with retained lactase activity come from the countries of Northern Europe (Scandinavia, Netherlands, United Kingdom), where the rate can be up to 90%. The opposite phenomenon is observed among the populations of Africa, South America and Asia, where lactase deficiency may occur in 70–100% of the people[3,4].

It has been demonstrated that the occurrence of lactase deficiency, or its retained activity, has its genetic origins and is connected with gene polymorphism. The predisposition to hypolactasia is demonstrated by 13910 C/C genotype in the lactose promoter gene, influencing the expression of the lactase gene[3,4]. It is currently emphasised that the loss of lactase activity in adulthood is a wild type, while it is a mutation which is responsible for the retained lactase expression occurring particularly frequently in the descendants of the population which domesticated cattle early, for whom milk is still an important nutrient[2,3]. It is estimated that, in Poland, the genetic predisposition to hypolactasia of the adult type is present in 30% of the adults, while the symptoms of lactose intolerance occur in a much smaller number of people[5].

LACTOSE IN DRUGS

Lactose contained in medicines acts as an excipient. Excipients are chemical substances or their mixtures which, combined with active substances, are used to form a storable medicinal product of the best possible quality. As a component of the drug, they cannot exert any pharmacological effect and should be inert with respect to the active substances. They perform different functions, such as giving the appropriate form, improving the appearance and taste of the drug as well as its bioavailability and stability. They also affect the rate of release and absorption of the drug in the body[6,7]. Lactose is among the excipients most commonly used in the pharmaceutical industry. It is estimated that it is contained in the approximately 20% of prescription medicines and in 6% of those available without prescription[8]. Lactose owes its popularity to, among others, the fact that it is relatively inexpensive and non-toxic. It is chemically inert, stable, and does not react with the active ingredient or other components of the drug. The fact that lactose is available in many types (grades) of various physical characteristics allows for the selection of the most appropriate component for a given product[1]. It is widely used for the production of tablets, capsules, lozenges as well as solutions for intravenous injections[1,6,7,9]. It is one of the exceedingly few excipients used for the production of medicinal products for inhalation[1]. Lactose, used in the pharmaceutical industry as a filler and solvent, bulks up tablets, granules or solutions, thus allowing to obtain the appropriate form of a drug when the active substance is used in very small quantities. Lactose also has adsorption properties, protecting the product against the excessive absorption of moisture from the air[1,6,7,9]. Furthermore, owing to its sweet taste, it makes drugs more readily accepted by patients[7,8]. For industrial purposes, lactose is produced from cow milk whey. In the solid state, lactose occurs as a white odourless slightly sweet tasting powder[1,6].

MALABSORPTION AND LACTOSE INTOLERANCE

Lactose malabsorption is defined as an impaired absorption of lactose by the small intestine. It may be diagnosed by means of hydrogen (or hydrogen-methane) breath test or by measuring the blood glucose concentration after lactose load. The term "lactose intolerance" is used to describe a set of clinical symptoms occurring after lactose ingestion[10]. It should be noted that lactase deficiency, that is its low activity on the brush border of the small intestine epithelium, is not synonymous with the occurrence of malabsorption. Similarly, the diagnosis of this syndrome does not mean that the patient develops symptoms. Hypolactasia occurs in three separate forms: primary, congenital and secondary. Innate lactase deficiency, which is an autosomal recessive inherited defect, is an extremely rare disease entity. Only about 40 cases of this condition have been noted in literature. It is characterised by, first and foremost, the occurrence of acute diarrhoea after the first intake of milk in newborns[4,10]. Primary hypolactasia, otherwise known as the adult-type hypolactasia, is the most common cause of lactose intolerance and is associated with the loss of the physiological activity of lactase described above. Secondary, or acquired, lactase deficiency occurs in many organic diseases of the bowel resulting in the damage to the mucosa. This is usually a reversible cause of lactose intolerance[2,4].

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A study by Mądry et al. on a group of 200 young and healthy Poles demonstrated that the genetic predisposition to hypolactasia occurs in approximately 30% of adults. However, lactose malabsorption confirmed by the hydrogen breath test was documented in 24.5% of the persons with the predisposition, which amounted to 7.7% of the study group. It should also be noted that the symptoms of intolerance occur only in 23% of people with clinically confirmed lactose malabsorption (after consuming 25 g of lactose, that is, approximately, 0.5 L of milk)[5].

SYMPTOMS OF LACTOSE INTOLERANCE

Patients with lactose intolerance complain of abdominal pain, bloating, watery stools or diarrhoea as well as a feeling of borborygmi. Symptoms usually appear up to 60–90 minutes after lactose intake[11]. Less frequently occurring symptoms may include: nausea, constipation, and fatigue, weight loss and headaches[3]. These symptoms are caused by undigested lactose in the small intestine and in the further parts of the gastrointestinal tract. Two phenomena are responsible for the occurrence of the symptoms. Undigested lactose increases the osmotic charge, resulting in greater secretion of water and electrolytes to the intestinal lumen. Furthermore, lactose is fermented by the bacteria present in the intestine into short-chain fatty acids and gases such as hydrogen, methane and carbon dioxide[1].

DIAGNOSTICS OF LACTOSE INTOLERANCE

Currently, the only objective test for measuring the lactase enzyme activity in the small intestine is a small intestine biopsy. However, due to the invasive nature of the biopsy, as well as the uneven distribution of the enzyme in the intestine, lactose intolerance is rarely an indication to perform this test. The indirect tests for the detection of lactose malabsorption include the measurement of blood glucose after lactose load and the hydrogen breath test[2,3]. The measurement of blood glucose after lactose load is conducted on empty stomach. A blood sample is taken before the administration of lactose and then at intervals of every 30 minutes for up to 2–3 hours after the ingestion of the disaccharide. Inadequate glucose level increase (typically of less than 20 mg%) may indicate lactose malabsorption syndrome[2]. This test, although easily available and inexpensive, is characterised by low sensitivity and specificity, which limits its wider use[3]. The method of choice is currently the hydrogen (or hydrogen-methane) breath test[2,3]. It consists in the oral administration of 25 g of lactose to a person on an empty stomach and conducting the measurement of the hydrogen concentration in the exhaled air prior to lactose administration and then at intervals of every 30 minutes for about 4 hours. The test is considered positive when at least 2 samples contain more than 20 ppm of hydrogen. There are studies showing that the test with the use of 12.5 g of lactose can be applied to better identify patients requiring a restrictive diet and, consequently, to avoid putting persons who can tolerate lower doses of lactose on such a diet[12]. Genetic testing to detect 13910 C/C genotype can also be used to identify a predisposition to hypolactasia but they are infrequently used in clinical practice[2,3].

TOLERATED DOSES OF LACTOSE

The dose of lactose causing symptoms in people with lactose intolerance depends on many factors, among others, on the activity of lactase in the intestinal mucosa, on the speed of gastric emptying, on the intestinal transit time and the kind of intestinal flora. What is also important is human variability with respect to the perception of pain as well as psychosocial factors[3,13].

Contrary to the prevailing opinion among patients, many authors emphasise that the majority of people with lactose intolerance can consume small amounts of lactose without developing any symptoms[4,13,14]. It has been shown in several studies that 12 g of lactose consumed in a single dose (which is the equivalent of a glass of milk) is a dose well tolerated by most patients with lactose intolerance[13–15]. A double-blind study confirmed these results also in people who claim that they develop significant discomfort after a very small amount of lactose in their food[16]. A study conducted in China, according to the recommendation of the National Institutes of Health (NIH), in which patients with lactose intolerance were given lactose in 3 different doses – of 10, 20 and 40 g – demonstrated that below 20% reacted to the dose of 10 g, which is even less than in the case of placebo (representing 30%) in other randomised and controlled trials. It was concluded that, in patients responsive to very small amounts of milk, the reaction may be associated with an allergy to cow's milk proteins, rather than lactose intolerance[17]. Furthermore, there is evidence that lactose is tolerated better when its absorption is accompanied by other nutrients. The dose of 15–18 g of lactose does not typically cause ailments if milk is taken with other types of food. Some authors also argue that the distribution of lactose intake into several smaller doses during the day has a positive effect on the reduction of symptoms[14,15]. What is more, research has shown that, in the case of lactose, there is a phenomenon of intestinal microflora adaptation to increasing doses of the disaccharide ingested daily. In persons with lactose intolerance, this can result in a gradual increase in tolerance. However, it has to be noted that there is currently too little evidence to consider this method of treatment of lactose intolerance to be sufficiently reliable[14,15].

As the NIH emphasises, self-diagnosed lactose intolerance is currently a significant problem. Many of the self-diagnosed persons do not suffer from lactose malabsorption at all[13,18]. Similar results were obtained in 2015 by Zheng et al. in a prospective cohort study on a large test group (n = 910). In the Chinese population, where almost 100% of adults have lactase deficiency, lactose intolerance declared by a patient was poorly linked to the

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development of symptoms demonstrated by the hydrogen breathing test with the use of 20 g of lactose. After this test, it was possible to confirm the malabsorption syndrome in 76% of the persons declaring lactose intolerance, while only 58% experienced any symptoms. In healthy individuals, the symptoms occurred in 22% following taking 20 g of lactose. It has to be concluded that even in a population where most people have hypolactasia not everybody develops symptoms of lactose intolerance and that many people tolerate smaller quantities of it in food[19]. Furthermore, as the research has shown, lactose intolerance subjectively determined by patients is often linked to a significant reduction in the consumption of dairy products, thus limiting the intake of calcium and vitamin D. This results in a higher incidence of reduced bone mass, osteoporosis and related complications[13,20]. Nicklas et al. demonstrated that such persons are much more frequently diagnosed with diabetes and hypertension than those who do not report the intolerance[20]. It was also found that both the subjectively experienced intolerance and the objectively confirmed malabsorption syndrome with the resulting diet excluding dairy products reduce the subjective quality of life[21]. Therefore, the correct diagnosis of patients by means of objective tests is important, as well as informing them that, in most cases, it is not necessary to completely eliminate lactose from their diet.

TOLERANCE OF LACTOSE IN DRUGS

The role of lactose contained in medicines in inducing symptoms of intolerance is not entirely known. There are few studies related to this issue to be found in literature, despite the fact that the problem of lactose intolerance is increasingly widely discussed throughout the world.

The lactose content in medicines varies, but it usually amounts to 100–200 mg and does not exceed 400 mg per tablet or capsule (Tab. 1)[8]. In patients treated with several drugs containing lactose, this dose is correspondingly higher, but it rarely exceeds 2 g per day[1]. The assessment of the amount of lactose ingested in medicines can be difficult, as many manufacturers still do not place accurate information on the lactose content in the summary of product characteristics. In addition, the amount of lactose differs depending on the type of drug, the manufacturer and the dose, and the differences between the original and generic drugs can be significant (Tab. 1)[22]. Also, it is not easy to predict how the amount of lactose in the medicinal product can change depending on the dose of the active substance – in some tablets, the amount of lactose will grow together with the dose, in others it will decrease, while in some cases it will remain unchanged.

Authors do not agree upon whether such small doses of lactose can cause the symptoms of intolerance. So far, no population studies have been conducted, reports on this subject are scarce and the research is often not up to date.

There are a few case reports in literature of severe diarrhoea caused by medicinal products containing lactose[23–25]. Petrini et al. described two cases of women with Graves–Basedow disease who developed severe diarrhoea following the administration of a thyreostatic, which necessitated the discontinuation of the drug. No gastrointestinal symptoms followed the administration of a thyreostatic which did not contain lactose. In both women, lactose intolerance was confirmed using the hydrogen test[23]. Yagoda, on the other hand, described intolerance to another drug in flutamide-treated patients with prostate cancer. The gastrointestinal symptoms resolved completely after the discontinuation of the drug and decreased following the administration of lactase[24]. Although the authors of these studies can only suspect that it was lactose which was responsible for the symptoms and the cases are sparse, it cannot be ruled out that there are indeed persons who are very sensitive to it, responding even to small doses, such as 200 mg. In 1996, Hertzler et al. observed that very small doses of lactose, that is 2 g, do not cause significant differences in the hydrogen breath test compared to placebo. Although the signs of malabsorption in the breath test began to occur after the ingestion of 6 g of lactose, the patients experienced the symptoms of it only after ingesting 12 g of lactose[26]. Similar results were obtained in 2008 by

Name of the active substance	Trade name	The dose of the drug [mg]	The amount of lactose in the drug [mg]
Atorvastatin	Sortis	10	27.25
		80	218
	Atrox	10	38.12
		80	304.96
Thiamazole	Metizol	5	94
	Thyrozol	5	200
		20	185
Bisoprolol	Bisocard	5	120
		10	115
	Bisoratio	5	135.20
		10	130
Ramipril	Axtil	2.5	158.8
		5	96.47
		10	193.2
	Vivace	2.5	150
		5	92
		10	184
Fluticasone propionate	Flutixon	0.125	25
		0.250	25
Levocetirizine	Zyx	5	79
	Lirra	5	60.27

Tab. 1. Examples of commonly used medications along with their lactose content, based on the summary of medicinal product characteristics

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Italian researchers who conducted a cross-over study with a double-blind test on a group of 77 persons with confirmed lactose intolerance. The patients were given capsules containing 400 mg of lactose or 400 mg of placebo, and then a hydrogen breath test was conducted. The severity of the symptoms of intolerance was rated by means of the VAS (visual-analogue scale). No significant differences in the results of the test and in the assessment of the severity of the symptoms were observed between the groups. Similar results were obtained in people who claimed before the study that lactose contained in medicines had an effect on the occurrence of the symptoms of intolerance. This may suggest that these persons often mistakenly connect the appearance of gastrointestinal symptoms occurring for other reasons with ingesting a drug containing lactose[8].

SUBSTITUTE FOR LACTOSE IN MEDICINES

Apart from lactose, the role of excipients may be played by other substances as well, such as starch, sucrose, glucose, mannitol and microcrystalline cellulose[7]. It has to be noted, however, that any excipient affects multiple properties of the drug, for example, solubility in water, the rate of absorption of the drug or its bioavailability. Therefore, any modification in the composition of the drug can significantly change its physical and chemical properties, resulting in the need for new, often time-consuming and costly, physicochemical and biopharmaceutical testing[7]. Starch is an excipient with properties other than lactose. Depending on its form, it may be insoluble or characterised by high swelling capacity. Therefore, it often acts as a disintegrant, causing a tablet to fall apart swiftly, which accelerates the release of the active substance[1,6].

It has to be kept in mind that other excipients can have various adverse effects. Sucrose, which is a common component of lozenges, adversely affects the condition of teeth and may cause adverse effects in patients suffering from diabetes or glucose-galactose malabsorption. Mannitol, on the other hand, used for the production of solutions for injections, sublingual tablets and lozenges, may cause irritation of the stomach and intestines, resulting in diarrhoea. Also, cases of anaphylactic reactions have been noted[9]. Replacing lactose contained in drugs with an alternative substance is possible, but its presence may cause other adverse effects. Furthermore, generic lactose-free medicines are available now. It should be kept in mind while talking to patients suffering from very severe lactose intolerance.

CONCLUSION

Hypolactasia occurs in about 70% of the world's adult population, but lactose intolerance and related symptoms occur much less frequently. Furthermore, as research has shown, many people with diagnosed lactose intolerance can consume small amounts of lactose without developing any symptoms. A diet devoid of dairy products entails many complications. Therefore, the confirmation of lactose intolerance by means of objective tests should be sought, as well as informing the patients that a complete elimination of the disaccharide from the diet is often not necessary. Also, information on the ways to increase the tolerated dose of lactose, such as the consumption of dairy products in the presence of other nutrients and the distribution of dairy products over several smaller portions consumed during the day, may prove important for the patients. The role of medicines in inducing the symptoms of lactose intolerance has not been confirmed so far. Despite the fact that there are studies proving the safety of medication in people with lactose intolerance, no appropriate population studies have been conducted so far and the information about the exact content of lactose in medicines is often limited. Therefore, a more detailed analysis of the problem in the future seems advisable. Doctors should be aware that the content of lactose in medicines can vary depending on the manufacturer and that there are generic drugs devoid of the disaccharide. Knowledge about the role of drugs in inducing symptoms of lactose intolerance may be useful in everyday practice, contributing to patient compliance with medical recommendations.

Conflict of interest

The authors did not report any financial or personal ties with other individuals or organisations which could negatively affect the content of the publication, and claim the right to this publication.

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