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THE EFFECTIVENESS OF ULINASTATIN IN PATIENTS WITH CHRONIC PANCREATITIS

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Abstract

The article presents the results of the anti-inflammatory efficacy of the new generation protease inhibitor ulinastatin in the treatment of exacerbation of chronic pancreatitis of moderate severity. It is shown that exacerbation of chronic pancreatitis of alimentary, alcoholic and biliary etiology was expressed by abdominal pain and dyspeptic symptoms. An increase in the level of serum aminotransferases, bilirubin and alpha amylase was noted, which was accompanied by a significant increase in the activity of pro-inflammatory cytokines. The use of ulinastatin in the complex of pharmacotherapy of chronic pancreatitis contributed to the effective relief of exacerbation of pancreatitis, which was due to the anticytokine effect of the drug.

Keywords: chronic pancreatitis, ULINASTATIN, abdominal pain, dyspeptic symptoms

Chronic pancreatitis (CP) is currently one of the most important and urgent problems of medicine. This pathology occurs in general clinical practice from 0.2 to 0.6%, and in the general structure of the incidence of gastrointestinal tract organs 5.1 - 9%. All over the world in the last 30 years there has been a tendency to increase the incidence of CP by more than 2 times. In Europe, the prevalence of this disease was 25-26.4 cases per 100 thousand population. In Russia, the prevalence of CP in adults ranged from 27.4 to 50 cases per 100 thousand population, and in children – from 9 to 25 cases per 100 thousand population. In developed countries, the average age of diagnosis of CP decreased from 50 to 39 years, that is, the development of the disease at an earlier age was noted. There was an increase in the proportion of women among the sick (by 30%) [1,2].

Treatment of patients with CP largely depends on the severity of its exacerbation (including the presence or absence of various complications), manifested by various, more or less pronounced symptoms in pain, dyspeptic, hypoglycemic, so-called "metabolic" and / or "icteric" options. Often it is not possible to accurately determine one or another clinical variant [3,4,5].

The appearance of complications of CP largely determines, as the disease progresses, and often significantly changes the clinical manifestations of chronic pancreatitis. In the treatment of patients with CP, depending on their condition, various drugs are used: those that reduce pancreatic secretion, most often proton pump inhibitors, anticholinergics, enzyme preparations, antispasmodics, prokinetics, painkillers, antibiotics, plasma-substituting solutions. At present, the use of drugs that suppress the activity of pancreatic enzymes (Contrykal, Gordox, Trasylol,etc.) in modern pancreatology has been significantly limited due to the emergence of more effective and safe antienzymatic drugs, one of which is an inhibitor of proinflammatory cytokine , tumor necrosis factor (TNFα) ulinastatin.

The aim of the study: to evaluate study the clinical efficacy and tolerability of ulinastatin (the drug "ROAN" 100,000 IU. lyophilisate for the preparation of an injection solution in patients with chronic pancreatitis in the acute stage of mild to moderate degree.

Materials and methods:

In the group that received the study drug, there were 20 patients with mild to moderate CP who were hospitalized, of both sexes (men 8, women 12), over the age of 18 years (mean age 52.5 $\pm$ 4.5 years) who agreed to participate in the study, with a diagnosis of chronic biliary pancreatitis, alcoholic, alimentary or mixed etiology in the acute stage. When diagnosing CP, the classification M - ANNHEIM was used , where the main diagnostic criteria were: M - Multiple, A - Alcohol, N - Nicotin, N - Nutrition, H - Heredity, E – Efferent pancreatic duct factors, I- Immunological, M – Miscellaneous and Metabolic factors[1]. In this case, the diagnosis of CP implies the presence of a typical clinical picture (recurrent pancreatic attacks, abdominal pain, etc.), as well as the presence of a number of the following criteria:

"Definite " CP (at least 1 criterion): calcification of the pancreas; moderate or severe changes in the ducts of the pancreas (Cambridge, 1984); severe exocrine insufficiency; morphological picture typical for CP.

"Probable " CP (at least 1 criterion): mild changes in the ducts of the pancreas (Cambridge, 1984); pseudocyst (s) - constantly existing or recurrent; pathological results of functional tests (fecal elastase, coprogram); endocrine insufficiency.

"Borderline " CP : typical clinical presentation without "probable"/"definite" CP criteria; expected after the first episode of acute pancreatitis.

Before and after treatment, all patients underwent a clinical examination (scored), including a general examination, clinical and biochemical studies: complete blood count, bilirubin, AlAT, AsAT , alpha amylase. Pro- inflammatory cytokines : IL-6 and TNFα, and also carried out the determination of fecal elastase. Of the instrumental studies, all patients underwent ultrasound examination (ultrasound) or, according to indications, computed tomography (CT) of the pancreas, where imaging criteria (Cambridge) were used to diagnose mild to moderate CP - the presence of two or more pathological signs:

- GPP width 2-4 mm;
- uneven width of the ducts
- moderate increase in prostate (up to 2 times)
- heterogeneity of the parenchyma with areas of increased and decreased echogenicity
- cavities less than 10 mm
- increased echogenicity of the MPD wall
- irregular contour of the pancreas.

The patients were prescribed ulinastatin 100,000 IU intravenously, drip, previously diluted in 100 ml of 0.9% sodium chloride 1 time per day for 3 days. The patients were also prescribed drugs necessary for the treatment of the underlying disease: proton pump inhibitors, antispasmodics, analgesics, enzyme preparations according to indications. The dose of drugs taken remained unchanged throughout the study period. If during the course of the study it became necessary to change the dose or prescribe a new drug, continuation of the study for this patient was allowed, provided that these changes do not have a significant positive or negative effect on the course of the underlying disease. A repeated clinical and instrumental study was performed 7 days after the start of therapy.

Results : In patients with CP, the etiological factors of exacerbation were calculous cholecystitis, alcoholic and alimentary factors, and in 3 patients a combination of alcoholic and alimentary factors (Table 1).

Table 1

Etiological characteristics of patients with chronic pancreatitis

Etiological factors of CP	Number of patients
Biliary	10 (50%)
Alcoholic	4 (20%)
Alimentary	3 (15%)
Mixed	3 (15%)

Determination of fecal elastase showed that exocrine pancreatic insufficiency (below 200 units) was noted only in 4 patients.

The effectiveness of the treatment was evaluated based on the improvement of the patient's clinical condition and the dynamics of laboratory tests. The conducted studies revealed high efficiency in patients in the form of reliable relief of abdominal pain and dyspeptic symptoms of exacerbation of CP (Table 2).

Table 2

Dynamics of clinical symptoms of patients before and after treatment, in points

Complaints	**Ulinastatin 100,000 IU, 3 days**	
	Before treatment	**After treatment**
Abdominal pain syndrome	2.8 ± 0.23	1.1 ± 0.05*
Nausea	2.9 ± 0.12	0.7 ± 0.04*
Vomit	2.2 ± 0.05	0.5 ± 0.05*
Flatulence	2.5 ± 0.06	0.7 ± 0.03*
Diarrhea	2.0 ± 0.06	0.5 ± 0.05*

Note: hereinafter* - the difference is significant in relation to the indicators before and after treatment ($p < 0.05$)

Points:

0- no symptoms

1-Moderately pronounced symptoms

2-Medium pronounced symptoms

3-Expressed symptoms

Analysis of the obtained results showed that in the general blood test in patients before treatment, a moderate increase in leukocytosis and ESR was noted (Table 3). In their biochemical parameters, a significant increase in the parameters of AlAT, AsAT, bilirubin and alpha amylase was also noted (Table 4).

Table 3

Dynamics of the main indicators of peripheral blood of patients before and after treatment

UAC indicators	Before treatment	After treatment
Hemoglobin , g/l	124,5 ± 3,42	120.5 ± 2.55
Erythrocytes , 10^{12}/l	4,8 ± 0,12	4.4 ± 0.17
Leukocytes , 10^{9}/l	12,5 ± 1,9	8.4 ± 0.20*
ESR mm / hour	1 5, 2 ±1 ,50	7.40 ± 0.90*

Table 4

Dynamics of hepatic transaminases and bilirubin in the blood of patients before and after treatment

	Before treatment	After treatment
AlAT , U/l	67,19 ± 4,20	37,2 ± 3,30*
AsAT , U/l	34,7 ± 2,85	17,8 ± 0,55*
Bilirubin , mmol /l	32,05 ± 3,02	19,05 ± 2,90 *
Alpha amylase, U/ l	323,5 ± 30,50	221,7 ± 22,40*

When studying the level of pro-inflammatory cytokines in the blood serum of patients with CP during the period of exacerbation, an increase in the levels of IL-6 and TNFα was found (Table 5).

Table 5

Dynamics of IL-6 and TNFα in patients before and after treatment

Interleukins	Before treatment	After treatment
IL-6 (pg / ml)	65,8±5,4	40,3±3,6*
TNFα (pg / ml)	124,0±7,4	66,5±5,2*

Tolerability of the drug was assessed on the basis of subjective symptoms and sensations reported by the patient and objective data obtained by the investigator during treatment. The dynamics of laboratory parameters, as well as the frequency and nature of adverse reactions, were taken into account. In our patients, no adverse reactions from the drug therapy used were observed. The drug was well tolerated. Only in 3 patients, laboratory tests over time revealed a slight increase in AlAT, AsAT and bilirubin, which was associated with an attack of existing cholelithiasis , as a result of which an exacerbation of CP occurred. These patients, after consulting an abdominal surgeon, were recommended to undergo cholecystectomy in a planned manner.

Discussion: CP is still an urgent problem of modern gastroenterology. The standards of treatment for such patients included anti-enzyme drugs (Aprotinin). However, due to their low efficiency and the presence of pronounced side effects, indications for their use in modern pancreatology have been extremely reduced. According to modern guidelines for the diagnosis and treatment of CP, inhibitors of proinflammatory drugs are most often used to relieve exacerbations, cytokines, in particular ulinastatin [6,7,8,9].

The study to study the clinical efficacy and tolerability of ulinastatin included 20 patients with exacerbation of CP.

Of the 20 patients with exacerbation of CP, 10 patients with etiological factors of the disease had calculous cholecystitis and a complication in the form of biliary pancreatitis. In 4 patients, exacerbation of the disease was associated with the use of strong alcoholic beverages. In 3 patients, exacerbation of the disease was associated with frequent malnutrition (excessive consumption of fatty foods). Also, in 3 patients, exacerbation of CP was due to a combination of factors such as alcohol and fatty foods. The clinic of exacerbation of the disease was expressed by a combination of abdominal pain and dyspeptic manifestations. Pain in patients was more often localized in the epigastrium and in the left upper square of the abdomen with irradiation into the interscapular space. Dyspeptic symptoms were manifested by nausea, vomiting, often not leading to relief, and flatulence. 18 patients also had diarrhea (more than 3 times a day or more) with steatorrhea. In 12 patients, a manifestation of exocrine pancreatic insufficiency was noted, which was expressed by a decrease in the level of mild fecal elastase (below 200 units in 4 patients). In 9 patients, moderate leukocytosis, an increase in ESR (in 15 patients), a moderate increase in transaminases, and an increase in bilirubin (often due to direct fraction) were noted in the blood serum. In 12 patients, an increase in the activity of alpha amylase in the blood serum was noted. Also, the majority of patients (16) showed an increase in the activity of IL-6 and TNF-alpha more than twice.

Thus, the studies revealed that the study drug in patients with exacerbation of chronic pancreatitis during treatment contributed to the relief of pain and dyspeptic symptoms, as evidenced by a decrease in patients' complaints about abdominal pain symptoms and dyspeptic disorders. Control studies of biochemical blood parameters 7 days after the start of treatment showed normalization of leukocytes and ESR. In blood plasma, a significant decrease in the level of serum transaminases, bilirubin and alpha amylase was recorded. Accordingly, there were significant decreases in IL-6 and TNFα levels. However, in three patients with CP, no significant dynamics of clinical manifestations and biochemical blood parameters was observed, which was associated with attacks of calculous cholecystitis. In these patients, on the recommendation of an abdominal surgeon, cholecystectomy was recommended in a planned manner.

CONCLUSIONS:

1. The anti-inflammatory efficacy of the protease inhibitor ulinastatin in the conservative pharmacotherapy of CP is associated with inhibition of the pro-inflammatory cytokines IL-6 (by 65%) and more than twofold TNFα.
2. The protease inhibitor ulinastatincan be effectively and safely used in the treatment of patients with chronic pancreatitis to relieve exacerbations of the disease.

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