NEW OPPORTUNITIES OF ENZYME THERAPY IN THE FIELD OF PANCREATOLOGY

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Introduction

For the last decades, incidence of digestive diseases steadily grows all over the globe. Incidence and prevalence rates for the digestive diseases among the population of Ukraine exceed similar rates in the European countries by 3−4 times [30, 38] and keep the tendency of growing, which is associated with poor food, alcohol abuse, smoking, psychological factors, decreased level of family living, co-morbidity etc. Thus, for the last 5 years, prevalence of digestive diseases among the population of Ukraine grew by 24.7%, incidence — by 8.7%, and lethality — by 14.0% [27].

A special place among digestive diseases belongs to pancreas pathology; its specific weight in the digestive diseases mix accounts for 10.5% [25]. Currently, pancreatic diseases annually develop in one person per 10 000 of the world population. For the last 30 years, total number of patients with pancreas pathology worldwide increased more than twofold. The rate of pancreatic disease prevalence in Ukraine, for the last 10 years, increased threefold, and the incidence rate in some regions reaches 200−290 per 100 thousand people. The number of newly identified cases of pancreatic diseases annually grows by 5−6 thousand patients [1, 26].

Most cases of pancreas pathology are represented with three diseases: acute pancreatitis, chronic pancreatitis (CP) and pancreatic cancer. As reported, incidence and prevalence of acute pancreatitis account for 4.8−24.0 and 26.4−45.1 per 100 thousand people, respectively. Acute pancreatitis develops more often than chronic pancreatitis in patients with biliary pathology, and in some cases such patients are subject to surgery. This form of pancreatitis rarely transforms into a chronic one, and

– as a rule – ends up with convalescence. CP refers to those digestive diseases which are most hard to diagnose and treat, which is attributed to polymorphic nature of clinical picture, to advanced stage (frequently) of pathological process at the moment of diagnosis, various etiology of the disease, peculiarities of pathogenesis, objective difficulties related to laboratory instrumental diagnostics, low effectiveness of available therapies [35, 36]. CP accounts for up to 25% of referrals to gastroenterologists in policlinics across Ukraine, and in specialized in-patient departments of our country such patients occupy 9−12% of beds [1]. CP prevalence among the population of various countries is reported to range from 5−10 to 68 per 100 thousand people. In 30% of CP patients are diagnosed at first referral with early and late complications (purulent-septic, bleeding erosive-ulcerous defects in gastroduodenal zone, compression of choledoch duct or duodenum, thrombosis in a portal vein system, and in case of long-standing history — functional insufficiency of pancreas, pancreatic cancer etc.). Lethality in case of primary hospitalization of CP patients achieves 5.1%. Natural course of the disease and its complications are the reason of death in one third of patients within 10 years from the disease onset and in nearly a half of patients within 20 years. Moreover, 20-year history of CP fivefold enhances the risk of pancreatic cancer. CP considerably impairs the quality of patients' lives and is one of the most frequent reasons of disability, preceded by liver cirrhosis [1, 6]. Incidence of pancreatic cancer in numerous developed countries is almost the same as the CP incidence — 5−10 per 100 thousand people. In Ukraine, incidence of pancreatic cancer accounts for 10.2 per 100 thousand people and shows negative tendency of steady increase [23]. Thus, for the last 30 years, incidence of pancreatic cancer grew by 2-4 times in various countries [35, 36].

The main reason of such unfavourable epidemiological CP rates lies in the fact that the disease pathophysiology and, consequently, its diagnostics and treatment still face a large number of unaddressed issues.

Physiology of Pancreas

Pancreas plays an important role in digestive and metabolic processes and has two major functions: exocrine and endocrine. The main part of this gland is exocrine,

and its accounts for 95% of the organ weight. The gland is characterized with lobulation and consists of acinuses and excretory ducts. The most of acinuses is made of secreting pancreatic cells, i.e. pancreacytes. Endocrine part of the gland is made of Langerhans islets, which differentiate with their ability to secrete polypeptide hormones: A-cells produce glucagon, B-cells – insulin, and D-cells - somatostatin. The majority of Langerhans islets (nearly 60%) are made of B-cells [11, 12].

Pancreas is the powerful secretory digestive organ, as it produces, per a day, 1.5−3.0 l of isoosmotic alkaline (pH≥8.0) secretion containing nearly 20 digestive enzymes. They include: proteolytic and nucleolytic enzymes (trypsin, chymotrypsin, carboxypeptidases, elastase, nucleases, aminopeptidase, collagenase, dipeptidase), amylolytic enzymes (α-amylase, pancreatic isoamylase, maltase, lactase, invertase) and lipolytic enzymes (lipase, phospholipase, cholinesterase, carboxylesterase, monoglyceride lipase, alkaline phosphatase) etc. Moreover, pancreatic juice contains electrolytes (sodium, potassium, chlorine, calcium, magnesium, zinc, copper) and significant number of bicarbonates which ensure neutralization of acidic duodenal content. Thus, optimal intestinal fluids are ensured for enzyme activity [11, 12].

Most of pancreatic enzymes (lipase, phospholipase, trypsin, maltase, nuclease etc.) are excreted inactive to be then normally activated in duodenum, which protects pancreatic tissue from autolysis. Proteolytic enzymes are activated with enterokinase of intestinal juice, and lipase is activated with bile acids. Amylase, unlike other enzymes, is excreted by pancreas in active state. Pancreatic enzymes are generated in acinar cells; liquid secretion and electrolytes are produced by duct cells, and mucoid fluid — by mucous cells of the main pancreatic duct. Pancreas also produces enzyme inhibitors which take part in regulation of pancreatic juice activity [11].

Pancreas activity is regulated with parasympathetic, sympathetic, pituitary-hypothalamic systems and other glands of internal secretion. In particular, a certain role in regulation of enzyme generation is played by a vagus nerve. Sympathetic nerves that innervate pancreas also have secretory fibres. I.P. Pavlov proved that secretion of pancreatic juice starts from seeing food or irritation of receptors in

mouth cavity and throat (so-called ‘brain phase’). Later, irritation and extension of stomach walls with food occurs at the background of increased pancreatic secretion via cholinergic and gastrin mechanisms. Contact of food with antrum mucosa causes gastrin release, which – in its turn – stimulates enzymatic pancreatic secretion. Secretion of hydrochloric acid in a stomach is important both for cholinergic effect on parietal cells and for gastrin release. When stomach content enters duodenum, intestinal phase of pancreatic secretion starts. Intestinal phase accounts for nearly 80% of the gland response to food ingestion. Humoral control is of special importance during this phase. Affected by hydrochloric acid contained in gastric juice, which gets into intestines, mucous membrane cells of the small intestine excrete prosecretin. Hydrochloric acid activates prosecretin and transforms it into secretin. Absorbed in blood, secretin affects pancreas and intensifies its excretion of juice, and simultaneously it suppresses the function of parietal glands in order to prevent excessively intensive secretion of hydrochloric acid. Secretin induces large amount of pancreatic secretion with low content of enzymes and high content of alkalies. Moreover, affected by the products of fat and protein digestion (long chain fatty acids, tryptophane, phenylalanine, valine, methionine etc.) duodenal and proximal empty intestine mucosa produce cholecystokinin-pancreozymin (CK-PZ) which stimulates secretion of enzymatic component of pancreatic juice. Synergistic effect of secretin and CK-PZ on pancreatic secretion is of great physiological importance. Beside secretin and CK-PZ, other substances – neurotensin, noradrenaline, nitrogen oxide, histamine, insulin etc. – may act as stimulators of pancreatic secretion. Furthermore, they have vasodilating effect and intensify blood flow to pancreas ensuring intensification of its secretion [12].

Along with stimulation of pancreatic secretion, there is also inhibition which acts directly (via specific receptors) or indirectly (through inhibition of secretion stimulators release and decreased blood flow to pancreas and, consequently, decreased delivery of secretory active hormones and substances required for synthesis of enzymes and bicarbonates). Inhibition of pancreatic secretion is intrinsic to neuropeptides (calcitonin-releasing-peptide, Y, YY, gastric inhibitory, pancreatic

and vasoactive polypeptides), glucagon, somatostatin, enkephaline, calcitonin etc. Moreover, pancreatic secretion is regulated also with a negative feedback mechanism. In other words, increased content and activity of pancreatic enzymes (to a greater extent, serine proteases – trypsin and chymotrypsin, and to a lesser extent – hydrolases (α-amylase and pancreatic isoamylase)) in blood and duodenal cavity decelerates pancreatic secretion. Leading role in reverse deceleration of pancreatic secretion are played by vagus, cholecystokinin and secretin mechanisms, and inactivation of several cholecystokinin-releasing stimulators (strong simulator of pancreatic secretion) with active trypsin [3, 10, 11, 13].

CP

CP is a notion which characterizes chronic inflammatory damage of pancreatic tissue with destruction of exocrine parenchyma, or its atrophy, fibrosis and destruction of endocrine parenchyma – at least at the later stages. This disease features stage-progressive course with periodic pancreatic attacks responsible for relapsing pain, which often is the only clinical syndrome of the disease. Destructive changes may be of focal, segmental or diffusive character. Then they are replaced with fibrous tissue, and pain episodes gradually decrease or disappear, and functional insufficiency of pancreas progresses [1].

Main etiological forms of CP are alcoholic and biliary [1, 4, 22, 31, 32].

The most frequent reason of CP is alcohol abuse [9]. Alcohol dose safe for liver and pancreas totals 210 ml of ethanol (530 ml of vodka) per week; dangerous dose totals 80−160 ml of ethanol (200−400 ml of vodka) per day; very dangerous – over 160 ml of ethanol (over 400 ml of vodka) per day [14]. Some scientists consider that a dangerous dose for pancreas is twice lower than for liver. Moreover, hepatopancreotoxic dose of ethanol for women is twofold lower than for men. Several mechanisms take part in pathogenesis of CP of alcoholic etiology [32]. Primary metabolite of ethanol and cigarette smoke is acetic aldehyde, which has a stronger toxic effect on cells - including acinal - than ethanol itself. At the same time, activity of enzyme which inactivates acetic aldehyde decreases in case of alcohol abuse. Ethanol suppresses bioenergetic processes in acinal cells, decreasing their

resistance to damaging influence and accelerating necrotic process. Ethanol increases gastrin and CK-PZ production. For this reason, pancreatic enzymes synthesis enhances and production of secretion and bicarbonates remains the same. The result is that the concentration of enzymes in pancreatic juice grows, and protein precipitates leading to formation of 'protein plugs' in acinus and small ducts clearances. Such 'plugs' are calcified and impede secretion outflow. Ethanol causes a spasm of Oddi's sphincter leading to intra-duct hypertension, and duct walls get permeable for the enzymes. The latter are activated with lysosomal hydrolases, thus 'launching' autolysis of pancreatic tissue. Ethanol disturbs synthesis of cell membrane phospholipids resulting in their increased permeability for enzymes, and contributes to fibrosis of small vessels and disordered microcirculation [1, 21].

Biliary tract diseases are the reason of 60−70% cases of CP. In these cases, biliary pancreatitis develops. Pathogenesis of biliary pancreatitis is explained with the fact that choledoch and Wirsung's ducts often mingle and have one clearance in the area of major duodenal papilla (the theory of 'common duct') [1]. Normally, pancreas duct pressure is higher than in choledoch, which prevents bile from getting into a pancreatic duct. In case of inflammatory process, pressure in biliary ducts increases and bile gets into a pancreatic duct. Pancreatic phospholipases activate and transform biliary lecithin into highly toxic lysolecithin. At the same time, in some cases pathogenic flora from infected bile also gets into the pancreatic duct. In case of cholelithiasis, all the above mentioned factors are supplemented with irritation of Oddi's sphincter with microlites, thus leading to its dysfunction [29]. Furthermore, sphincter hypertension leads to hypertension in the duct, and hypotension – to duodenopancreatic reflux and intra-organ activation of proteolytic enzymes with enterokinase. Small and very small calculi (microlites) are the most dangerous in terms of acute pancreatitis development and CP attacks. Thus, frequent CP relapses occur in cases when ultrasound investigation and cholecystography reveal biliary sludge in a gall bladder or a choledoch rather than calculi. Such sludge contains microlites of not more than 1 mm in diameter. Calculi of 1−1.9 mm in diameter are called 'gravel', and calculi of more than 2 mm in diameter are considered 'common'.

However, in the latter category, small calculi sized up to 4 mm are the most dangerous [28]. Cholecystectomy not always decreases, and in some cases even increases the risk of pancreatitis due to cicatrical constriction in the end of choledoch (constrictive papillitis) [1].

Despite the variety of reasons for acute and chronic pancreatitis, their pathogenesis, in the majority of cases, is confined to increased pressure in the pancreatic duct system, reflux of bile and/or duodenal content to Wirsung's duct. The result is that enzymes are activated inside of organs and permeate pancreatic tissue through the duct, thus leading to autolysis. An essential prerequisite for this process is the disorder in mechanisms of pancreas self-protection, as the enzymes fail to affect integral tissue [2, 7]. In case of acinal cells necrosis, enzymes synthesized in them get into blood in abundant quantity, activate kinin system, phagocytosis, complement cascade, and contribute to mediators release by mast cells (histamine, serotonin), disturb a balance between coagulation and fibrinolysis, microcirculation, morphofunctional properties of erythrocytes [19]. Lipid peroxidation activates, and its products accumulate, leading to depression of antioxidant protection which, in its turn, contributes to aggravation of enzyme-inhibitor imbalance, joining the vicious circle of pancreatitis pathogenesis [7]. Over the last years, cytokines – substances excreted by leukocytes (interleukins 1, 6, 8, TNF, platelet-aggregating factor) – were proved to have great importance for any inflammatory process, including pancreatitis pathogenesis. In case the balance between pro- and anti-inflammatory interleukins shifts to the pro-inflammatory ones, inflammation during pancreatitis enhances. Such imbalance increases the risk of pancreatitis complications, as the inflammation mediators cause both local and systemic effects [1, 34].

Thus, intra-duct hypertension, which essential role is proved, is important for pathogenesis of CP of both alcoholic and biliary etiology. Dilation of ducts during pancreas visualization, in case this variant of pathogenesis dominates, gave ground for the term of 'the dilated (large) duct disease', unlike 'small duct disease' which development is triggered with other less studied mechanisms (primarily, perineuritis) [34, 39].

Intra-duct hypertension may be basically caused by three factors: narrowing of Wirsung's duct, mostly in its terminal part; increased viscosity of pancreatic secretion; and increased pressure in duodenum which exceeds the pressure in a pancreatic duct [32]. In case of CH of biliary etiology, two first factors are present. Thus, microlites contained in biliary sludge, if excreted with bile into duodenum, first cause Oddi's sphincter dysfunction and then constrictive papillitis [32]. Moreover, formation of biliary sludge and biliary calculi is preceded with changes in physical and chemical composition of bile, which surely affects not only viscosity of bile itself but the content of biliopancreatic ampoule as well [28]. In case of CP of alcoholic etiology, spasm of Oddi's sphincter develops, and viscosity of pancreatic secretion enhances resulting in formation of protein 'plugs' in small ducts, which lead to duct hypertension [32]. Moreover, ethanol contributes to duodenostasis, due to which intra-duodenal pressure exceeds Wirsung's duct pressure, creating another impediment to pancreatic secretion outflow [1, 18]. The reason of obstruction in major and lateral pancreatic ducts is chronic obstructive pancreatitis - 'the large duct disease' – which accounts for more than a half of all CP cases. In this respect, development of effective therapeutic approaches to ductal decompression is an important scientific and practical task. All the more so, as the methods of endoscopic and operative decompression are indicated only in the event of organic changes in Wirsung's duct (for example, its corrosive strictures, calcification in its clearance etc.); not all healthcare facilities have appropriate equipment for such manipulations, moreover, negative consequences may follow (Oddi's sphincter deficiency with persisting cholangitis, bacterial complications etc.) [1].

Among the most vivid and severe CP manifestations diminishing the quality of patients' lives, are the pain and pancreatic exocrine insufficiency. Important role in pathogenesis of pancreatic pain is played by CK-PZ stimulation, increased production of concentrated secretion, formation of protein precipitates, blocking of pancreatic ducts, intraductal hypertension, as mentioned above [5, 31].

Long-standing inflammatory process in pancreatic tissue results in irreversible changes (atrophy and fibrosis) which inevitably lead to decreased number of

functioning pancreacytes and development of primary exocrine insufficiency. Moreover, disordered outflow of pancreatic secretion to duodenum due to any obstructions in the gland ducts caused by dense and viscous secretion, calculi, Oddi's sphincter spasm, or constrictive papillitis, also leads to lack of pancreatic enzymes in duodenum lumen, maldigestion and malabsorption. Primary exocrine insufficiency may be aggravated with secondary insufficiency, when activation of pancreatic enzymes in intestines is disturbed or they are inactivated for some reason [1].

When primary or secondary pancreatic exocrine insufficiency develops, pancreatic proteases do not get into duodenum, which act as physiological inhibitors of CK-PZ. Regulation of feedback mechanism is disturbed, and decelerating effect on pancreas disappears.

Major Principles of CP Conservative Therapy

One of main prerequisites for effective treatment is a lifestyle change, first of all, refusal from alcohol and smoking and normalization of nutritional status. The key task which a doctor faces while treating a patient with CP is a pain management (including application of narcotic analgesics, if non-narcotic analgesics are of low efficacy), ensuring 'functional rest' to pancreas (prescription of medicinal products decreasing gastric acidic secretion), correction of exocrine and endocrine pancreatic insufficiency (replacement therapy with enzymatic preparations with high lipase content, adjustment of glucose profile), antispasmodic and neuroleptic therapy, struggle against excessive bacterial growth in small intestine, which often complicates the primary disease course and aggravating maldigestion and malabsorption, adjustment of intestinal biocenosis, prevention of the disease complications and relapses if the etiological factor is still in effect.

Efficacy of enzymatic preparations for pain management is proved with numerous clinical trials. In this situation, enzymatic preparations act as physiological inhibitors of CK-PZ and contribute to 'functional rest' of pancreas. Sufficient amount of proteases in duodenum and deceleration of pancreatic secretion through a feedback mechanism is nonsurgical medicated ductal decompression and facilitates pathogenetical pain management [1, 31, 39, 41].

A routine method for treatment of exocrine pancreatic insufficiency of any severity in case of CP is a replacement therapy with pancreatin preparations [1, 3, 37, 39]. Beside the individually-prescribed adequate dose of an enzymatic preparation, the efficacy of replacement therapy in case of CP is influenced by other conditions. Such conditions include: availability of acid-resistant membrane which prevents from lipase inactivation with hydrochloric acid contained in gastric juice, and small sizes of a dosage form which allow an enzymatic preparation to get from a stomach into duodenum freely and simultaneously with chyme [15].

Efficacy of capsular pancreatin mini-tablets in case of pancreatic exocrine insufficiency and pain syndrome in the event of CP is currently widely discussed. In Ukraine, such preparation is Ermytal. Ermytal contains standard highly-active pancreatin obtained from swine pancreas. The preparation compensates for lacking pancreatic enzymes and provides proteolytic, amylolytic and lipolytic actions. Dosage form of Ermytal ensures full release of mini-tablets resistant to gastric juice from a capsule in a stomach which facilitates preservation of enzymatic activity of the preparation in acidic medium, contributes to fine adequate blending of mini-tablets with the stomach content, which creates a large area of contact with chyme – i.e. digestive area – and free flow of enzymes and chyme from a stomach to duodenum where they are excreted (with pH over 5.0). Ermytal is produced in three strengths: 10 000, 25 000 and 36 000 IU, which gives a possibility for its wide use for pancreatic diseases and states concurrent with primary and secondary pancreatic exocrine insufficiency.

Some researches show good efficacy of Ermytal for maintenance of adequate nutritional status in patients with mild steatorrhea even if no clinical evidence of pancreatic insufficiency is available [33, 40].

It was also reported that Ermytal is highly effective for adjustment of exocrine pancreatic insufficiency developed due to cystic fibrosis, pancreatic cancer, condition after surgery of pancreas, and the such efficacy is comparable to the efficacy of mini-microspheric enzymatic preparations. In such cases, patients usually have severe pancreatic insufficiency and must receive high doses of modern safe

enzymatic preparations lifelong [8, 16, 17, 40]. Under such conditions, pharmacological and economic aspects of treatment are of particular topicality. Analysis of such indicators as ‘cost of illness’ and ‘expenses/efficacy’ provided conclusive advantages of Ermytal for reduction of expenses related to treatment [24].

High content of proteases in Ermytal suppresses pancreatic secretion through a feedback mechanism and contributes to effective pain management in patients with CP [20].

Thus, Ermytal complies with up-to-date requirements set to enzymatic medicinal products and may be effectively applied in conservative therapy regimens for pancreatic exocrine insufficiency and pain syndrome in case of CP.

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New opportunities of enzyme therapy in the field of pancreatology

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Key words: pancreas, pancreatic secretion, chronic pancreatitis, exocrine insufficiency, enzymatic preparations

This article analyzes the peculiarities of pancreatic secretion in a normal state and upon such two main etiopathogenetic variants of chronic pancreatitis as alcohol and biliary ones. Author covered the modern approaches to the treatment of the main manifestations of pancreatic diseases, namely pain syndrome and exocrine insufficiency. Analysis of the published data proved the effectiveness of the microtableted enzymatic preparation Ermital in the treatment of the main manifestations of chronic pancreatitis and its advantages over the other polyenzymatic preparations in the pharmaco-economic aspect.