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CLINICAL AND THERAPEUTIC ASPECTS OF THE COMBINED COURSE OF GASTROESOPHAGEAL REFLUX DISEASE AND CHRONIC PANCREATITIS

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Summary: Despite the meaningful achievements in modern diagnosis and farmacotherapy a problem of diseases which combine with each other still remains one of most complicated parts of therapy. In gastroenterology we could set for example combination GERD and pancreatitis. In this case pancreatitis
is more severe and more often than not has a number of complications. This article includes the information about circumstances of pathogenesis and treatment such kind of patients. It has been regarded specialy the aspects of treatment of abdominal pain syndrome using secretolytic and enzymatic therapy.

Key words: GERD, pancreatitis, abdominal pain syndrome.

The widespread prevalence of chronic acid-related diseases (CARDs) of the digestive system, the frequent inadequacy of diagnostic testing, the potential for serious complications, and the need for significant financial resources to implement treatment programs make this problem relevant to practical healthcare. Certainly, the phenomenology of this group of diseases has recently expanded to a qualitatively new level, going beyond gastroenterology itself, attracting the attention of specialists in various fields: cardiologists, pulmonologists, otolaryngologists, surgeons, and even oncologists.

Currently, a relatively large number of gastrointestinal diseases are classified as acid-dependent diseases, in the development and maintenance of which the acid-peptic factor plays a significant role. Among this group of diseases, the most common are gastroesophageal reflux disease (GERD); peptic ulcer disease; non-ulcer (functional) dyspepsia; gastropathy induced by non-steroidal anti-inflammatory drugs; and Zollinger-Ellison syndrome.

The commonality of pathogenetic mechanisms in the development of acid-dependent forms of digestive organ pathology stems from the proposition put forward by the renowned Austrian scientist K. Schwarz (1910), which states: "Without acid, there is no ulcer." From a modern perspective, this allows us to assert: "Without acid, there is not only no ulcer, but also no other acid-dependent diseases." In this regard, it is quite reasonable to classify chronic gastritis as acid-dependent diseases.

Pancreatitis (CP), the theoretical basis for which serves the globally recognized research of I. P. Pavlov's laboratory staff, devoted to the study of the functional relationships of the physiological regulation of the digestive system. As early as the late 19th century, I. L. Dolinsky and L. D. Popelsky demonstrated the close relationship between pancreatic secretion and hydrochloric acid entering the duodenum from the stomach, which is a physiological stimulator of the secretory activity of the pancreas through the formation of hormonal substances such as secretin and cholecystokinin [5].

However, despite the leading role of the damaging effects of pancreatic enzymes themselves in the development of inflammatory and dystrophic changes in the pancreas, hypersecretion of

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hydrochloric acid also plays a crucial role in triggering these pathological processes. Significant advances in modern diagnostics and pharmacotherapy have not resolved the problem of chronic pancreatitis, which remains one of the most challenging areas not only of pancreatology but of clinical gastroenterology in general. Chronic pancreatitis in terms of prevalence, increasing incidence, temporary disability, and cause of disability is a pressing issue from both a social and economic perspective, as confirmed by epidemiological analysis. Thus, in the structure of gastrointestinal tract pathologies, it accounts for 5.1 to 9%, and in general clinical practice, from 0.2 to 0.6% [14].

The global trend toward increasing incidence of acute and chronic pancreatitis persists, and in Russia, the dramatic situation is due to the increasing prevalence of chronic pancreatitis not only among adults (27.4–50 cases per 100,000 population), but also among adolescents and young adults [13]. At the same time, the clinical and social significance of the progressive course of this disorder is manifested in its extremely negative impact on patients' quality of life. It is known that in most cases, CP has a progressive course with a gradual increase in exocrine pancreatic insufficiency, persistent pain, requiring patients to adhere to a strict, often lifelong, diet and receive ongoing medication. The extremely high clinical significance of CP is inherently associated with the risk of complications, with a mortality rate of up to 5.5% [14].

The clinical course of chronic pancreatitis is often determined by its combination with other diseases, given the polymorbidity of modern patients. These combinations typically contribute to a more sluggish clinical course of pancreatitis and often an increased incidence of complications. Thus, according to our study, we found that CP combined with hypertension (HT), compared with the isolated form of the disease, is characterized by greater severity of abdominal pain and dyspeptic syndromes, with a tendency toward longer exacerbations and lower efficacy of basic therapy [15]. Concomitant obstructive pulmonary diseases associated with CP, along with impaired ventilation and gas exchange, and hemostatic disorders also influence the clinical course and relapse of CP [7].

A characteristic feature of the clinical course of CP combined with coronary artery disease (CAD) is hyperviscosity syndrome, which is accompanied by ventricular systolic-diastolic dysfunction, moderate pulmonary hypertension, and moderate blood gas imbalances. This leads to hemostatic disorders and the development of ischemia and fibrosis of the RV tissue, worsening the patient's condition and reducing their quality of life [7]. This fact also applies to the combined course of gastrointestinal diseases. Thus, when CP and duodenal ulcers, or CP and chronic cholecystitis (both calculous and acalculous), are combined, the course of the pathological process is significantly aggravated [1, 7]. This increases the risk of complications (gastroduodenal bleeding, etc.).

According to recent studies, the combined course of CP and GERD is often observed [3, 6].

Moreover, against the background of exacerbation of pancreatic pathology, GERD symptoms are often "ignored," which, of course, affects not only the quality of treatment for this category of patients, but also affects the socioeconomic aspects of the problem of combined diseases. Meanwhile, over the past decades, the clinical and epidemiological structure of GERD has acquired widespread global relevance, due not only to the increase in extraesophageal complaints, but also to the rise in complications such as Barrett's esophagus and esophageal adenocarcinoma [29]. Thus, heartburn, which is the most common symptom of GERD, worsens quality of life in 60% of European respondents [10], with the degree of quality of life reduction comparable to that in patients with coronary heart disease, arterial hypertension, and peptic ulcer disease [8].

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It was noted that heartburn affects approximately 60% of Novosibirsk residents and approximately 46% of residents of St. Petersburg and Krasnoyarsk [10].

Regarding the clinical manifestations of CP, which largely determine the decline in quality of life, it is known that abdominal pain and exocrine pancreatic insufficiency syndrome are the most distressing for patients. It is important to note that abdominal pain and exocrine pancreatic insufficiency are the dominant symptoms of CP, not only in clinical terms but also in terms of frequency. It is known that pain in the advanced stage of chronic pancreatitis is recorded in 80-90% of cases, exocrine insufficiency syndrome in 5-15%, and pancreatogenic diabetes mellitus in 3-10% [21]. The leading and most persistent symptom at the onset of CP is abdominal pain, which can sometimes lead to malnutrition, cachexia, drug addiction, and in some cases, even surgical intervention.

Pancreatic dysfunction at the onset of the disease has minimal manifestations, but as the organ progresses to fibrosis and atrophy of acinar and islet cells, when at least 90% of the actively functioning pancreatic parenchyma is involved in the pathological process, the pain typically subsides, while pancreatic insufficiency progresses, leading to maldigestion and malabsorption. At the same time, at this stage of CP, an increase in pancreatic pain may be noted, caused by flatulence, which occurs both due to decreased exocrine pancreatic activity and as a result of impaired motility and normal intestinal microflora [2]. It is important to note that the occurrence or increase of flatulence in patients with combined CP and GERD inevitably leads to a worsening of the latter, causing severe heartburn, as well as discomfort and pain in the epigastrium and/or behind the sternum, in the xiphoid process region. It is also important to note that in elderly patients (according to our observations) with a long history of CP and GERD, pain may not be observed at all, with only occasional heartburn, while morphological changes in the pancreas and esophageal mucosa can be pronounced. Furthermore, almost all patients with both isolated and combined GERD and CP experience disturbances in the evacuation function of the stomach, manifested by a feeling of early satiety, bloating, nausea, and vomiting. Given the above-mentioned clinical and epidemiological data on the incidence of both CP and GERD, it can be concluded that the problem of the combined course of these two pathologies is highly relevant in terms of both early disability and decreased productivity in this category of patients, as well as the possible interference of key predictors reflecting the risk of fatal outcomes. These facts are often due, along with the high prevalence of GERD and CP in the Russian population, to the relatively low awareness of patients about their condition, sometimes inappropriate prescription of medications, frequently low efficacy, and polypharmacy.

Among the possible pathogenetic aspects of the development of combined pathology within CP and GERD, including duodenostasis, upper gastrointestinal motility disorders, etc., hyperacidity occupies a significant place. We have already mentioned that both GERD and CP are currently considered acid-dependent diseases, in which aggressive factors of gastric contents, particularly hydrochloric acid, play important and, in some cases, priority positions. According to N. B. Gubergrits et al., almost all patients suffering from CP have esophagitis of varying severity [6].

Given the acid-dependent nature of these diseases, it seems entirely logical to use drugs aimed at neutralizing or suppressing the production of hydrochloric acid by parietal cells. Among antisecretory drugs, proton pump inhibitors (PPIs), as the most potent suppressors of gastric secretion, are, according to the 1997 Genval Agreement, the primary treatment for GERD (23). However, treating CP with abdominal pain and exocrine pancreatic insufficiency is a challenging task, both due to the objective difficulties associated with the multifactorial nature of the

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pathogenetic mechanisms underlying their development and the wide range of options for choosing the optimal treatment regimen or the most effective drug.

Analgesics and antispasmodics are almost always used in the treatment of exacerbations of CP, possessing universal properties for the relief of abdominal pain, especially in cases of organ ischemia, perineural inflammation, and fibrosis [18].

The relevance of the problem of comorbidities is due to certain difficulties not only in diagnosis but also in the selection of high-quality and appropriate therapy, since the likelihood of side effects depends on the number of medications taken [17].

In this regard, one of the most important issues in the treatment of patients with a combination of CP and GERD is the problem of overcoming polypharmacy, which is especially relevant in the treatment of the elderly. Moreover, in the Russian context, it is necessary to consider the factor of drug selection, taking into account not only clinical and pathogenetic but also socioeconomic conditions.

Consequently, the focus should be on prescribing drugs with a cumulative clinical effect. An example of this approach in pancreatology is multienzyme therapy, which for many years was prescribed only as a replacement therapy.

However, recently, special attention has been paid to the possibility of using enzyme preparations to relieve pancreatic pain through the mechanism of reverse inhibition of pancreatic enzyme production, a mechanism that began to be studied as early as 1970 [22].

It is known that the physiological regulation of the pancreas's own enzyme production is carried out by a feedback mechanism [7]. When enzymes (particularly proteases) enter the lumen of the duodenum, they interact with cholecystokinin (CCK)-releasing peptide. With sufficient levels of pancreatic enzymes in the duodenum, the releasing peptide is inactivated, CCK synthesis decreases, and, as a result, pancreatic enzyme production decreases. If pancreatic enzymes in the lumen of the duodenum are insufficient, CCK-releasing peptide is not inactivated, increasing CCK production and, consequently, stimulating pancreatic enzyme production. As a result, in the presence of chronic pancreatitis, autolysis increases, intraductal pressure rises due to the increased secretion volume, and pancreatic pain intensifies. Thus, enzyme therapy not only compensates for the deficiency of pancreatic enzymes in intestinal digestion, but also minimizes pancreatic secretory activity, promoting "functional" rest of the organ by inhibiting pancreatic enzyme production through feedback [9]. It should be emphasized that the addition of antisecretory agents to enzyme therapy has been shown to increase the effectiveness of the latter in the treatment of chronic pancreatitis [8]. It is also important to note the use of multienzyme preparations as replacement therapy for pancreatic exocrine insufficiency. Indications include steatorrhea, flatulence, and weight loss.

The choice of enzyme preparation is based on its high lipase content, the presence of a protective acid-resistant coating, and the absence of bile acids (bile acids cause increased pancreatic secretion and chologenic diarrhea).

In this regard, enteric-coated microspheroid enzyme preparations appear to have an advantage in relieving exocrine pancreatic insufficiency, while pain symptoms are reduced less significantly [24, 26]. This phenomenon can most likely be explained by the fact that feedback inhibition of pancreatic secretion depends on the presence of high concentrations of proteases in the proximal duodenum, while enteric-coated enzyme preparations achieve maximum activity in the distal duodenum, while being less effective in inactivating CCK-releasing peptide, reducing cholecystokinin levels, and, consequently, in relieving pancreatic pain [24].

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A reduction in the severity of abdominal pain syndrome with the use of polyenzyme preparations has also been demonstrated in a number of foreign studies [26, 27].

Furthermore, it should be emphasized that the treatment algorithm for chronic pancreatitis with pain syndrome, proposed in 1998 by the American Gastroenterological Association, specifically recommends the use of tableted enzyme preparations [28].

Among the tableted enzyme preparations with an acid-resistant coating, Mezim Forte 10000 is widely used in the treatment of various forms of chronic pancreatitis.

The acid-resistant coating of Mezim Forte 10000 tablets does not dissolve in the presence of hydrochloric acid in the stomach, thereby protecting the enzymes contained in the preparation from inactivation. Dissolution of the coating and release of enzymes occur at pH values close to neutral, which occurs in the proximal portions of the duodenum. Russian authors have conducted a number of studies using this enzyme preparation in the treatment of pancreatic pain syndrome, which showed that abdominal pain in patients taking Mezim Forte 10000 was relieved significantly ($p < 0.05$) faster (on average, by the fifth day) than in the group of patients treated with an encapsulated pancreatin preparation [4], as well as the possibility of using Mezim Forte 10000 in most patients without the use of hydrochloric acid secretion inhibitors (the latter are mandatory when prescribing non-encapsulated enzyme preparations) in the relief of pain in CP, which significantly increases the cost-effectiveness of treatment [19]. Our clinical experience using the enzyme preparation Mezim 10000 to correct exocrine pancreatic insufficiency in patients with CP showed that the dynamics of stool frequency and consistency while taking Mezim 10000 were practically comparable to those in patients taking encapsulated pancreatin (Creon 10000). When assessing coprological elastase levels during treatment, positive dynamics were noted in patients taking Mezim 10000, comparable to the results of elastase-1 dynamics in patients receiving Creon 10000 [16].

Depending on the presence and/or prevalence of pain syndrome and exocrine pancreatic insufficiency, a number of dosage options and regimens for Mezim Forte 10000 can be used, as presented in the table. For the relief of abdominal pain in patients with chronic pancreatitis, Mezim Forte 10.000 should be prescribed 1–2 tablets 3 times daily (during each main meal). Two tablets per meal are indicated for severe pain, when increasing the concentration of orally administered proteases in the enzyme preparation will facilitate the rapid achievement of the desired clinical effect. The criterion for discontinuing Mezim Forte 10000 treatment for isolated pain syndrome is persistent pain relief (usually achieved by the 10th to 14th day from the start of treatment). Subsequently, the drug can be taken on demand. If a patient with chronic pancreatitis combines abdominal pain and exocrine pancreatic insufficiency, the latter will determine the duration of polyenzyme replacement therapy, up to the need for continuous Mezim Forte 10000 in severe cases of severe exocrine insufficiency.

Thus, polyenzyme therapy is currently one of the leading areas of a comprehensive approach to the treatment of pancreatitis. Patients with CP. It is also important to note that, by minimizing and/or relieving maldigestion and malabsorption, polyenzyme preparations indirectly affect the manifestations of flatulence, thereby reducing the clinical symptoms of GERD (frequent belching, a feeling of discomfort and heaviness in the epigastrium), which is especially important for patients with a combined course of CP and GERD. The use of Mezim 10000 significantly increases the clinical potential for relieving abdominal pain of pancreatic origin, as well as correcting exocrine pancreatic insufficiency, while antisecretory therapy additionally ensures physiological rest for the pancreas, increases the effectiveness of polyenzyme therapy, and also alleviates the manifestations of GERD. Therefore, treatment for patients with combined CP and

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GERD should be based on a comprehensive treatment approach, including multienzyme preparations, antisecretory agents, and, if necessary, analgesics.

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