Pathogenetic approaches to the treatment of chronic hepatitis combined with chronic pancreatitis of toxic etiology

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Key words: alcoholic liver disease, chronic alcoholic pancreatitis, treatment, metadoxine, Liveria IC

Actuality of the problem

Diseases of the digestive system are an actual medical and social problem in the world. Of particular importance is a chronic diffuse liver disease. Despite considerable progress in diagnosis and treatment of this pathology, achieved over the past 30 years, it is now chronic liver disease in Europe, affecting about 29 million people. Among these diseases is dominated by cirrhosis and primary liver cancer — the final stage of chronic diffuse liver diseases. Approximately 0.1% of the European population has cirrhosis of the liver, with recorded 14-26 new cases per 100,000 in a year and 170,000 of deaths from cirrhosis of the liver in a year [14, 17 43].

Hepatocellular carcinoma (70-90% of cases of primary liver cancer) is the fifth in frequency localization of cancer in Europe and the most severe outcome of liver cirrhosis. The incidence of hepatocellular carcinoma in Europe is 1-13 per 100,000 in a year. This disease is the cause of 1-10 deaths per 100,000 in a year. According to the WHO, hepatocellular carcinoma in Europe is the cause of 47,000 deaths per year [25]. There are four main causes of liver cirrhosis and primary liver cancer: alcohol abuse, chronic viral hepatitis B and C, nonalcoholic fatty liver disease (NAFLD) against obesity and metabolic syndrome.

The main cause of liver cirrhosis in Europe is alcohol abuse. Its frequency decreased slightly in 1990, but increased again in the last decade of the 20th century, and has stabilized at a high level — an average of more than 9 liters of pure ethanol per year [25]. More than 20% of the European population over the age of 15 years, occasionally consume large amounts of alcohol (more than 50 grams of pure ethanol

at the reception at least once a week) [54]. The average mortality due to alcoholic liver disease among men and women in Europe varies from 3 per 100,000 of population in Latvia to more than 47 per 100,000 of population in Hungary.

Data on the frequency of acute alcoholic hepatitis are controversial. In the period from 1999 to 2008, frequency of acute alcoholic hepatitis in Denmark increased from 37 to 46 per 100,000 of males and from 24 to 34 per 100,000 of females. The mortality rate was 47% in the absence of cirrhosis and 69% in the presence of cirrhosis, and 56% on the average [39].

Increased frequency of NAFLD is due to the growth of epidemiological indicators of obesity in Europe. The frequency of this pathology is 2-44% of the total European population, including children, and 42,6-69,5% of patients with type II diabetes. NAFLD significantly increases the risk of cirrhosis and liver cancer.

Being overweight or obese are more than 50% of adults living in the EU. The big epidemiological studies found that the frequency of NAFLD is 26,0% [40, 42], 30.4% [52], 33.0% [37]. The presence of NAFLD in a patient increases the risk of mortality associated not only with this disease, but also with diseases of the cardiovascular system. In patients with sonographic signs of fatty liver disease and elevated alanine aminotransferase (ALT) expenses for medical care for 5 years are 26% higher than in the general population [25].

The increased prevalence of pathology of the digestive system in the last five years has increased significantly in Ukraine. For example, the prevalence of chronic hepatitis (CH) in our country from 2008 to 2012 years increased 2.2 times, cirrhosis of the liver — by 59.6%, and diseases of the pancreas — 3.2 times [19]. This is the most severe pathology of gastrointestinal profile, as it requires long-term treatment of patients and monitoring of their condition for even longer period. It is the disease of the liver and the pancreas often leads to disability of patients of working age. Tactics of treatment is particularly complicated upon combined lesions of the liver and the pancreas, and in this case the prognosis is rarely favorable. [2]

At the same time, the majority of patients diagnosed with several gastroenterological clinics diseases. Thus, 70-90% of patients aged 40-60 years

revealed an average of nearly five simultaneously occurring diseases. This is explained by the influence of environmental factors, poor nutrition and irrational, often developed secondary immunodeficiency, alcohol abuse, unhealthy lifestyle due to the low level of health literacy, in some cases — the lack of qualified doctors, appointment of a large number of unwarranted medication and so on [20, 21].

One of the most common diseases that accompany CH and liver cirrhosis is a chronic pancreatitis (CP).

Epidemiological studies conducted in Europe, particularly in France, have shown that the incidence of CP is 7.8 per 100,000 of population, and the prevalence is between 120 and 143 per 100,000 of population. Average life expectancy of CP patients after diagnosis is 15-20 years. Over the past 30 years we have seen a global trend of the increasing incidence of pancreatitis in more than 2 times. In developed countries, pancreatitis began to develop at a younger age: the average age after diagnosis fell from 50 to 39 years, and among the 30% of cases, the proportion of women. Primary disability of patients is 15%. Twenty-year-old history of CP increases the risk of pancreatic cancer by 5 times. Mortality after initial diagnosis of CP is up to 20% within the first 10 years and more than 50% — in 20 years [34].

Analysis of the Center of Health Statistics of MH of Ukraine for 8 years (2006-2013) on the epidemiology of pancreatic diseases showed the following. It was found that the prevalence of diseases of the pancreas per 100,000 of the adult population in the country increased by 56.8%; the growth rate of incidence was lower by 2.5 times and amounted to 23.1%. Hospitalization rates increased by 11.6% in acute pancreatitis and 30.2% in the chronic course of the disease. Indicator of late hospitalization was 37-40%, what is inextricably linked with postoperative mortality rate, which in acute pancreatitis in the past 8 years was 14,0-10,8%, upon CP this figure gradually increased, and in 2013 stood at 7,8%, well above the global values [4].

The drug Liveria IC (metadoxine) is pathogenetically appropriate in the treatment of associated diseases of the liver and pancreas, which was the rationale for this study.

Metadoxine is a pyridoxine-L-2-pyrrolidone-5-carboxylate. Pyridoxine is a precursor of pyridoxal and pyridoxalphosphate that as coenzymes participate in a hepatic metabolism of carbohydrates, amino acids and bile, increased utilization rate of acetaldehyde and ethanol. Pyrrolidone carboxylate is a precursor of glutathione, facilitating the synthesis of ATP via activation of purine synthesis and increasing the number of precursors of glycine and glutamine, and activates cholinergic and GABAergic systems. Pyridoxine and pyrrolidone carboxylate are connected by salt formation, exhibit a synergism of their pharmacological properties. Receiving each component alone does not achieve the appropriate therapeutic effect inherent to metadoxine [47].

Further explored is the mechanism of action of metadoxine detoxification. The experiments demonstrated that in chronic alcohol intoxication significantly reduced alcohol dehydrogenase activity and the introduction of metadoxine supports the activity of the enzyme at normal levels [22]. Furthermore, metadoxine reduces the level of ethanol in the blood in chronic abuse [9, 26]. Similar data were obtained in clinical studies in patients with acute alcohol intoxication. Significant increase in the rate of elimination of ammonia, ethanol, ethanol metabolites from blood was shown, symptoms of severity of intoxication also decreased [45, 46, 47].

A double-blind clinical trial demonstrated efficacy in the treatment of metadoxine of abstinence syndrome [24]. Moreover, several studies have demonstrated the ability of metadoxine to reduce biochemical markers of cytolysis and cholestasis in alcoholic liver disease [1, 5, 15, 41, 45, 48, 50].

Metadoxine is effective not only in alcohol but also in other intoxications. In particular, it allows to reduce the adverse effects of antiviral therapy for chronic viral hepatitis C and also improves the biochemical parameters in this disease [18]. Metadoxine had a positive impact in the chronic toxicity of chemotherapy in cancer patients [6].

Particular interest of researchers is aimed at anti-fibrotic effect of metadoxine which demonstrated in experimental and clinical way. The results of experimental studies have shown that metadoxine inhibits the growth of the content of tumor

necrosis factor α in Ito cells. The drug prevents the increased collagen synthesis in these cells induced by acetaldehyde [38]. In an experiment on rats treated with carbon tetrachloride, the data were got on slowing inflammation and fibrosis of the liver, as well as reduced gene expression of fibronectin and procollagen [27]. Metadoxine showed anti-fibrotic properties and cholestasis in the simulation experiment with ligation of the bile duct. The animals in this study had a glycogen in the liver preserved [12]. The clinic antifibrotic effect of metadoxine is shown in alcoholic liver cirrhosis, NAFLD [7, 13, 15]. Metadoxine prevents and inhibits the development of cirrhosis of the liver by reducing the synthesis of precursor fibrous structures (fibronectin and procollagen), lowers enzyme activity of proline hydroxylase, promotes the conversion of soluble procollagen to collagen [5, 47].

Metadoxine has a pronounced antisteatosis effect both in alcohol, and in NAFLD [23]. In the experimental alcoholic intoxication metadoxine inhibited accumulation of free saturated and monounsaturated fatty acids in cells of the heart, liver, brain and kidneys [29]. This explains the membrane-effect of the drug. In animal experiments with the introduction of alcohol, acetaldehyde and carbon tetrachloride it was proved that treatment by metadoxine reduced synthesis of pro-inflammatory cytokines, production of collagen, triglyceride and fatty acid esters, as well as increased the concentration of ATP in liver. Metadoxine inhibits lipogenic differentiation upon hormonally induced lipogenesis. It is believed that metadoxine is capable of blocking the stage of differentiation of preadipocytes, as well as their late differentiation [44].

Metadoxine is used for the treatment of NAFLD, as mentioned above. In this respect, not only antisteatosis effect of the drug is important, but also its antioxidant action. In particular, in experiment metadoxine supported redox potential of different organs, which was expressed in the absence of reduction of glutathione and glutathione reductase activity upon administration of alcohol to animals [30]. In one of the aforementioned studies [44] with the introduction of alcohol, acetaldehyde and carbon tetrachloride to animals, the liver tissue revealed a dramatic decrease of reduced glutathione with simultaneous increase of oxidized glutathione, and the

luminescence caused by the presence of free radicals. The animals treated with metadoxine revealed significantly higher levels of reduced glutathione in synchronous reducing oxidized glutathione, as well as reducing amount of free radicals as a result of the normalization of oxidative phosphorylation.

Energy effect of metadoxine is confirmed by the fact that its introduction to animals with alcohol intoxication prevented the decrease in the ATP level in the liver and brain [32]. Metadoxine supports the normal ratio of pyridine nucleotides in the cells of rats with alcohol intoxication [31].

Metadoxine anti-inflammatory effect is also above-mentioned, which is reflected in the reduction of tumor necrosis factor α in the liver during upon its pilot alcoholic lesion [38].

Metadoxine is widely used in psychiatry in toxic encephalopathy, hyperactive conditions and other pathologies, for improvement of thinking and short-term memory, reducing the craving for alcohol, for antidepressant and anxiolytic effects [8, 33]. Efficacy of metadoxine in this pathology is associated with dopaminergic effect and the fact that pyridoxine as a component of metadoxine is a precursor of neurotransmitters (GABA, serotonin, epinephrine and norepinephrine) [28, 49, 53].

The aim of research is to evaluate the efficacy and safety of the drug Liveria IC in the treatment of CH in conjunction with CP of toxic etiology.

Objectives of research:

1. To study the influence of the drug Liveria IC on the clinical manifestations of comorbidities.
2. To analyze the therapy with the drug Liveria IC on the functional state of the liver and pancreas upon combined pathology.
3. To study the dynamics of structural changes of the liver and pancreas during therapy with Liveria IC according to the results of sonography.
4. To evaluate the efficacy of treatment with the inclusion of the drug Liveria IC on the indirect indicators of liver and pancreatic fibrosis on the results of the ultrasound histography.

This clinical study was conducted as an open, controlled, randomized, parallel.

Materials and methods

The study involved 60 patients with a combination of CH and CP, who were examined and treated in the gastroenterology department of DRCTMU or on the outpatient basis. The age of patients ranged from 33 to 67 years. Among the patients there were 32 (53.3%) women and 28 (46.7%) men.

Inclusion criteria were: patients aged 18-60 years with a combination of CH and CP of toxic etiology.

Exclusion criteria were: liver cirrhosis; diabetes; chronic viral hepatitis B, D, C; continuously recurrent pancreatitis with severe pain; liver and/or renal failure; severe diseases of the cardiovascular system, respiratory system; AIDS; pregnancy and lactation; failure to comply with the procedures laid down in the study protocol; mental illness; drugs addiction.

Intensity of complaints and palpation pain was assessed using the medium severity of symptoms (MSS) [11]. We used semi-quantitative scale:

0 points — no symptoms;

1 point — minimal symptoms;

2 points — moderate symptoms;

3 points — severe or extremely severe symptoms.

In view of the scale, we calculated MSS of different clinical symptoms by the formula:

$$CCT = \frac{a + 2b + 3c}{a + b + c + d}, \quad (1)$$

where MSS is the medium severity of symptoms;

a — number of patients with severity of symptoms at 1 point;

b — number of patients with severity of symptoms at 2 points;

c — number of patients with severity of symptoms at 3 points;

d — number of patients with absent symptoms.

The patients underwent a complete blood analysis, urinalysis, scatoscopy, biochemical blood analysis.

Patients were examined for viral markers by ELISA (studied markers of hepatitis B and C). In identifying the positive results, the patients were not included in the study.

To evaluate the phenomenon of "deviation" of enzymes in the blood and the state of exocrine pancreatic function we studied α-amylase activity of blood and urine, pancreatic isoamylase (P-isoamylase), blood and urine tests, blood lipase, evaluated debits of uroamilase — D1 (basal), D2 (30 minutes after consuming a standard breakfast), D3 (60 minutes after administration of the same breakfast), calculated coefficients of induction of endogenous pancreozymin — K1 (30 minutes after consuming a standard breakfast) and R2 (60 minutes after administration of the same breakfast). The standard breakfast consisted of 100 g of white bread, 20 g of butter, 100 g of cheese, 200 ml of tea with 5 g of sugar [3].

In addition, we studied indicators of fecal pancreatic elastase-1 in patients [35, 36].

All studies were performed on the biochemical analyzer Vitalab Flexor-2000 (Netherlands).

The activity of α-amylase, P-isoamylase in blood, urine, duodenal contents was investigated on the same analyzer with Lachema kits (Czech Republic). The lipase activity in blood and duodenal contents were determined on the same analyzer with Sentinell kits (Italy).

Contents of pancreatic elastase-1 in the feces was examined on the immune-enzyme analyzer Sanofi (France) using a kit produced by Schebo (Germany) [35, 36].

We studied the following parameters reflecting liver function: total bilirubin, direct and indirect, aspartate aminotransferase (AST), ALT, alkaline phosphatase (ALP), GGT, total protein, protein fractions, cholinesterase, prothrombin index, fibrinogen. We applied a kit of firm Coultronics (France) and manual methods.

Sonography of the pancreas was performed using the device ALOKA SSD-630 (Japan). We estimated the pancreas and its parts (head, body, tail), clearness of the contours, homogeneous structure, echogenicity, diameter of the Wirsung’s duct, presence of pseudocysts, calcifications. In addition, we conducted an ultrasound

histography in the pancreatic head with the assessment of index L, homogeneity index (N), histographic coefficient K_{gst} [10]. Liver sonography was performed, and L index of its right and left lobes was evaluated.

The study consisted of the qualifying period (screening) of 7-15 days, treatment period of 6 months, and the follow-up period of 3 months after treatment. Examination of patients and registration of studied parameters were performed before treatment, then in 3 and 6 months from the beginning of treatment and in 3 months after treatment.

The frequency of examinations of patients and the registration of the data was performed in accordance with the following schedule:

Visit 0 — preliminary evaluation of the respective patient according to the inclusion/exclusion criteria. Obtaining of the written informed consent. Presupposed by the protocol distribution in one of the treatment groups, and preliminary examination (after signing the informed consent form).

Visit 1 — clinical and laboratory and instrumental studies, randomization, treatment assignment.

Visits 2, 3 — clinical and laboratory and instrumental examination.

Visit 4 — observation in 3 after end of treatment.

The control group included 30 healthy aged from 35 to 62 years, 16 of them (53.3%) women and 14 (46.7%) men, i.e. sex and age of healthy matched sex and age of our patients.

Treatment

30 patients (control group) received conventional therapy of CH and CP (hepatoprotector based on the thistle — Legalon 140 1 capsule 3 times a day, antispasmodics, antisecretory and enzyme preparations, infusion therapy) — a comparison group. Treatment continued for 2-3 weeks in the hospital, then on the outpatient basis.

30 patients (main group) had traditional therapy, but instead of hepatoprotector based on the thistle they were assigned drug Liveria IC 1 tablet 2 times a day 15-20 minutes before a meal during 6 months.

Statistical data processing was performed on the computer IBM PC Intel® Core i5 using standard software packages Microsoft Excel. We calculated: the average value (M) and its error (m). The validity of the data was evaluated using Student's t test, considering that the probability (p) was not less than 95%. To identify homogeneous groups according to certain criteria we used cluster analysis [11, 16].

Results

Clinical description of patients before treatment

The main complaint of the patients was pain at the top of the stomach. Intensity of pain in the right upper quadrant in the vast majority of cases was low — in 36 (60.0%) patients. Only four (6.7%) patients with pain in the right part of the abdomen had more marked one (moderate intensity). In some cases, patients have interpreted discomfort in the right upper quadrant not as pain, but as discomfort, heaviness, bursting — 20 (33.3%) patients. MSS of abdominal pain caused by CH — 1.07.

The intensity of the pain associated with CP, was different: dominated by intense pain, which occurred in 32 (53.4%) patients, less frequent pain of moderate intensity — in 20 (33.3%) patients, and finally, minimal pain bothered 8 (13.3%) patients. Thus, MSS of pain caused by CP was 2.40.

Persistent pain with gain within 20-30 minutes after eating dominated. Such a course of pain was typical of 34 (56.7%) patients. 26 (43.3%) patients had recurrent pain, i.e. it occurred only after a meal. Before eating these patients reported discomfort, distension, heaviness in the epigastrium, hypochondria.

52 (86.7%) patients indicated that the pain intensified after receiving a large volume of food, fatty, fried, spicy, smoked, salted foods, fizzy drinks. 26 (43.3%) patients indicated increased pain after ingestion of fresh bread and other fresh pastries, sweets (especially chocolate). 49 (81.7%) patients noted increased pain and even the development of episodes of abdominal pain after drinking alcohol.

All patients surveyed indicated dyspepsia. The most frequent of these were belching — in 52 (86.7%), nausea in 49 (81.7%), heartburn in 28 (46.7%), vomiting in 14 (23.3%), bloating, rumbling in stomach in 22 (36.7%), unpleasant taste (bitter,

metallic taste, etc.) in 19 (31.7%) patients. 33 (55.0%) patients indicated the violation of a stool, 14 (23.3%) patients had constipation, 10 (16.7%) patients — loose stools, and 9 (15.0%) patients mentioned alternating constipation and loose stools. MSS of dyspepsia in the examined patients was 2.12.

Clinical manifestations of exocrine pancreatic insufficiency (weight loss, effects of hypovitaminosis) occurred in 13 (21.7%) patients. MSS of clinical manifestations of pancreatic insufficiency only among patients who had its manifestations was 1.45.

Clinical manifestations of diabetes occurred in 8 (13.3%) patients and included the complaints of dry mouth, thirst, polyuria. MSS of clinical manifestations of diabetes only among patients who had its manifestations was 1.50.

Also draws the attention of intoxication symptoms (in 28 (46.7%) patients), which was shown complaining of general weakness, loss of appetite, headache, dizziness. 11 (18.3%) patients also indicated an increase in temperature to subfebrile. MSS of clinical manifestations of intoxication was 1.15.

Yellowness of the skin and mucous troubled 9 (15.0%), itchy skin — 6 (10.0%) patients.

Complaints specific to liver cirrhosis (bleeding, swelling, abdominal enlargement, etc.) were not present in our patients, as patients with this disease were excluded.

Patients also had complaints related to co-morbidities (see below).

Upon examination, all patients revealed icteritiousness or subicteritiousness of skin and mucous membranes. In 56 (93.3%) patients tongue was coated whitish, yellowish, less frequently grayish incrustation, in 49 (81.7%) patients tooth imprints on the edges of the tongue were defined.

Upon superficial palpation, sensitivity in the projection of the pancreas was determined in 16 (26.7%) patients. Upon deep palpation, pain was detected in all patients, but palpation pain in the projection of the entire pancreas was present in 15 (25.0%) patients. Soreness mostly in the projection of the head of the pancreas (in Chauffard area) was determined in 30 (50.0%) patients, in the projection of the body

and tail of the pancreas (in Gubergrits-Skulsky area) — in 15 (25.0%) patients. Palpation of the pancreas succeeded in 6 (10.0%) patients.

All patients had moderate enlargement of the liver — by 1.0-2.5 cm below the right costal arch. In 20 (33.3%) patients liver was sealed, in 14 (23.3%) patients liver edge was sharpened. All patients had a smooth surface of the liver, spleen not palpable.

In addition, symptoms of associated diseases were determined by palpation in patients.

The patients were diagnosed following comorbidities: cholelithiasis — in 12 (20.0%) patients, chronic cholecystitis without stones — in 15 (25.0%) patients, chronic gastroduodenitis — in 16 (26.7%) patients, peptic ulcer of the stomach and/or duodenum (post-ulcerous scars) — in 4 (6.7%) patients, irritable bowel syndrome — in 11 (18.3%) patients, gastroesophageal reflux disease — in 16 (26.7%) patients, chronic bronchitis — in 22 (36.7%) patients, ischemic heart disease — in 11 (18.3%) patients, arterial hypertension — in 8 (13.3%) patients, urolithiasis — in 3 (5.0%) patients, eczema — in 1 (1.7%) patient. All concomitant diseases were in remission or in stable condition and did not require additional appointed drugs (except for patients with coronary heart disease and hypertension, who received routine therapy, and the state did not require additional assignments). Among 12 patients with cholelithiasis, 7 patients underwent cholecystectomy in terms of at least one year prior to the survey in our clinic.

Diabetes mellitus was diagnosed in 12 (20.0%) patients.

Functional state of the liver in the patients examined

Since all patients had been diagnosed with a chronic alcoholic hepatitis, we found significant changes in the functional state of the liver: a significant increase in indicators of ALT and AST, GGT, total and direct bilirubin (Table 1). These changes reflect the syndrome of cytolysis and reducing detoxification function of the liver. At the same time, the combination of increasing the content of total and direct bilirubin with increased ALP activity indicates the presence of cholestasis.

Transaminases in the surveyed patients did not exceed 5 norms, i.e. the study included only patients with minimal or moderate biochemical activity. Thus, the minimal activity of hepatitis was found in 41 (68.3%) patients, and moderate activity — in 19 (31.7%) patients.

In addition, patients revealed changes in proteinogram, although the level of total protein did not differ significantly from that of healthy (Table 1). Albumin index was significantly reduced, and γ -globulins — substantially increased. These changes reflect a violation of protein-synthetic liver function. Indicators of α_1-, α_2-, β-globulins did not have significant changes in comparison with the data of the control group (Table 1).

We should note the trend to lower prothrombin index, fibrinogen indices, while blood cholinesterase activity was significantly reduced (Table 1).

Table 1

Functional state of the liver in the patients examined

Indices	**Patients (n=60)**	**Healthy (n=30)**
	M±m	**M±m**
Total protein, g/l	58±3	69±4
Albumins, %	38,6±2,5*	54,3±3,6
Globulins, %		
α_1	2,3±0,6	2,9±0,5
α_2	7,1±0,6	8,2±0,8
β	12,7±1,1	14,4±1,3
γ	39,4±1,2*	20,7±2,1
Prothrombin index, %	84,4±2,9	87,2±2,8
Fibrinogen, g/l	2,98±0,71	3,12±0,66
Cholinesterase, U/l	7820±184*	8900±212
Total bilirubin, mcmol/l	28,2±2,4*	16,4±2,0
Direct bilirubin, mcmol/l	6,8±0,7*	2,8±0,4
ALT, U/l	78,3±2,7*	26,5±2,1
AST, U/l	62,7±2,9*	21,4±2,3
ALP, U/l	242,4±8,3*	187,8±9,2
GGT, U/l	71,4±3,2*	40,5±3,6

Note: * — the difference between patients and healthy is significant ($p<0.05$).

Functional state of the pancreas

In analyzing the results of general clinical blood test, mild anemia was defined only in 2 (3.3%) patients. Leukocytosis, leukocyte formula shift to the left, accelerated ESR occurred more often — in 14 (23.3%) patients. In 3 (5.0%) patients who were suffering from urolithiasis the minimal proteinuria, leukocyturia, microscopic hematuria were detected in the urine, without signs of an exacerbation of the disease.

Upon scatoscopy steatorrhea was found in 7 (11.7%) patients, creatorrhea — in 5 (8.3%) patients, amylorrhea — in 4 (6.7%) patients.

Indicators of fecal pancreatic elastase-1 were normal in 14 (23.3%) patients. In 20 (33.3%) patients mild pancreatic insufficiency was determined (i.e. indicators of elastase-1 fluctuated within 150-200 mcg/g), 16 (26.7%) patients had moderate pancreatic insufficiency (indicators of elastase -1 — 100-150 mcg/g), and only in 10 (16.7%) patients pancreatic insufficiency according to elastase test was severe (indices lower than 100 mcg/g). The median fecal elastase-1 in patients was significantly lower than in healthy: respectively 156,3±5,6 mcg/g and 392,3±7,4 mcg/g ($p<0,05$).

Results of other tubeless methods to assess the state of exocrine pancreatic function and the severity of the phenomenon of "evasion" of enzymes in the blood are shown in Table 2.

Indicators of blood α-amylase before treatment were increased only in 3 (5.0%) patients, however averages were not significantly different from the control group data. The activity of urine α-amylase was increased more often — in 10 (16.7%) patients, but it did not fundamentally affect the average data, and they remained in the normal range (Table 2).

More informative was a research of P-isoamylase in blood and urine. Results were increased respectively in 32 (53.3%) and 42 (70.0%) patients. Since the increase in P-isoamylase activity in blood and urine occurred in more than half of the patients, this had effect on the average indices, which respectively were increased (Table 2).

The lipase activity was increased in the blood in 21 (35.0%) patients, and the average data acquired only non-significant trend to an increase (Table 2).

Thus, we obtained evidence that in patients with CP in conjunction with CH P-isoamylase of blood and urine is the most informative diagnostic indicator.

Significant information we received in determining the uroamilase debits and coeeficients of induction of endogenous pancreozymin (Table 2). Given the high incidence of the phenomenon of "deviation" of enzymes in the blood of patients examined (at least for blood and urine P-isoamylase activity), it was found that basal uroamilase output (D1) was significantly increased. Debits of uroamilase in 30 and especially 60 min after food intake were increased to a greater extent than D1. Thus, if D1 was increased 1.68 times, compared with the norm, then D2 — 2.21 times, and D3 — 2.63 times (Table 2). Importantly, the D2 average figures were higher than D3, which indirectly reflects the difficulty of outflow of pancreatic secretion. In accordance with the uroamilase rate changes, we found a significant increase in K1 and K2, whereas K2 was higher than K1 (Table 2), which also confirms the existence of violations of the outflow of pancreatic secretion. It is important that the wrong ratio D3> D2 and K2> K1 disclose a violation of the outflow of pancreatic secretion at the level of the main (Wirsung's) duct that is characteristic of biliary pancreatitis. This is consistent with the frequent presence of our patients with concomitant biliary pathology (see above). In addition, 23 (38.3%) patients in sonography were detected to have biliary sludge in the gall bladder (see below), which is also a significant cause of not only Oddi's sphincter dysfunction, but stenotic papillitis.

Table 2

Results of tubeless survey methods of exocrine pancreatic function

Indices	**Patients (n=60)**	**Healthy (n=30)**
	M±m	**M±m**
blood α- amylase, μkat/L	1,53±0,41	1,16±0,45
urine α- amylase, μkat/L	5,81±0,62	5,08±0,68
blood P-isoamylase, μkat/L	1,49±0,15*	0,71±0,12
urine P- isoamylase, μkat/L	5,73±0,39*	3,09±0,42

Uroamylase debits, μkat/L:		
D1	41,26±1,61*	24,63±1,98
D2	74,84±3,79*	33,82±4,96
D3	83,81±4,65*	31,99±5,32
Pancreozymin induction coefficients:		
K1	1,77±0,03*	1,36±0,09
K2	2,03±0,09*	1,31±0,07
Blood lipase, U/L	41,0±6,0	24,0±8,0

Note: * — the difference between patients and healthy is significant ($p<0.05$).

Results of USD of the liver, pancreas and gall bladder in the examined patients

Since all patients had been diagnosed with CH, then the liver sonography showed an enlarged liver and enhancing its echogenicity in all cases, the attenuation of the echo to the periphery — in 47 (78.3%) patients, the depletion of the vascular pattern of the liver — in 45 (75.0%) patients, the rounded edges of the left lobe of the liver — in 36 (60.0%) patients. The heterogeneity of the structure of the liver with the presence of different areas of echogenicity, as a manifestation of fibrosis, focal fatty degeneration, occurred in 21 (35.0%) patients. Increased splenic and portal veins, splenomegaly, free fluid in the abdominal cavity were not detected in either case (Fig. 1 and 2). L index of the left and right lobe of the liver was increased accordingly up to 33,5±1,1 and 33,7±1,3 (healthy — 22,3±1,2 and 22,5±1,1; $p<0.05$).

The patients in the pancreatic sonography revealed changes characteristic of CP. The increase in all or part of the pancreas was detected in 24 (40.0%) patients, and often in the head of the pancreas — in 18 (30.0%) patients, rarer — increase of the head and body of the pancreas — in 4 (6.7%) patients, even rarer — all increased pancreas — in 2 (3.3%) patients. Rough contours of the pancreas were diagnosed in 54 (90.0%) patients. The combination of fuzzy and rough outline of the pancreas was detected in 49 (81.7%) patients. Changes in echogenicity of the tissue and pancreas were found in all patients. More often it was the increased echogenicity (up to high) — in 45 (75.0%) patients. In 15 (25.0%) of patients with cancer there was the decreased echogenicity. The heterogeneity of the structure of the pancreas was also

determined in all patients. Dilated Wirsung's duct was determined in 24 (40.0%) patients, and the extension of the common bile duct that was not more than 0.7 cm — in 6 (10.0%) patients. Stones in the lumen of the main pancreatic duct were found in 5 (8.3%) patients. Calcification of pancreatic parenchyma was determined in 28 (46.7%) patients. These patients were examined by a surgeon who recommended the planned surgery in future. Pseudocysts of the pancreas were found in 9 (15.0%) patients, but in all cases the size of pseudocysts did not exceed 5 cm, i.e. there were no indications for surgery.

The index L in the region of the head of the pancreas in the patients examined was raised to 37.4±0.6 (compared to the norm $p<0.05$), the rate of the homogeneity of N has been reduced to 3.23±0.07% ($P<0.05$), K_{gst} – reduced to 46.4±9.1 ($P<0.05$). The corresponding figures in healthy: L — 17.3±0.5%, N — 15.20±0.05%, K_{gst} – 122.4±12.3.

In 5 (8.3%) patients were determined concretions in the gall bladder, and in 7 (11.7%) patients the gall bladder was absent, as cholecystectomy was performed due to cholelithiasis. In 15 (25.0%) patients were defined symptoms of chronic calculous cholecystitis (gall bladder wall thickening of no more than 0.4-0.5 cm, enhancing its echogenicity), but there were no signs of an exacerbation of the disease. In 23 (38.3%) patients in the lumen of the gall bladder there was a biliary sludge.

Examples of the results of sonography of the pancreas and gall bladder are shown in Fig. 3 a, b; 4. An example of the results of computed tomography of the abdomen and retroperitoneal space is shown in Fig. 5.

All complaints, objective data, the results of laboratory and instrumental investigations did not have significant differences in the main and comparison group. That is, treatment in both groups was started with the same initial level.

Dynamics of clinical data (complaints, results of objective research) under the influence of treatment

Patients of the main group (receiving the drug Liveria IC) noted a marked improvement with respect to pain, heaviness in the right upper quadrant. Thus, in patients of the main group after 3 months of therapy discomfort, pain in the right

subcostal decreased or disappeared in 50.0% of cases and in the control group (treatment using the drug-hepatoprotector silymarin) — only in 40.0% of cases. However, the dynamics of pain in the right abdomen in 3 months after therapy was unreliable. In 6 months of treatment, a positive trend was noted in 70.0% of cases in the study group and in 60.0% of cases in the control group (Fig. 6). Again, the differences were not significant. In a three-month follow-up after treatment, discomfort, heaviness, distension in the right upper quadrant disappeared in 80.0% of cases in the study group and in 73.3% of cases in the comparison group ($p>0.05$). Therefore, the effect of Liveria IC and Legalon on pain in the right half of the abdomen, caused by CH, was similar. This is confirmed by the absence of substantial differences in MSS index in all stages of treatment and observation. After a six-month course of treatment MSS in the study group was 0.30, while in the comparison group — 0.40 ($p>0.05$).

We did not observe a significant difference in the effect of the two treatment options and pancreatic pain. In 3 months MSS in the study group was 1.82, in 6 months — 1.12, in 9 months — 0.84. In the control group the corresponding figures were as follows: 1.76; 1.08 and 0.76. In respect of pancreatic pain we establish similar efficacy of the two treatment options.

Intensity of dyspeptic syndrome during treatment and observation clearly decreased, but we found differences in the effectiveness of treatment in both groups of patients. MSS of dyspepsia in the main group in 3 months of treatment — 1.32 in the control group — 1.42; in 6 months in the main group — 0.84, in the control group — 0.94; in 9 months from the start of the study in the main group — 0.52 in the control group — 0.68. In any case, there were no significant differences between the MSS of two groups. However, we noticed a tendency for a more pronounced positive therapeutic effect of combined therapy with the inclusion of Liveria IC on nausea. Within 3 months of therapy it disappeared in all patients of the main group and did not appear again in studies in 6 and 9 months of starting treatment. In the control group in 3 months nausea retained in 26.7%, in 6 months — 16.7%, in 9 months — in 10.0% of cases. Thus, we observed a significant advantage of the drug Liveria IC on

the impact of nausea in patients with concomitant diseases. Vomiting disappeared in both groups in 3 months of treatment.

Clinical manifestations of exo- and endocrine pancreatic insufficiency did not bother all the patients who had them before treatment, even upon re-examination in 3 months of treatment. In our opinion, this is due not so much to the influence of hepatoprotectors applied, but to the appointment of an adequate replacement therapy.

By the end of the treatment primary treatment option had a distinct advantage with respect to the asthenic syndrome and the effects of intoxication. Thus, reducing the overall weakness in 3 months of treatment noted 27 (90.0%) patients of the main group and only 18 (60.0%) patients of the comparison group. In 6 months of treatment only 2 (6.7%) of patients receiving Liveria IC and 7 (23.3%) patients treated with Legalon complained of weakness. Upon monitoring in 9 months from the start of the study 1 (3.3%) patients from the main group and 5 (16.7%) patients in the control group (Fig. 7) complained of general weakness. At the end of the study MSS of intoxication and fatigue in the main group — 0.32, in the control group — 0.56. Therefore, the complex therapy with the drug Liveria IC has advantages in the elimination of subjective manifestations of intoxication.

Yellowness and itching did not worry any patient in 3 months of treatment.

In 3 months of treatment with the objective study icteritiousness was not found in any case. Subicteritiousness was determined in 28 (93.3%) patients of the main group and all patients of the comparison group. In 6 months of treatment, the symptom was present in 26 (86.7%) patients of the main group and in 28 (93.3%) patients of the comparison group. In 9 months of the study it was, respectively, in 22 (73.3%) and 25 (83.3%) and patients. We can conclude that there was no reliable statistical difference in the elimination of icteritiousness and subicteritiousness depending on the applied treatment.

In 3 months of treatment, pain upon surface palpation in the projection of the pancreas has not been determined. Sensitivity towards deep palpation persisted in 24 (80.0%) patients of the main group and 26 (86.7%) patients of the comparison group. In 6 months of treatment — respectively in 16 (53.3%) and 18 (60.0%) patients. In 9

months of the study — in 8 (26.7%) and 10 (33.3%) patients. Therefore, both treatment options have similar positive effects on a manifestation of CP.

In all patients before treatment liver enlargement was determined by palpation (see above). Distinct dynamics in this respect in 3 months of treatment was not observed. In 6 months of treatment, reducing the size of the liver was palpable, but not normalization, in 12 (40.0%) patients of the main group and in 14 (46.7%) patients of the comparison group. In 9 months from the start of the study the essential dynamics of the size of the liver was observed.

In 3 months of treatment, anemia, leukocytosis, accelerated erythrocyte sedimentation rate were not detected in any case.

Table 3 reflected the dynamics of the functional state of the liver under the influence of treatment.

Table 3

Dynamics of the functional state of the liver in the patients examined

	Main group		**Comparison group**		**Healthy**
	3 months	**6 months**	**3 months**	**6 months**	
Total protein, g/l	64±3	68±2	61±5	65±4	69±4
Albumins, %	44,3±4,1	48,6±2,7	41,7±2,4	45,9±3,1	54,3±3,6
Globulins, %					
α_1	2,5±0,3	2,7±0,5	2,4±0,2	2,7±0,3	2,9±0,5
α_2	7,6±0,7	7,9±0,4	7,4±0,4	7,8±0,9	8,2±0,8
β	13,4±1,5	14,1±0,8	13,1±0,7	14,3±1,3	14,4±1,3
γ	34,2±3,6	28,7±3,1	36,4±2,8	30,3±2,5	20,7±2,1
Prothrombin index , %	85,3±1,4	86,1±1,8	84,8±1,2	85,7±2,3	87,2±2,8
Fibrinogen, g/l	3,01±0,34	3,08±0,27	2,99±0,71	3,04±0,52	3,12±0,66
Cholinesterase, U/l	8143±196	8824±174*	8056±162	8272±194	8900±212
Total bilirubin, mcmol/l	19,7±1,3	16,1±2,1	20,6 ±1,5	18,4±1,7	16,4±2,0
Direct bilirubin, mcmol/l	3,1±0,4	2,9±0,5	3,7±0,6	3,1±0,4	2,8±0,4
ALT, U/l	39,7±1,4	33,7±2,1	40,3±1,1	35,4±1,8	26,5±2,1
AST, U/l	32,1±1,6	26,8±2,3	33,6±1,4	28,6±2,5	21,4±2,3
ALP, U/l	201,6±6,4	193,4±5,2	213,4±6,8	197,6±8,1	187,8±9,2
GGT, U/l	42,4±2,9*	40,1±2,7*	63,6±2,3	61,8±3,5	40,5±3,6

Note: * — the difference between the indices of the two groups is significant ($p<0.05$).

Synthetic liver function according to the parameters of total protein and proteinogram, prothrombin, fibrinogen was not significantly reduced (Table 1). Under similar treatment was observed in both groups of patients with a tendency to increase the level of total protein, albumin, and fibrinogen and prothrombin index. This focus has been expressed similarly both in the inclusion of drug therapy by Liveria IC, and Legalon. Lack of reliable dynamics of these indicators is likely due to the fact that the expression hepatodepressive syndrome was not observed before treatment. Only cholinesterase activity of all the synthetic indicators of liver function was significantly reduced before treatment. Under the influence of treatment in 3 months in both groups we found unreliable thrust to increase this figure without reaching norms. In 6 months in patients receiving Liveria IC, there was a significant increase in cholinesterase activity in comparison with the baseline level to the achievement of the control group. In patients treated by Legalon, significant increase in active cholinesterase was not reached, and the index remained significantly below norm in 6 months (Fig. 8).

In analyzing the dynamics of markers of cytolysis of hepatocytes (total and direct bilirubin, ALT, AST) we noted a similar significant decrease in these parameters between the two groups: in 3 months of treatment up to 1.5 norms, and in 6 months to 1.2-1.3 norms. It is important that in 6 months of treatment in both groups markers of cytolysis were not significantly different from normal.

With respect to ALP as a marker of cholestasis, dynamics was the same as markers of cytolysis. We found more pronounced positive effect of Liveria IC on GGT activity. According to the literature, this figure reflects not only the severity of cholestasis, but increases with toxic liver damage, including alcohol lesions [51]. In the main group in 3 months of treatment, GGT activity was significantly reduced and reached the norm. In 6 months of treatment we noted non-significant trend to a further reduction in enzyme activity with the preservation of this activity in the normal range. In the comparison group GGT index in 3 and 6 months after treatment had only unreliable a downward trend, remaining above normal. Therefore, according

to our data, the drug Liveria IC has advantages in terms of optimizing the antitoxic function of the liver. The data correspond to a distinct positive effect of the drug on the subjective symptoms of intoxication.

Upon scatoscopy steatorrhea, amylorrhea and creatorrhea were not defined in any single patient, as all patients received adequate enzyme replacement therapy.

Exocrine function of the pancreas on the results of fecal elastase test during treatment gradually improved. In 3 months of treatment in the study group we noted non-significant trend to an increase in fecal elastase-1 to 184,5±6,1 mcg/g (as compared to baseline ($p>0,05$), in the comparison group severity similar trend 3 months of treatment and was not significant — increased to 172,3±5,9 mg/g (as compared to baseline) ($p> 0,05$). In 6 months of treatment in the main group level of fecal elastase-1 amounted to 191,8±5.7 mcg/g, and in the comparison group — 179,1±6,3 mcg/g (as compared to baseline there is no credible dymanics) (Fig. 9). In both cases, there was no significant difference between the performance of the two groups. By the end of the treatment remained significant decrease fecal elastase test results as compared to the control group. However, higher rates of fecal elastase-1 were achieved in the main group.

This is confirmed by the frequency of normalization of fecal elastase test results in 6 months of treatment. Before treatment, each group had 7 (23.3%) of patients with normal results of this study. After treatment there were 11 (36.7%) patients in the main group, and in the comparison group — 8 (26.7%).

Dynamics of blood pancreatic enzymes was as follows. Activity of blood and urine α–amylase, blood lipase before treatment did not exceed norm (Table 2). During the therapy, we noted only inaccurate fluctuations of these indicators that upon study in 3 and 6 months of treatment did not go beyond the norm and lacked credible dynamics.

A significant decrease in the activity of blood and urine P-isoamylase was reported only in 6 months of treatment in both groups. Trends in this indicator were similar under the influence of the two treatment options. At the end of treatment, we

recorded a normal average blood and urine P-isoamylase in both groups (Table 4, Fig. 10).

Table 4

Dynamics of the functional state of the pancreas during treatment

	Main group		Comparison group		Healthy
	3 months	6 months	3 months	6 months	
blood α- amylase, μkat/L	1,24±0,38	1,19±0,43	1,36±0,48	1,25±0,37	1,16±0,45
urine α- amylase, μkat/L	5,53±0,34	5,12±0,27	5,57±0,36	5,32±0,41	5,08±0,68
blood P-isoamylase, μkat/L	1,22±0,13	0,72±0,06	1,26±0,07	0,74±0,12	0,71±0,12
urine P-isoamylase, μkat/L	5,01±0,34	3,24±0,18	5,18±0,45	3,27±0,21	3,09±0,42
Uroamylase debits, μkat/L: D1 D2 D3	 26,42±0,25* 66,17±1,73 76,14±2,86	 24,87±0,18* 43,05±1,22* 40,18±2,04*	 37,14±0,42 68,34±1,96 71,36±3,16	 28,64±0,37 64,51±2,07 69,37±2,97	 24,63±1,98 33,82±4,96 31,99±5,32
Pancreozymin induction coefficients: K1 K2	 2,50±0,07* 2,88±0,16*	 1,73±0,05* 1,61±0,07*	 1,83±0,13 1,92±0,16	 2,25±0,21 2,42±0,23	 1,36±0,09 1,31±0,07
Blood lipase, U/L	32±6	26±4	31±8	28±7	24±8

Note: * — the difference between the indices of the two groups is significant ($p<0.05$).

We identified the benefits of treatment with the inclusion of Liveria IC in the analysis of the dynamics of uroamilase debits and ratios of induction of endogenous pancreozymin. For example, in the main group D1 achieved significant positive dynamics and normalization in 3 months of treatment. In the comparison group in these terms was recorded only significant trend to lower D1 without reaching the standards. D2 and D3 in the two groups at the end of 3 months of therapy were not significantly decreased (Table 4). In 6 months of treatment in the main group achieved significant dynamics of D2 and D3 as compared to the baseline data with the achievement of the control group. In the comparison group after 6 months of

therapy there was no significant reduction of D2 and D3, however, D1 achieved significant dynamics and normalization (Table 4).

At the same time, we noted the relevant dynamics of coefficiemts inducing endogenous pancreozymin K1 and K2, as they are derived from the figures of uroamilase debits. It is important that under the influence of therapy with Liveria IC in 6 months of treatment ratio between debits and the coefficients equalized. In 6 months of therapy in the main group, we recorded the correct ratio of D2> D3 and K1> K2, whereas in the comparison group these ratios were changed: D2<D 3 and K1<K2 (Table 4).

The obtained data suggest the normalization of reactions of the pancreas to food stimulation. Perhaps this is due to the marked antitoxic, antioxidant and anti-inflammatory action of metadoxine (see above).

Dynamics of the results of sonography of the liver and pancreas under the influence of treatment

Patients in both groups at sonography in 3 months of treatment the size of the liver had no significant dynamics. In 6 months of treatment, the size of the liver decreased in 16 (53.3%) patients of the main group and in 15 (50.0%) patients of the comparison group. The attenuation of the echo to the periphery of the end of treatment occurred in 10 (33.3%) patients of the main group and in 14 (46.7%) patients of the comparison group. Depletion of vascular pattern was observed respectively in 9 (30.0%) and 15 (50.0%) patients, the rounded edges of the left lobe of the liver — in 7 (23.3%) and 11 (36.7%) patients. Heterogeneity of liver tissue was recorded at the end of treatment, respectively, in 8 (26.7%) and 7 (23.3%) patients. In the main group L index of the left and right lobe of the liver was significantly decreased to 28,7±0,8 and 28,5±0,6 (compared to baseline $p<0,05$), although it remained significantly higher than the norm. In the comparison group L index also decreased to 32,1±2,6 and 31,2±1,4, but the difference between the initial and final figures was unreliable ($p>0,05$). At the same time, a significant difference remained between the control group and the comparison group in 6 months of treatment ($p<0,05$). As a result, the difference between L index of the right and left lobes of the

liver of patients in the main group and the comparison group was significant. This, in our view, is an indirect evidence of more efficient anti-fibrotic effects of the drug Liveria IC and its ability to reduce the severity of fatty liver, as the main reasons for increased rates of L index are fibrosis and excess fat in the liver tissue [10]. Our findings are confirmed by more pronounced decrease in the frequency of subjective sonographic signs of hepatic steatosis in patients of the main group (see above).

In 6 months of treatment, an increase in all the pancreas or its part was detected in only 1 (3.3%) patients of the main group and in 2 (6.7%) patients of the comparison group. The frequency of other sonographic symptoms of CP was similar in both groups (Fig. 11).

In the main group L index in the head of the pancreas in 6 months of treatment significantly decreased to 22,3±0,9, N and K_{gst} — substantially increased to 7,84±1,22% and 84,5±6,4 (compared to baseline $p<0,05$). However, these indicators did not reach the norm. In the comparison group only non-significant trend to the positive dynamics of L, N and $K_{gst.}$was determined. It is important that L index in the end of treatment in the area of pancreatic head in the study group was considerably lower than in the comparison group.

An example of the dynamics of the pancreatic sonography is shown in Fig. 12.

Results of catamnestic observation

We have observed our patients for 3 more months after treatment. Worsening of CH in patients of the main group during this period was not observed. In the comparison group 3 (10.0%) patients had worsening of CH (discomfort worsening, heaviness in the right upper quadrant, appearance of the skin and mucous subicteritiousness, enlarged liver upon palpation not for more than 1.0-1.5 cm compared to the end of treatment. These episodes were associated with alcohol intake.

Exacerbations of CP during 3 months after the end of treatment were observed in 2 (6.7%) patients of the main group and in 5 (16.7%) patients. All exacerbations were also associated with alcohol and/or fatty, spicy food.

Conclusions

Liveria IC drug is effective in treating patients with a combination of CH and CP of toxic (alcoholic) etiology. Under the influence of complex treatment with the inclusion of this drug, it reduces symptoms of intoxication, degree of liver enlargement on palpation, improves the functional state of the liver, including synthetic and antitoxic function, improves pancreatic exocrine function according to the results of fecal elastase test, decreases the expression of "deviation" of pancreatic enzymes in the blood, seizing results of sonography of the liver and the pancreas, L index of the right and left lobes of the liver decreases, as well as in the area of the head of the pancreas, other indicators of ultrasonic pancreatic histography are improved (N and K_{gst}). During the treatment period we did not observe a single case of worsening of CH and CP, and in 3 months after treatment there were rare moderate exacerbations due to the alcohol and food provocation.

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Pathogenetic approaches to the treatment of chronic hepatitis combined with chronic pancreatitis of toxic etiology

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Key words: alcoholic liver disease, chronic alcoholic pancreatitis, treatment, metadoxine, Liveria IC

The article presents an overview of the literature on the therapeutic opportunities of metadoxine. The authors conducted an open study on the efficacy and tolerability of Liveria IC in a complex treatment of patients with chronic hepatitis combined with chronic pancreatitis of toxic etiology, as compared to a group of patients with the same pathology, receiving only basic therapy.

It was demonstrated that symptoms of intoxication and degree of large liver mass in palpation reduced, exocrine pancreatic function and functional state of the liver improved, including synthetic and antitoxic functions, ‘deviation’ of pancreatic enzymes in the blood decreased, results of the liver and pancreatic sonography improved under the influence of treatment with the inclusion of this drug.

Подписи к рисункам

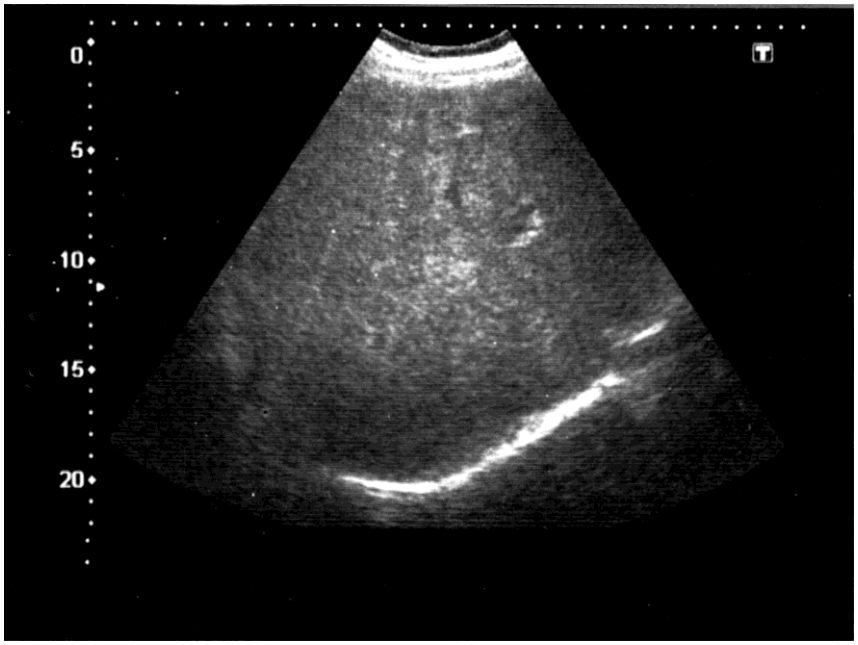


Fig. 1. Sonogram of the liver of patient S., slightly enlarged liver (right lobe 14.5 cm, left lobe 7.6 cm), clear contours, heterogeneous structure, marked attenuation of the echo to the periphery. Increased echogenicity, vascular pattern is depleted. Portal vein is not expanded — diameter of 0.8 cm. Conclusions: diffuse changes in the liver.

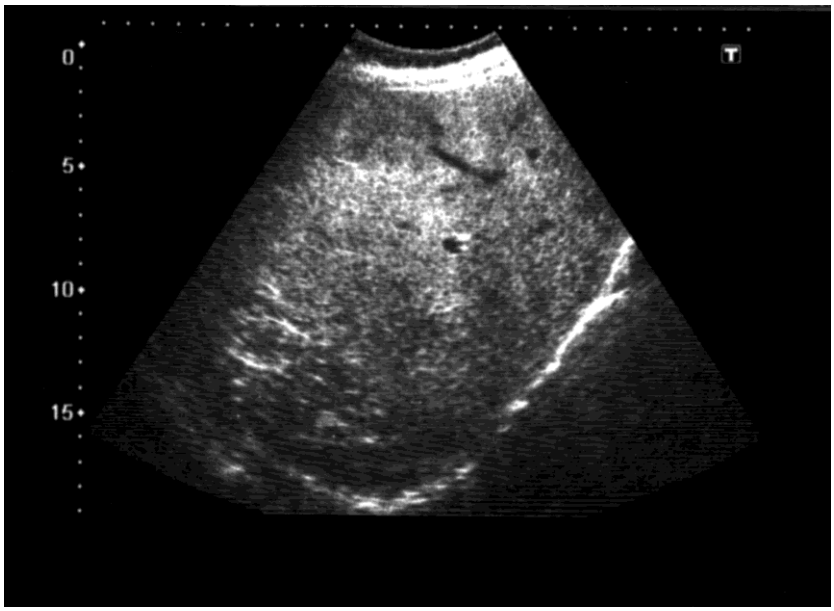
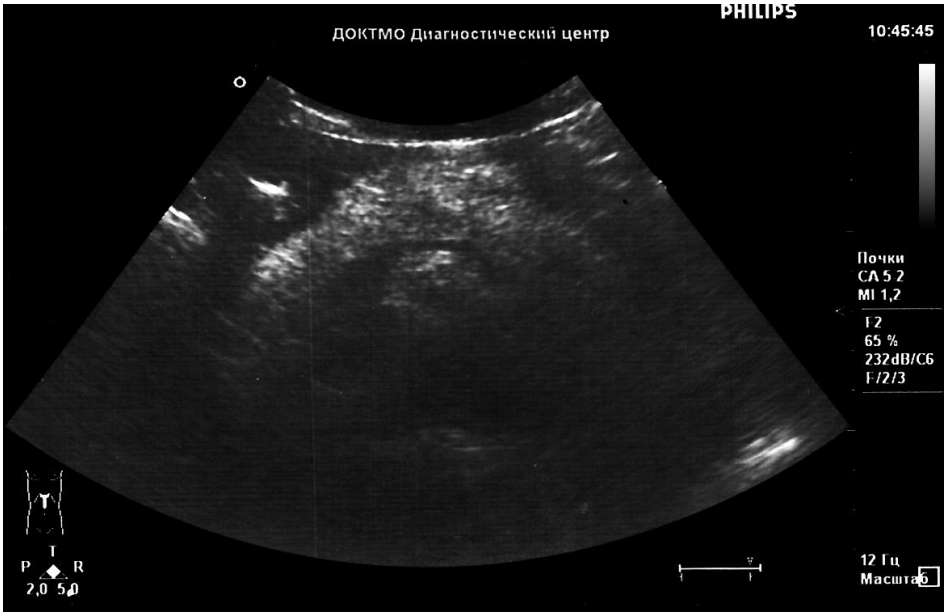


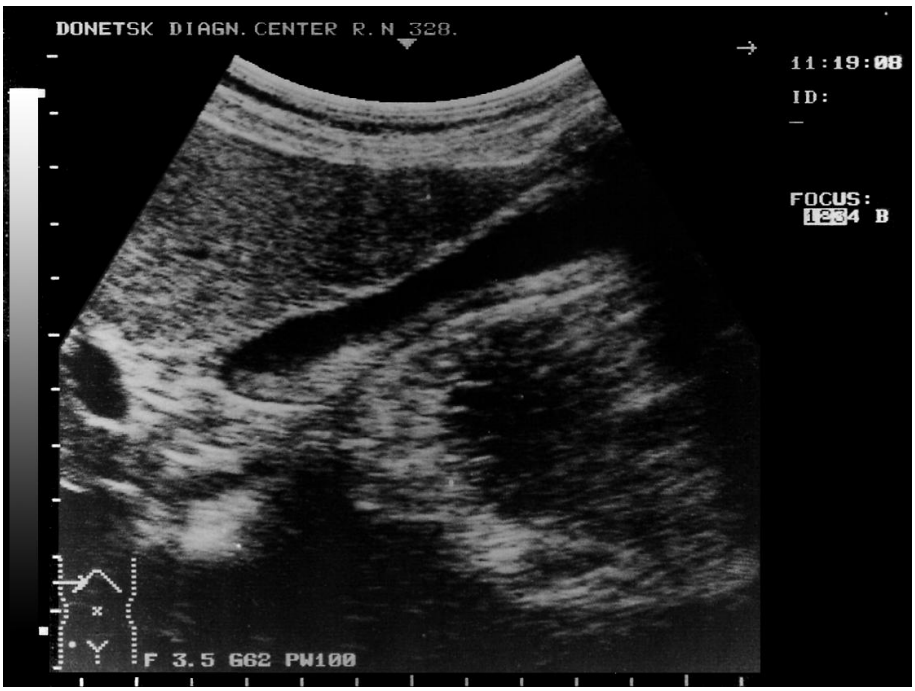
Fig. 2. Sonogram of liver of patient B. The liver is enlarged by the left lobe (left lobe 7.2 cm, right lobe 11.8 cm), clear contours, structure diffusely heterogeneous due to different areas of echogenicity, total increased echogenicity,

vascular pattern is depleted. Portal vein is not extended — 0.9 cm. Conclusion: moderate diffuse changes in the liver.

Fig. 3. Results of USD of patient S., suffering from CP in the acute stage combined with CH.



a) Sonogram of the pancreas. Pancreas is slightly increased in the head (3.5 cm), body — 1.9 cm, tail — 2.7 cm. The contour is uneven, clear. Structure is diffusely heterogeneous, granular, bundled, with areas of different echogenicity. Total echogenicity of the pancreas is moderately increased. Wirsung’s duct is not dilated.



b) Sonogram of the gall bladder. The gall bladder is not enlarged, thickened wall, increased echogenicity; on the rear wall — biliary sludge.

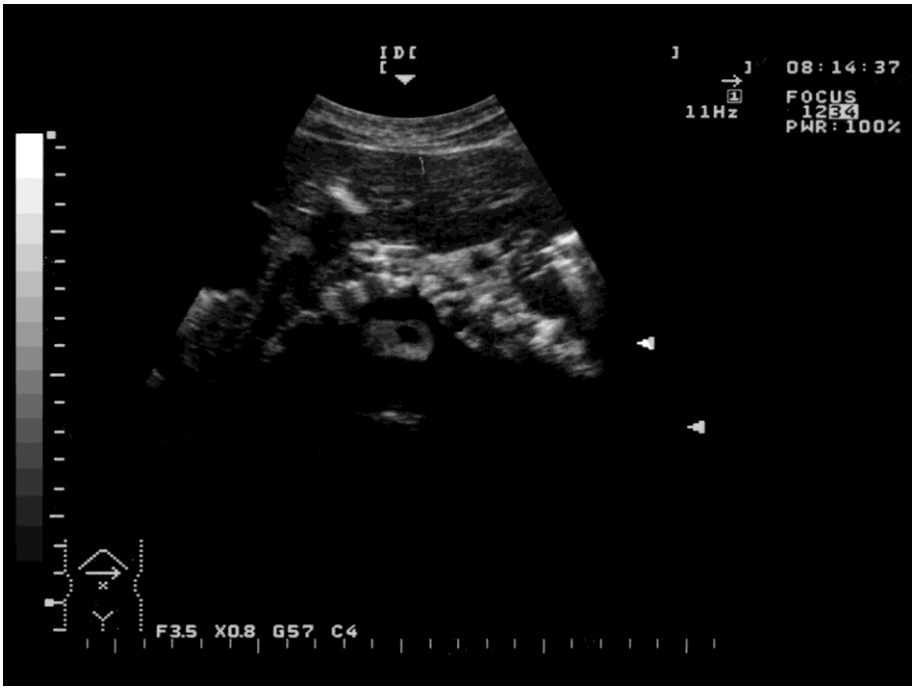


Fig. 4. Sonogram of patient L. with CP in the acute stage, combined with CH. Pancreas increased in size due to head to 3.5 cm, contours wavy, fuzzy. Structure is diffusely heterogeneous, coarse-grained, with a presence of small calcifications. Wirsung's duct is not dilated. Total reduced echogenicity. Conclusion: chronic calcifying pancreatitis.

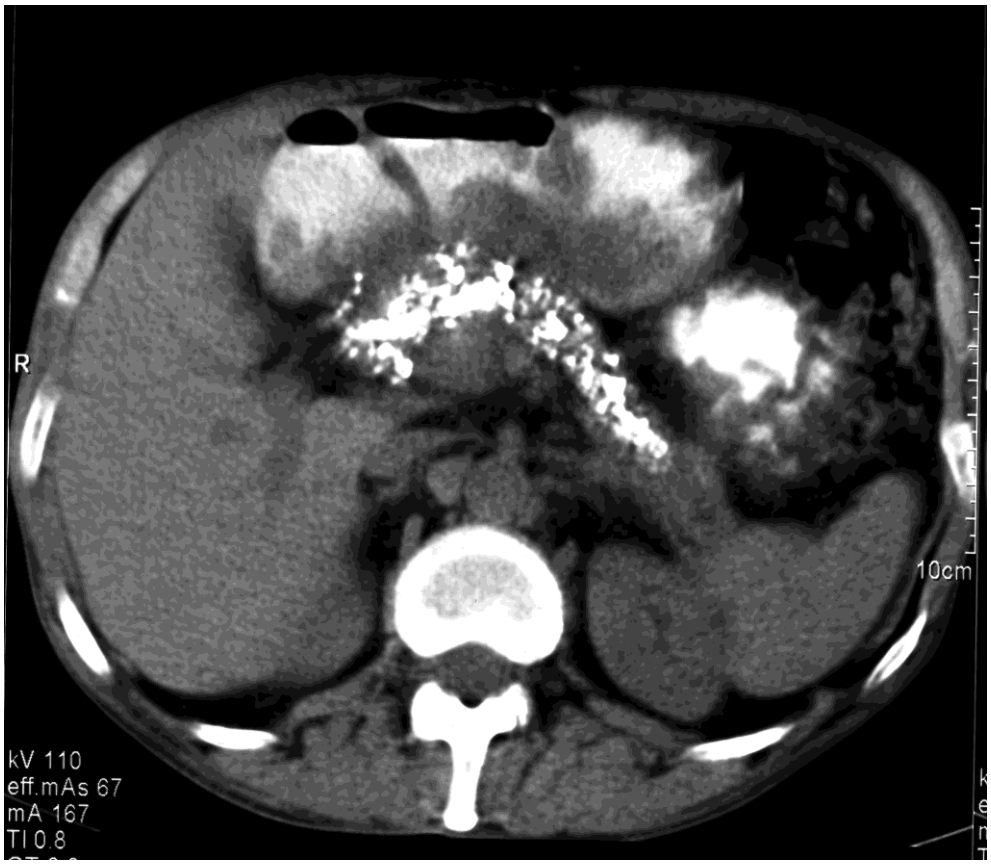


Fig. 5. CT of the abdomen and retroperitoneal space with per os contrasting of patient P. with CP combined with CH. The liver is enlarged, mildly inhomogeneous structure, no additional formations and foci of pathological density. Pancreas is increased slightly in size in the head region, the rough outlines, structure markedly heterogeneous due to the presence of numerous small calcifications with a tendency to merge. Conclusion: calcific pancreatitis, diffuse changes in the liver.

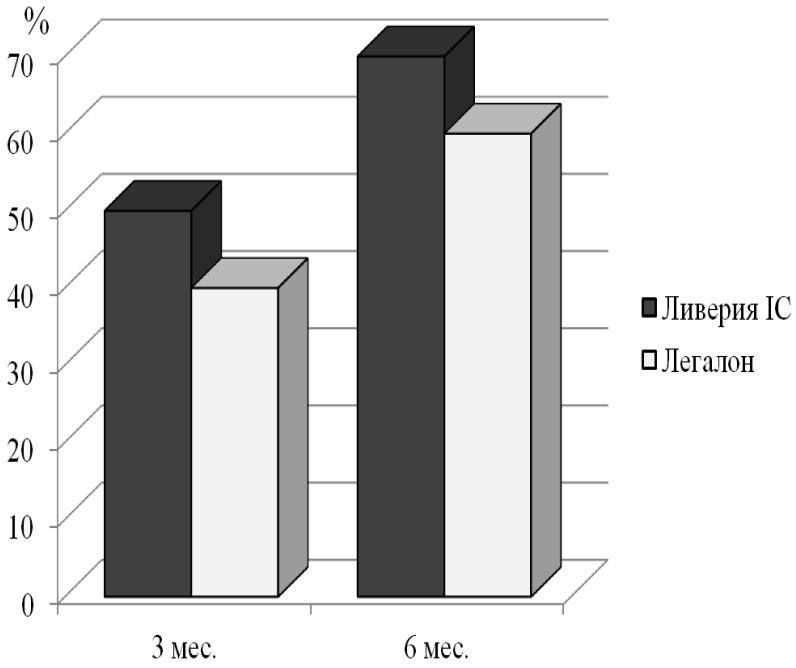


Fig. 6. Frequency of reduction or disappearance of discomfort, pain in the right half of the abdomen, depending on the applied therapy.

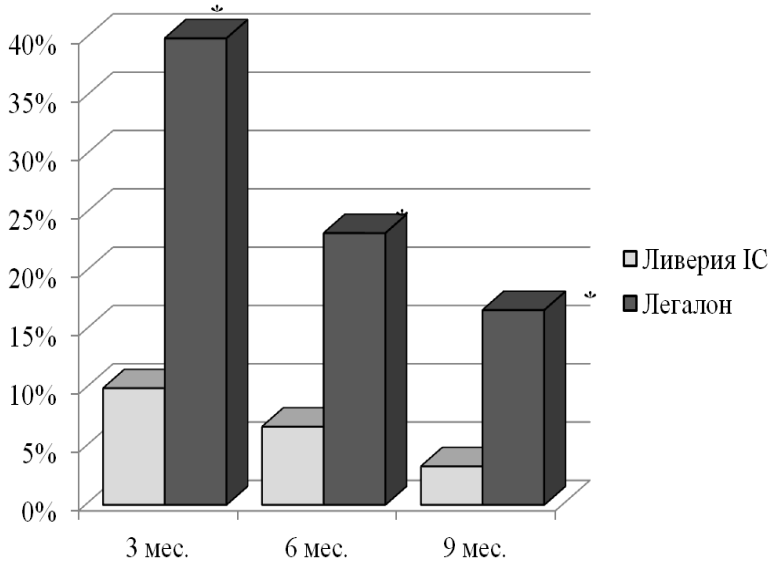


Fig. 7. The frequency of complaints of fatigue phenomena and general weakness in the dynamics of treatment.

* — the frequency of symptoms between the two groups differs significantly ($p<0.05$).

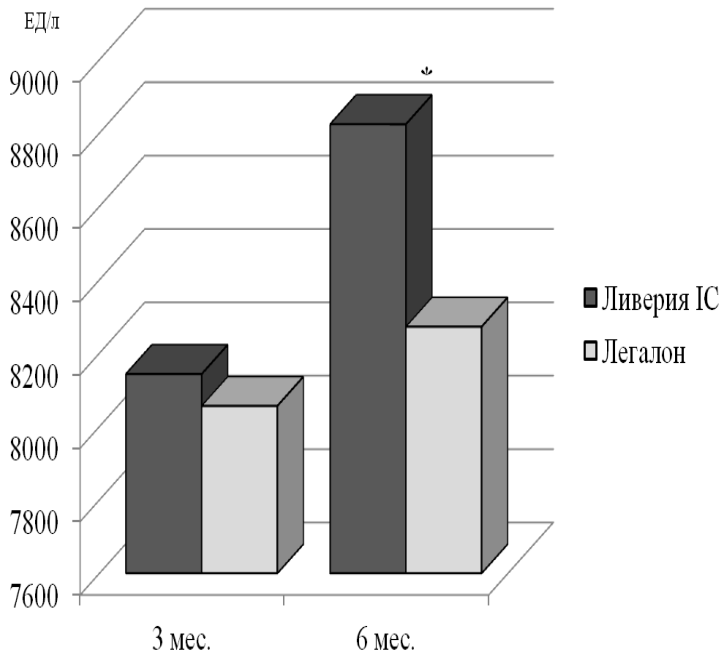


Fig. 8. Dynamics of blood cholinesterase activity in the treatment process.

* — the frequency of symptoms between the two groups differs significantly ($p<0.05$).

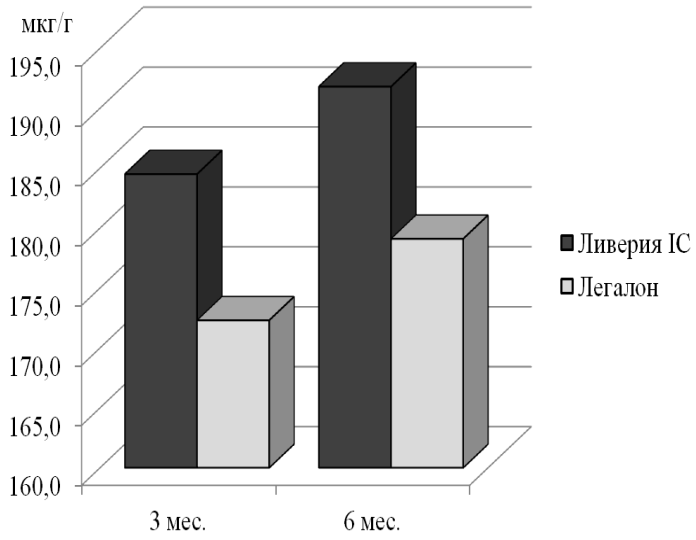


Fig. 9. Impact of the two treatment options on pancreatic exocrine function according to the results of fecal elastase test.

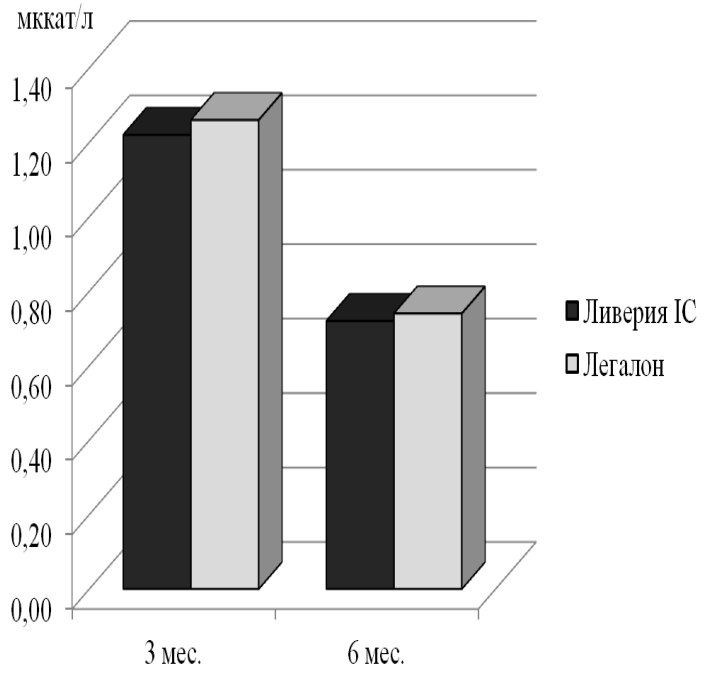


Fig. 10. Dynamics of activity of blood P-isoamylase under the influence of various treatment options.

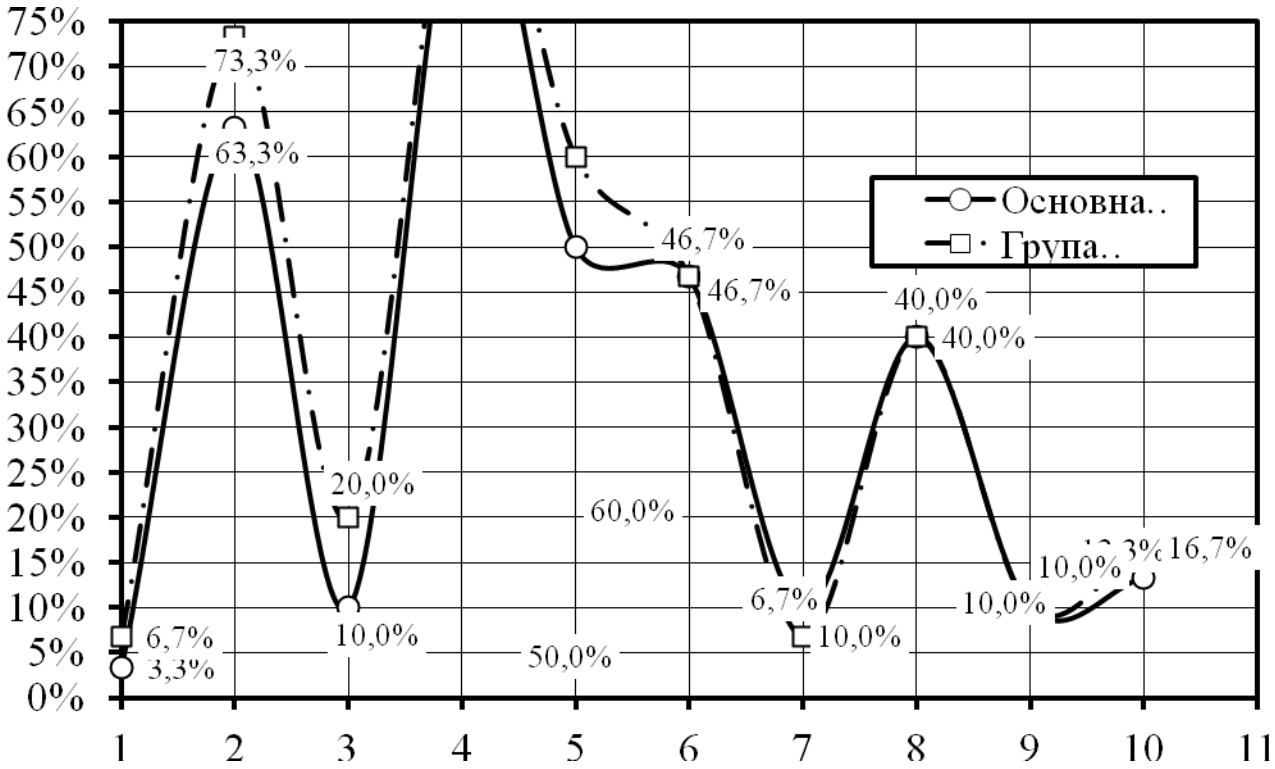


Fig. 11. The frequency of sonographic changes of the pancreas in 6 months of treatment in patients of the two groups.

1 — enlargement of all the pancreas or its part

2 — increased echogenicity

3 — decreased echogenicity

4 — heterogeneity of structure

5 — blurring of the circuits

6 — calcifications in the pancreatic tissue

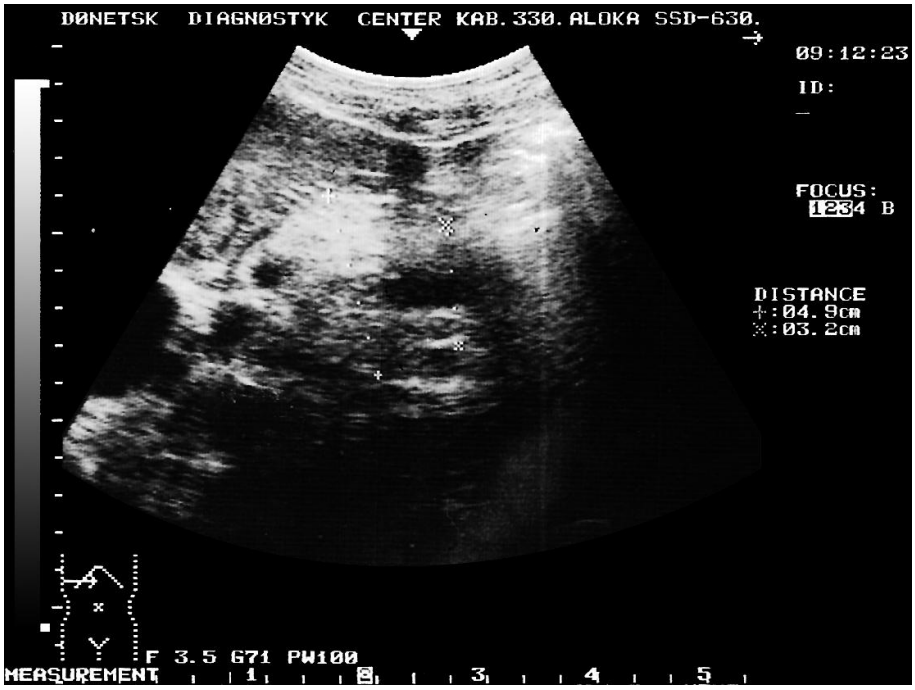
7 — calcifications in the pancreatic ducts

8 — Wirsung’s duct dilation

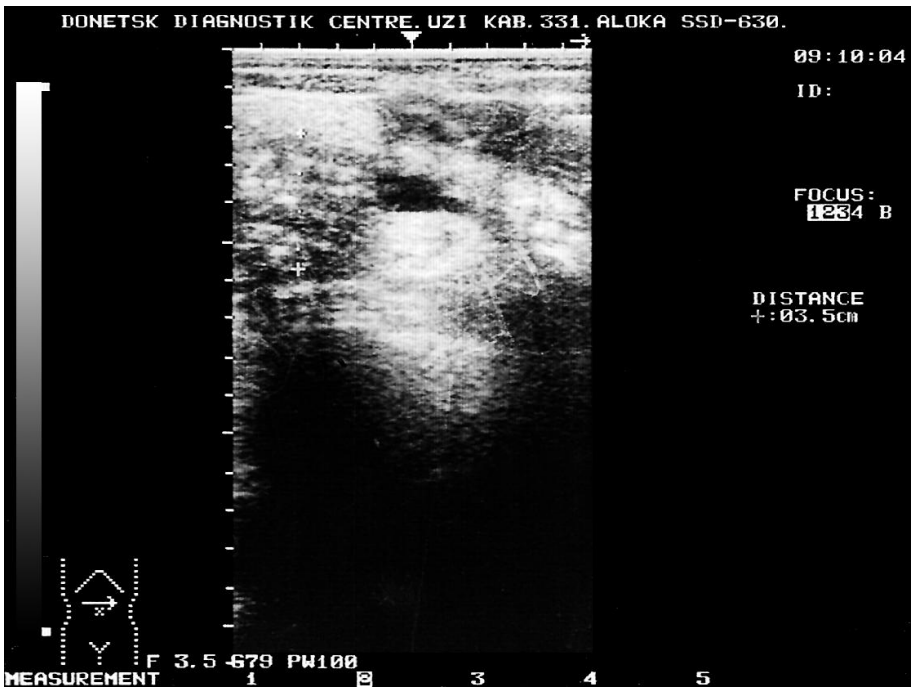
9 — extension of the common bile duct

10 — cysts and pseudocysts

Fig. 12. An example of the dynamics of the results of sonography of patient S. with alcoholic chronic hepatitis C and CP in the acute stage under the influence of the basic variant of treatment (6 months).



a) Increased pancreas — head 4.9 cm, body 3.2 cm, the tail is not clearly visualized due to flatulence. Circuit of the pancreas is wavy, fuzzy. Diffusely heterogeneous structure, mass of the calcifications is determined in the projection of head. Total increased echogenicity of the pancreas.



б) After treatment, size of the pancreas decreased: head — 3.5 cm, body — 2.7 cm, the tail is clearly visualized. Circuit wavy, fuzzy. Diffusely heterogeneous structure, small calcifications preserved in the projection of head. Total increased echogenicity of the pancreas.