Advantages and therapeutic capacities of digestive enzymes preparations of non-animal origin

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Food that the body does not digest,
eats the one who ate it.
Abul-Faraj, a Syrian poet of the 13th century

Some of the most frequent complaints for e IU at the family doctor, general practitioner, gastroenterologist — a complaint dyspepsia Ia.

In Greek, "dyspepsia" means " dys " (violation), " peptein " (digest), that is, dyspepsia is "indigestion." What will help with this "indigestion", how not enzymatic preparations (EP)?! The term "dyspepsia" has developed historically, the practical experience of physicians logically led them to EP, because they stop the manifestations of dyspepsia of different origin [20, 26].

In general, "indigestion," that is, dyspepsia, can develop when there is a violation of cavitary digestion, membrane digestion, and also with impaired absorption. If it is adisorder of the digestive system, that is, e. violation of hydrolysis in the lumen of the digestive tract, this condition is called maldigestia, and if — about the violation of membrane digestion and absorption, then — malabsorption. The main cause of maldigestia is pancreatic insufficiency, and malabsorption is usually based on the defeat of the small intestine mucosa. In addition, the failure of membrane digestion also occurs when the amount of pancreatic enzymes absorbed on the membrane of the brush border of enterocytesdecreases, that is, the deficiency of pancreatic enzymes is involved in pathogenesis and maldigestia, and malabsorption. A more rare mechanism for the formation ofmalabsorption is the impairment of absorption in the event of damage to active transport systems that provide amino acids, carbohydrates, fatty acids, vitamins, minerals, water to the bloodstream, which is observed in certain diseases accompanied by damage to the blood (vasculitis, atheroma) or lymphatic (lymphangiectasia) of the vessels of the small intestine [14, 15, 16, 26].

All variants of dyspepsia are clinically divided into gastric, intestinal and biliary. Symptoms of gastric dyspepsia include severity, discomfort in epigastrium, early satiety, belching, heartburn, nausea, vomiting, decreased appetite. Manifestations of intestinal dyspepsia include flatulence, flutulenia, rumbling, diarrhea, constipation, unstable stools.The syndrome of biliary dyspepsia is characterized by a decrease in appetite, a feeling of bitterness in the mouth, stool disorders (constipation, diarrhea or alternation), flatulence, a feeling of discomfort, severity, raspiraniya in the right hypochondrium [10, 11, 20].

When overeating, all three variants of dyspepsia are observed, therefore, first of all, we will understand the pathogenesis of complaints developing during overeating, ie, precisely in the case when the volume and composition of the ingested food significantly exceed the possibilities of digestion. The pathogenesis of disorders developing during overeating is an ideal model for the formation of both gastric, intestinal, and biliary dyspepsia in their interrelation. One of the first pathophysiological reactions to overeating is duodenosis. Insufficiently hydrolyzed chyme, located in the duodenum, involves a number of reflex possibilities in order to require the pancreas of additional enzymes. If the prostate can not respond to these requirements, the chyme is delayed in the duodenal lumen, waiting for additional pancreatic enzymes. Only after a while the pancreas synthesizes and excretes them. And then, when the components of the chyme are subjected to sufficient hydrolysis, their passage through the digestive tract will continue. Consequently, when overeating, the chyme is delayed in the PDC, which leads to duodenosis [28].

But back to the stomach. What happens in his cavity during overeating? Let us recall the duodenopiloric inhibitory reflex, which was described by one of the employees of the laboratory I. P. Pavlova — S. I. Lintvarev [9]. The reflex is that when the pressure in the duodenal lumen increases, the pyloric spasm develops, preventing the evacuation of contents from the stomach at a time when there is still a certain amount of chyme in the DPC. Given duodenostasis, characteristic of overeating, it is logical that this duodenosis is inevitably accompanied by a pyloric spasm and delayed evacuation from the stomach. It duodeno — and gastrostasis are the cause of severity, raspiraniya, discomfort in the upper abdomen after taking abundant, fatty foods. The increased pressure in the cavity of the stomach easily finds the direction of its discharge. Below — pylorospasm, therefore increased intragastric pressure spreads into the esophagus, which entails the emergence of belching, heartburn, which are also invariable satellites of overeating [26].

To prevent overeating symptoms or to cope with already developed symptoms, it is necessary to restore the balance between volume, the composition

of the food intake (very important the amount of fats), on the one hand, and the activity of pancreatic enzymes in the duodenal lumen, on the other. If your own PZ delays the release of enzymes for the complete hydrolysis of chyme, i.e., does not cope with the requirements imposed on it, then it is necessary to add digestive enzymes from the outside. It is quite obvious that EP is needed, but at present there are quite a lot of them. What to choose in a situation of overeating?

The main factor in the inactivation of enzymes is the acidic environment of the stomach. It should be taken into account that at pH < 4.0-4.5 inactivation of pancreatic enzymes occurs. Thus, when passing through the acidic environment of the stomach of "unprotected" enzymes, more than 80% of lipase activity is lost, more than half of the activity of trypsin. The activity of amylase suffers less [1, 3, 5, 23]. There are following with grants conservation of activity enzymes falling at EP [5, 20, 21, 24, 28]:

- acid-resistant shell;
- concurrent administration of antisecretory agents (H_2-blockers, aluminum-containing antacids);
- enzymes of microbial, plant and fungal origin;
- increase in the ratio of lipase / protease;
- the ratio of colipase / lipase is not less than 1;
- inhibition of chymotrypsin.

Of all the above possibilities of protecting enzymes from inactivation, the most effective is the first [26].

Parallel assignment with EP antisecretory drugs with replacement therapy until recently was quite popular. However, the appointment of antisecretory drugs should continue for the same amount of time as is continued with e FF. If talk about substitution therapy, it is often it is a lifetime. Under these conditions, if prolonged for e IUantisecretory agents increases the likelihood of their side effects. In addition, prolonged with e m powerful antisecretory drugs can aggravate flatulence, loosening of the stool, available in patients due to the underlying disease, for example, because of chronic pancreatitis [18, 19].

Of particular interest are EP, created on the basis of enzymes not of the animal, but of microbial, plant, fungal origin. Thus, in Japan, where non-animal origin of non-animal origin has been developed for the first time, currently more than 80% of EP in the pharmaceutical market are bacterial, 10% — fungal nature, and only a small part of the EP has an animal origin [17]. The reasons for this preference are numerous factors that need to be addressed in more detail [25, 26].

First, the enzymes of plant, bacterial and fungal origin retain their activity at a much broader pH range than animal enzymes — from 3.0 to 9.0. Consequently,

they do not need the above e zhnoy acid resistant shell and / or concomitant administration of antisecretory agents [17, 20, 23]. Enzymes of non-animal origin are stable and active in both acidic and alkaline environments [23]. This feature achieves a good bioavailability of non-animal EP. For example, acid-fast enzyme concentrate of Aspergillus fungus cultureSingle oryzae actively used in combination with a pancreatic enzyme (Kombizim forte) and a samosa toyatelnyh dosage forms. Microbial hydrolases of these preparations are released from the dosage form in the stomach, which ensures an earlier and uniform hydrolysis of food substrates. Therefore, despite the relatively low specific activity of enzymes, the enzyme concentrate from Aspergillus oryzae proved to be more effective than pancreatin in the elimination of digestive disturbances (according to the results of coproscopy) with experimental pancreatic insufficiency in rats [23]. Especially important is the stability in the acidic environment of lipase microbial, fungal and plant origin, since the preservation of ee activity is essential to ensure the effectiveness of substitution therapy. Where e m, is important not only tolerance of non-animal lipase to the acidic environment of the stomach of the patient, but also to the acidification of the duodenal contents while reducing the production of bicarbonate in the pancreas case of severe exocrine pancreatic insufficiency [7, 28].

We have practical experience in treating patients with chronic pancreatitis EP animal origin, wherein f m, in some cases in combination with acid diseases [2, 4, 6].

The presence of a neutral or alkaline medium is also unfavorable for the realization of the action of traditional EP of animal origin. As a rule, the microspheres of such preparations are encapsulated, which dissolves in an acid medium. Consequently, with hypoacidity, the dissolution of the capsule slows down, while the evacuation of the chemical from the stomach is accelerated. That is, the capsule in this case prevents the timely release of enzymes and their mixing with food substrate [8, 18, 19, 21].Therefore, in patients with gastritis hypoacid, have undergone resection of the stomach enzyme granules should be before or caplet as e IOM extract from a capsule [7]. Enzymes of non-animal origin do not need to be encapsulated, since they are active in a wide pH range. Sun e it should be noted and used fungalnyh lipase deficiency — inhibition of their activity salts w e lchnyh acids at physiological concentrations [23, 28].

The second essential advantage of lipase of microbial origin — no need to activate e e g e lchnymi acids [25].

Must be present to ensure lipolysis animal lipase w e lchnyh acids to activate the enzyme and fat emulsification. Therefore, the conventional EP may not be

sufficiently effective in short supply rail e lchnyh acids in the duodenum (gepatogennaya pancreatic insufficiency in cholestatic liver diseases, and w e hypomotility lchnogo bladder after cholecystectomy, and in some cases is due to a deficiency of pathogenically low gastric secretion). Of course, this problem can be solved by adding w e w e lchi or lchegonnyh components in the EP animal proish ozhdeniya (turmeric et al.). However, the addition of these components to the OP also has negative aspects (a "double-edged sword"). F elchnye acid increases the osmotic pressure of the intestinal contents, where e m under the conditions of the intestinal microbial contamination occurs deconjugation w e lchnyh acids with the development of osmotic and secretory diarrhea. F e lchnye acid entering into the enterohepatic circulation, increases the burden on the liver function.Dekonyugirovannye w e lchnye acids have damaging effects on the mucosa of the digestive tract [1, 13, 23]. With duodenopancreatic reflux w e lchnye acid exacerbate autolysispancreas. T. e. preparations containing w e lch contraindicated in hepatitis and cirrhosis of the liver, expressed aggravation of chronic pancreatitis in patients with erosive and ulcerative changes in the mucosa of the digestive system [1, 13, 23]. But these drugs are appropriate when hypomotility g e lchnogo bubble, in some cases after cholecystectomy, in the presence of constipation in a patient with low gastric secretion. In the latter case, reduced the impact of stimulating reduction w e lchnogo bubble, and the appointment of Animal EP containing w e lchnye acid can smooth out the situation [28].

Of course, the purpose of non-animal EP, which does not require activation by ferric acids, has advantages in the above situations. Furthermore, bacterial (but notfungalnaya) lipase not inactivated w e lchnymi acids in the usual concentrations, which is important if the patient insufficiency of the sphincter of Oddi, and in patients undergoing cholecystectomy when possible excess w e lchnyh acids within the lumen of duodenum [20, 23].

The third positive quality of microbial enzymes, and fungalnog of plant origin — a broader substrate specificity than the enzymes in animals. Because of this, non-animal PTs do not need to introduce additional hydrolyzing components (for example, cellulase / hemicellulase for cleavage of plant shell polysaccharides) [23, 28]. But all is, as part of some drugs, such as Digest 365, Cellulase is introduced to enhance the effect on meteorism.

The fourth advantage of non-animal enzymes — resistance to proteases that reduce lipase activity, and to inhibitors of human and animal prostate enzymes. Thus, EP microbial, plant and fungalnogo origin ud e tsya retain its activity in the human body, that is to be held n e m high "efficiency". EP animals, despite the

higher lipase content in some of them, in practice may have less pronounced therapeutic effect due to a decrease in lipase activity in the internal environment of the human body due to the inactivation ofthis lipase by proteases, enzyme inhibitors and acidic gastric environment [23, 25].

A fifth advantage of the OP of non-animal origin — the lack of suppression of the patient's own pancreatic secretion, and even stimulating effect on the not e (see below.).This is due to the fact that the feedback mechanisms that are included in the KDP in response to ingestion of animal-derived enzymes do not respond to EP of another origin because of differences in structure [26].

The sixth advantage of OP non-animal origin: can be used in patients who have hypersensitivity to pancreatin (observed in 5% of patients with chronic pancreatitis) [20,23].

Among the non-animal-based EP enzymes preference is given fungalnym and microbial enzymes produced as their paths fermentation e m which is a natural process and is carried out by microorganisms present in the food. The disadvantages of using plants as sources of enzyme production include the difficulty of cultivating crops, the dependence of accumulation of active substances on climatic conditions, the dependence of harvesting plants on the season, etc. [17]. In addition, the likelihood of allergic reactions when using plant enzymes is higher than with the appointment of EP microbial and whether fungal origin [28].

Goes e determines advantage non-animal EP is also to maintain their activity over a broad temperature range, which facilitates the storage conditions [17, 23].

Thus, non-animal enzymes are "not afraid" important factors of inactivation (acidic environment of the stomach, the deficit w e lchnyh acids in duodenal lumen).Preparations based on enzymes of non-animal origin do not need to provide such methods of preserving the activity of these enzymes, such as an acid-resistant shell, an increase in the ratio of lipase / protease, inhibition of chymotrypsin [26].

Abroad (Japan, Germany) non-animal origin of the fauna are represented quite widely. Thus, in Japan, based on a concentrate from Aspergillus oryzae produced Sons drugwhich possesses lipo -, amilo — proteolytic activity and are stable in acidic and alkaline medium. Germany produces complex preparations based on a concentrate fromAspergillus oryzae : Combisim, Elzim. In the United States, Milaza-100 is produced, which has amylolytic action, combined preparations of Digolase and Rosim CL. In Of France is issued lipolytic a drug Lipancryl [25].

In recent years, non-animal origin PT Sun e wider part of the clinical practice and applied even in cases involving e cord loi pancreatic insufficiency, eg cystic fibrosis.Note erom such preparation is l iprotamaza (USA).

Initially, the drug Lipotamaz was discovered and developed by the company Altus Pharmaceuticals, which was spent 25 million US dollars. Currently liprotamazamanufactured by Anthera under the trade name Sollpura as a powder for oral administration for e ma. Liprotamase is a biotechnological product derived from enzymes of bacterial origin. Several randomized clinical trials of lipoproteinase efficacy and safety have been conducted. Based on the results of the Phase III multicenter, randomized, placebo-controlled, double-blind study in parallel groups of patients with cystic fibrosis, it has been shown that lipoprotease significantly increases the fat and nitrogen absorption indexes (i.e., improves the hydrolysis and assimilation of fat and protein), reduces stool mass, is well tolerated [22].

In 2016. the results of another double-blind, randomized, placebo-controlled, cross-sectional study, showing the efficacy of preparation of microbial lipase at a liquid form for oral administration at the treatment of cystic fibrosis, have been published [27].

Vernemsya to dyspepsia in overeating. In its pathogenesis, the lack of bile acids in the duodenal lumen is essential. Or they are trivial lacking in the presence of a large amount of fats entering the DPC, or the gall bladder sluggishly shrinks and supplies insufficient amounts of bile acids for their participation in the hydrolysis of fats, ie, hypomotor hypokinetic dysfunction of the gallbladder occurs. But with the appointment of a non-animal origin of OP, the amount of zinc acid in the duodenal lumen is not critical, since enzymes do not need them to realize their effect (see above). Excessive consumption of fruits and vegetables also contribute to the symptoms of overeating. Therefore, one more component of the EP, which we will prescribe for overeating, is called cellulase and / or hemicellulase [20]. Cellulase is included in the new preparation of fungal origin Digest 365 (the complete composition see below) to facilitate the splitting of the components of plant envelopes. After all, the insufficient hydrolysis of the poly-saccharides of the cell walls of vegetables and fruits leads to fermentation and flatulence. Therefore, cellulase provides a reduction in flatulence in overeating. This aspect of the action Digest 365 justifies its effectiveness in intestinal dyspepsia.

The presence of lactase in Digest 365 is important. This component is the basis for treatment with lactase deficiency (it occurs in different countries with a frequency of 12-93%), which manifests itself as intestinal dyspepsia: flatulence, diarrhea with the intake of products containing lactose milk sugar). Patients with this pathology should exclude dairy products from food or use special products without lactose. But to exclude all products containing lactose, it is difficult,

because it is a very common component of many of them. Substitution therapy of Lactase-based EP is a principal method of treatment of hypolactasia [16].

The above-mentioned preparation Digest 365, which is a digestive enzyme complex from yeast fermentation products Aspergillus or y z a e (Sante Naturelle (AG) LTEE, Canada) is represented on the Ukrainian market. Digest 365 is a preparation containing 1200 IU of amylase, 300 IU proteases, 200 IU of lactase, 50 IU of lipase, 10 IU of cellulase. According to lipolytic activity, Digest 365 is several times lower than highly active preparations of pancreatin, however, all of the above features of non-animal enzymes, including lipase, and a significant "EFF" pathogenetically substantiate the therapeutic effect of the drug for dyspepsia of various origins (overeating, etc.). The drug can be used as a part of complex therapy for patients with a light course of chronic pancreatitis with normal fecal elastase test results, for dyspepsia in patients with diabetes mellitus, for preparation for radiographic and ultrasound examinations. And, of course, the indication for the appointment of Digest 365 is the primary (congenital) and secondary (due to diseases of the small intestine) lactase deficiency.

We finish the article with the words of the outstanding pathologist AI Polunin: "A doctor, learning how nature cures diseases, only helps her" [12].

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Advantages and therapeutic capacities of digestive enzymes preparations of non-animal origin

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The article presents a literature review on the features and benefits of digestive enzymes preparations of non-animal origin, i.e. drugs which include plant, microbial or fungal enzymes. Diseases and conditions upon which such drugs are prescribed have been pathogenetically substantiated. The results of evidence studies are presented, the outcomes of which conclude that the biotechnological enzyme preparation of bacterial origin is effective and safe in the treatment of cystic fibrosis. Peculiar attention is paid to Digest 365 that contains not only amylo-, proteo- and lipolytic enzymes, but also cellulose and lactase.