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Prebiotic prevents the development of gastrointestinal motility disorders caused by omeprazole

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The synthetic disaccharide lactulose, consisting of fructose and galactose, after oral administration in an unchanged form reaches the lower part of the gastrointestinal tract, where under the action of normal flora it is broken down into short-chain fatty acids that stimulate colon motility. The effect of lactulose on gastrointestinal tract motility in the conditions of its long-term suppression by omeprazole has not been investigated. We studied the influence of lactulose on spontaneous and carbachol-stimulated gastric and colonic motility in rats treated with omeprazole for 28 days. The animals were divided into 3 groups. The first group of animals served as a control. The animals in the second group were administered omeprazole intraperitoneally at a dose of 14 mg/kg orally once a day for 28 days. The animals in the third group were simultaneously injected intraperitoneally with omeprazole and prebiotic lactulose at a dose of 0.2 g/kg orally once a day for 28 days. On the day after the last injections of drugs, we investigated the spontaneous and carbachol-stimulated contractions in the stomach and colon by the balloon graphic method. It was found that the frequency of spontaneous and stimulated contractions in the stomach and colon did not change significantly after 28 days of omeprazole treatment. The amplitude and index of spontaneous and carbachol-stimulated contractions in the stomach and colon were significantly weaker compared to the control. One day after the 28-day simultaneous administration of omeprazole and lactulose the amplitude and index of spontaneous and stimulated contractions in the stomach and colon increased compared with the group of rats treated with omeprazole alone. We concluded that the positive effect of lactulose on gastric and colon motility is a result of the prebiotic properties of lactulose which leads to the normalization of the microbiocenosis in the gastrointestinal tract and the elimination of the inflammatory process in it.
Key words: stomach; colon; spontaneous and stimulated contractions; carbachol; omeprazole; lactulose.

INTRODUCTION

Despite the successes of modern pharmacology, the problem of constipation treatment remains an urgent problem today. This pathology occurs in all age groups but is most common in women and the elderly. According to various data, the prevalence of constipation among the population of industrialized countries ranges from 10 to 40% [1-3]. Various factors are involved in the pathogenesis of constipation, including type of diet, genetic predisposition, a violation of the motor activity of the gastrointestinal tract (in particular, the colon), absorption, behavior, biological factors, and pharmaceuticals [4]. Our attention is focused on motility disorders of the digestive tract, which occur against the background of reduced secretion of hydrochloric acid in the stomach, called hypoacidity.

To date, it has been established that under the condition of a hypoacid state of the stomach caused by long-term administration of omeprazole, spontaneous and stimulated motility of the stomach and colon is inhibited. This suppression is accompanied by hypergastrinemia and pronounced dysbacteriosis in the stomach and colon, which are the causes of inflammation in the digestive tract [5,6]. We know several ways to restore the qualitative and quantitative composition of the intestinal microbiota. First of all, it is the use of probiotics and prebiotics. Probiotics are food additives and medicines that contain live cells of microorganisms, most

of which are bacteria similar to the beneficial bacteria that occur naturally in the gut, and are used to eliminate dysbacteriosis [7]. Probiotics are widely used in the treatment of various diseases of the gastrointestinal tract such as acute infectious diarrhoea, antibiotic-associated diarrhoea, Clostridium difficile-associated diarrhoea, irritable bowel syndrome, pouchitis and Helicobacter pylori infection eradication [8-11]. However, the lack of clear guidelines regarding when to use probiotics and which of them are most effective for various conditions of the gastrointestinal tract leaves the doctor with a choice. However, the lack of clear guidelines regarding when to use probiotics and which of them are most effective for various conditions of the gastrointestinal tract leaves the doctor with a choice. It should be noted that there is evidence of ineffectiveness of probiotics in acute pancreatitis and Crohn's disease [10]. While safe for most patients, probiotics should be used with caution in immunocompromised individuals.

Another way to restore intestinal microflora is the use of prebiotics. Prebiotics are a groop of biological nutrients that are broken down only in the colon with the participation of bacteria, primarily Lactobacilli and Bifidobacteria [12]. After taking probiotics in the form of food additive or a supplements, the colonic microflora degrade them. As a result, short-chain fatty acids (SCFA) are formed. Synthetic disaccharide lactulose works in a similar way. Lactulose (4-O-beta-D-galactopyranosyl-D-fructose) is a disaccharide consisting of residues of galactose and fructose molecules, a synthetic structural isomer of milk sugar - lactose. Does not occur in nature. In the colon lactulose is metabolized to SCFAs. These acids lower the pH in the lumen of the large intestine and due to the osmotic effect increase the volume of intestinal contents. It stimulates peristalsis of the large intestine and normalizes the consistency of feces. Constipation is corrected, and the physiological rhythm of digestion is restored. As a prebiotic, lactulose enhances the growth of beneficial bacteria such as bifidobacteria and lactobacilli, while inhibiting the growth of potentially pathogenic bacteria such as clostridia and Escherichia coli. This can lead to a more favorable balance of intestinal flora [13, 14]. Thus, we suggested that lactulose eliminates one of the causes of the inflammatory process in the intestine, which develops against the background of long-term hypoacidity of gastric juice, namely, it normalizes the content of intestinal microflora. The data about influence of lactulose on gastro-intestinal motility on the background of long-term of hypoacidity are absent.

The aim of the study was to investigate the influence of lactulose on spontaneous and stimulated by carbachol motility of the stomach and colon on the background of 28-days administration of omeprazole to the rats.

METHODS

Manipulations with animals and their keeping in the animal house were carried out in compliance with the standards of international recommendations and national legislation on conducting medical and biological research.

All animals were divided into 3 experimental groups. The first group of animals served as a control. For 28 days, they were administered intraperitoneally 0.2 ml and orally 0.5 ml of water for injections once a day. The animals of the second group were administered intraperitoneally omeprazole in dose 14 mg/kg dissolved in 0,2 ml of water and 0.5 ml of water for injections orally once a day for 28 days. The animals of the third group were simultaneously injected with omeprazole (manufactured by "Sigma-Aldrich", USA), intraperitoneally and prebiotic "Lactulose" (private joint-stock company «Pharmaceutical Factory «Viola», Zaporizhzhia, Ukraine) in dose 0.2 g/kg dissolved in 0.5 ml of water orally once a day for 28 days.

In a day after last injections of drugs we investigated the motility of stomach and colon. The investigations were done in acute experiments under urethane anesthesia (1.1 g/kg, intraperitoneally). Spontaneous and stimulated by

carbachol (10 μg/kg, intraperitoneally) motility of the stomach and colon was recorded by the balloon graphic method [15]. For this purpose, rats were injected with latex canisters into the stomach and colon, which were filled with 1.2 ml and 0.8 ml of water, respectively, and connected to the Jaguar automated complex. The complex is a modification of the classic method of balloonography with the use of modern registration methods, i.e. the ink-writing two-channel recorder is replaced by a computer with the appropriate software. It has been proven that balloons of a similar volume, they are called miniature, do not stimulate the motility of the stomach and intestines by themselves.

After a 2-hour recording of spontaneous motor activity of the stomach and colon, the standard stimulator of motility, the non-selective agonist of acetylcholine receptors, carbachol in a dose of 10 μg/kg, was injected intraperitoneally into the rats. Then the recording was continued for another 2 hours, based on the duration of action of carbacholin, which is 1.5-2 hours.

Statistical processing of experimental data was carried out using generally accepted methods of variational statistics. The reliability of the difference in indicators was assessed using the Student's t-test.

RESULTS AND DISCUSSION

It was established that after a 28-day administration of omeprazole, the frequency of spontaneous contractions in the stomach did not undergo significant changes. However, the amplitude of spontaneous contractions in the stomach was smaller compared to control by 80.7% ($P < 0.001$; Table 1). One day after the 28-day simultaneous administration of omeprazole and lactulose the amplitude of spontaneous contractions in the stomach increased by 28.7% ($P < 0,01$) in comparison with group of rats which were treated only by omeprazole.

In the group of rats with long-term hypoacidity of gastric juice evoked by omeprazole the stimulating effect of carbachol on the contractile activity of gastric smooth muscles was significantly weaker compared to the control group: the amplitude of contractions decreased by 54.3% ($P < 0.01$). When omeprazole and lactulose were administered simultaneously to rats for 28 days, the amplitude of carbachol stimulated contractions in the stomach was 62.5% greater compared to the group of rats that were administered omeprazole alone.

After 28 days of administration of omeprazole, the motor activity of the colon was also sig-

Table 1. The influence of lactulose on the amplitude of contractions in the stomach and colon in the rats against the background of long-term administration of omeprazole

Amplitude of contractions (centimeters of the water column)	The stomach	The colon
Spontaneous contractions (control)	5.02±0,32	2.73±0.25
Spontaneous contractions in a day after 28-days of omeprazole injections	0.97±0,08***	1.19±0.96**
Spontaneous contractions in a day after 28-days of omeprazole and lactulose injections	1.36±0,11**/##	2.23±0.21*/#
Contractions stimulated by carbachol (control)	15.10±1.32	11.04±0.88
Contractions stimulated by carbachol in a day after 28-days of omeprazole injections	6.90±0.48**	3.31±0.19***
Contractions stimulated by carbachol in a day after 28-days of omeprazole and lactulose injections	11.21±0,98*/##	9.97±1.02###

*P < 0.05; **P < 0.01; ***P < 0.001 compared to control group of rats. #P < 0.05; ##P < 0.01; ###P < 0.001 compared to group of rats which were treated only by omeprazole.

nificantly weaker: the amplitude of spontaneous contractions decreased by 56.4% (P<0.01) compared to control. When omeprazole and lactulose were administered simultaneously to rats for 28 days, the amplitude of spontaneous contractions in the colon was 87.4% greater compared to the group of rats that were administered omeprazole alone.

The amplitude of carbachol stimulated contractions in the colon was smaller compared to controls by 70.0% (P < 0.01). When omeprazole and lactulose were administered simultaneously to rats for 28 days, the amplitude of stimulated by carbachol contractions in the colon reached control values and was 201.2% greater compared to the group of rats that were administered omeprazole alone.

Similarly, lactulose affected the index of motor activity in the gastrointestinal tract (Table 2).

In the rats after a 28-day administration of omeprazole the index of spontaneous motor activity in the stomach was smaller compared to control by 15.3% (P < 0.05; Table 2). One day after the 28-day simultaneous administration of omeprazole and lactulose the index of spontaneous contractions in the stomach increased to the level of control values.

In the group of rats after a 28-day administration of omeprazole index of motor activity in the stomach stimulated by carbachol diminished by 40.2% (P < 0.01) in comparison with control group of rats. Simultaneous administration of omeprazole and lactulose to rats led to a significant increase in the index of motor activity in the stomach stimulated by carbachol, although it did not reach control values.

In the group of rats with long-term hypoacidity of gastric juice, evoked by omeprazole spontaneous contractions of smooth muscles in the colon were weaker: index motor activity decreased by 19.6% (P < 0.05). Against the background of the simultaneous 28-day administration of omeprazole and lactulose to rats, the index of spontaneous motor activity of smooth muscles in the colon did not undergo changes compared to the control.

The index of colon motility stimulated by carbachol in rats after 28 days of omeprazole administration was lower by 22.5% (P < 0.05) compared to the control.

When omeprazole and lactulose were administered simultaneously to rats for 28 days, the amplitude of spontaneous contractions in the colon reached control values and was 22.9% greater compared to the group of rats that were administered omeprazole alone.

Therefore, the stimulating effect of lactulose on spontaneous and carbachol-stimulated

Table 2. The influence of lactulose on the index of motor activity in the stomach and colon in the rats against the background of long-term administration of omeprazole

Index of motor activity (conditional units)	The stomach	The colon
Spontaneous contractions (control)	700.0±35.3	722.7±60,3
Spontaneous contractions in a day after 28-days of omeprazole injections	592.9±41,2*	581.2±40.1*
Spontaneous contractions in a day after 28-days of omeprazole and lactulose injections	698.4±42,1$^{\#\#}$	702.3±59.8$^{\#}$
Contractions stimulated by carbachol (control)	1350.1±80.3	1050.0±88.4
Contractions stimulated by carbachol in a day after 28-days of omeprazole injections	806.9±60.5**	813.3±60.2*
Contractions stimulated by carbachol in a day after 28-days of omeprazole and lactulose injections	1110.21±80.98*/$^{\#}$	999.8±78.0$^{\#}$

*P < 0.05; **P < 0.01 compared to control group of rats. #P < 0.05; ##P < 0.01 compared to group of rats which were treated only by omeprazole.

contractions in the stomach and colon against the background of their suppression caused by long-term administration of omeprazole is beyond doubt.

It is known that long-term hypochlorhydria leads to the development of dysbacteriosis and hypergastrinemia, which in turn cause the inflammatory process in the stomach and intestines, the syndrome of excessive growth of microorganisms in the small intestine, and functional disorders in the liver and pancreas [16, 17]. Also, it enhances the risk of enteric infections in patients with gastric acid suppressive drugs [18]. In turn, impaired motility of the digestive tract contributes to the colonization of the stomach by intestinal microflora. Klebsiella, Staphylococcus aureus, Staphylococcus epidermidis (with hemolysis) enter the stomach by migrating from the intestines in an ascending way due to a decrease in the motor activity of the digestive tract [19]. First, excessive bacterial growth develops in the small intestine, where bacteria from the colon easily migrate. The pyloric sphincter, it would seem, was supposed to prevent intestinal bacteria from entering the stomach. However, thanks to duodeno-gastric reflux, microorganisms enter the stomach. Duodeno-gastric reflux is one of the components of the motor activity of the digestive tract. Under normal conditions, the contents of the duodenum, which due to reflux enters the stomach, remain in it for a short time. But under the conditions of inhibition of gastric motility, which occurred after long-term administration of omeprazole, the intestinal contents were retained in the stomach for a long time, which contributed to the adhesion of microorganisms that inhabit the large intestine to the mucosa-epithelial layer. Depressed motility of the stomach contributed to the retention of transient microflora in the stomach. Earlier, it was shown that dysbacteriosis in the stomach and colon did not develop under conditions of 28-day simultaneous administration of omeprazole and multiprobiotic drugs [5, 6]. The effect of lactulose is due to the inhibition of the growth of proteolytic bacteria due to an increase in the number of acidophilic bacteria (for example, lactobacillus), the transformation of ammonia into an ionized form due to the acidification of the contents of the intestines, the cleansing of the intestines due to low pH, as well as the osmotic effect, a change in bacterial nitrogen metabolism by stimulating the utilization of ammonia by bacteria for synthesis of bacterial proteins [20, 21].

CONCLUSIONS

With simultaneous 28-day administration of omeprazole and lactulose spontaneous and carbachol-stimulated motor activity of the stomach and colon was stronger than under conditions of administration of omeprazole alone. We concluded that this effect is a result of the prebiotic properties of lactulose which leads to the normalization of the qualitative and quantitative composition of the microflora in the gastrointestinal tract. As a result, inflammation decreases, and the contractile activity of smooth muscles normalizes.

The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of co-authors of the article.

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ПРОБІОТИК ПОПЕРЕДЖУЄ РОЗВИТОК ПОРУШЕНЬ МОТОРИКИ ШЛУНКОВО-КИШКОВОГО ТРАКТУ, ВИКЛИКАНИХ ОМЕПРАЗОЛОМ

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Синтетичний дисахарид лактулоза, що складається з фруктози і галактози, після перорального прийому в незмінному вигляді сягає нижнього відділу шлунково-кишкового тракту, де за дії нормофлори вона розщеплюється до коротколанцюгових жирних кислот, які стимулюють моторику товстої кишки. Вплив лактулози на моторику шлунково-

кишкового тракту в умовах тривалого її пригнічення омепразолом не досліджений. Ми вивчали вплив лактулози на спонтанну та стимульовану карбахоліном моторику шлунка і товстої кишки у щурів на тлі введення омепразолу. Всі тварини були розділені на 3 групи. Перша група слугувала контролем. Тваринам другої і третьої груп внутрішньоочеревинно вводили омепразол у дозі 14 мг/кг, а щурам третьої групи ще і перорально пребіотик лактулозу в дозі 0,2 г/кг. Через день після останнього введення речовин балонографічним методом визначали спонтанні та стимульовані карбахолом скорочення в шлунку та товстій кишці. Було встановлено, що після 28 днів введення омепразолу ці показники не змінювалися. Амплітуда та індекс спонтанних і стимульованих скорочень були суттєво слабшими порівняно з контролем, а через день після одночасного введення омепразолу і лактулози вони зростали порівняно зі значеннями у щурів, яким вводили лише омепразол. Зроблено висновок про те, що позитивний ефект лактулози на моторику шлунка і товстої кишки є результатом пребіотичних властивостей лактулози, що призводить до нормалізації мікробіоценозу в шлунково-кишковому тракті і усунення запального процесу в ньому.

Ключові слова: шлунок; товста кишка; спонтанні та стимульовані скорочення; карбахолін; омепразол; лактулоза.

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