CLINICAL EFFECTIVENESS OF ESSENTIALLE N AND GLUTARGIN COMBINATION IN CHRONIC ABDOMINAL ISCHEMIC SYNDROME

N. B. Gubergrits, N. G. Agapova

Donetsk National Medical University n. a. M. Gorky, Ukraine

Key words: abdominal ischemic syndrome, functional state of liver and pancreas, nitric oxide, Essentialle N, Glutargin

In practice, the doctor often meets the patients with "unexplained" abdominal pain, without detection of organic changes of the abdominal cavity, which could explain such intense pain. In some cases, this pain is associated with abdominal ischemia. Chronic abdominal ischemic syndrome (AIS) has been a difficult problem for practitioners for many years. If 2-3 decades ago AIS diagnostics was really difficult because of the need to confirm the diagnosis by angiography, at the present time diagnosis can be made with the use of available non-invasive method — dopplerography. Diagnostics and treatment of AIS are important tasks in both scientific and practical purposes. Unresolved parts of the overall problem of AIS are insufficient knowledge of the pathogenesis, functional disorders of the abdominal organs and the lack of efficacy of treatment [3, 4].

The aim of our study is to investigate the efficacy and tolerability of combined therapy of chronic AIS with Essentialle N and Glutargin.

Research tasks are:

- to study the effect of the studied drug combination on the state of the liver and pancreas, lipid and carbohydrate metabolism in patients with chronic AIS;
- to study the effect of the studied drug combination on the psychosomatic status and quality of life;
- to explore tolerability and possible side effects of studied drug combination.

Materials and methods. Study included 60 patients with AIS before and after treatment, and 30 healthy. In the selection of patients, we were guided by the following inclusion criteria:

- men and women aged 50-75 years;
- clinical and instrumental AIS signs;
- absence of a sharp increase (not more than triple) of ALT, AST, alkaline phosphatase, γ-glutamyl transpeptidase, α-amylase, pancreatic isoamylase, blood lipase;
- patients capable of giving consent before entering the study and performing research procedures.

Exclusion criteria were: participation in any clinical trial in the previous 30 days; simultaneous participation in another clinical trial; discrepancy of patient to inclusion criteria protocol; alcoholism, alcohol addiction (ethanol >80 g/day for men and >40 g/day for women); HIV-infected patients; drug addiction; hepatic impairment; cirrhosis; jaundice; viral hepatitis (positive response to HBsAg, anti-HBcor, anti-HCV); signs of encephalopathy; neoplasms of the liver and other organs and systems; acute infectious diseases; acute cholecystitis; acute pancreatitis; signs of portal hypertension; mental illness; signs of blood coagulation; permanent hemodialysis; known hypersensitivity to essential phospholipids, arginine glutamate or any inactive component of the study drugs; chronic diseases with decompensation of organs and systems of the II-III degree; patients who are not likely to comply with the protocol or are not able to fulfill it, including the giving of consent (the inability to consent because of mental retardation or language barrier); the difficulty of maintaining contact with the patient during the study; excessive, according to the doctor, tea, coffee, tobacco abuse; pregnancy and lactation; kidney and urinary system diseases with chronic pyelonephritis (creatinine ≥0.15 mmol/L); leukocytes below 2.000 /mcL; platelets below 70.000 /mcL; severe hyperbilirubinemia. In addition, the study did not include patients who required admission of "forbidden" for the protocol medications: agents affecting blood lipids (except Essentiale H); other "hepatic protectors"; other preparations containing L-arginine (except Glutargin); glucocorticoids (including inhaled ones); interferons; immunosuppressants; immunomodulators; any drugs with hepatotoxic activity.

In order to assess the effectiveness of treatment, we evaluated dynamics of AIS subjective manifestations (pain, dyspeptic syndromes), performed auscultation of abdominal aorta, measured body mass index, psychosomatic status (questionnaire SAN) and quality of life (SF-36 questionnaire).

The intensity of pain and other subjective manifestations were evaluated semiquantitatively according to the special scale [10]: 0 points — no manifestations; 1 point — slight manifestations; 2 points — moderate manifestations; 3 points — severe or highly severe manifestations. In accordance with the assessment of this scale, we counted average severity rate (ASR) of various clinical manifestations as follows [10]:

$$\text{ASR} = \frac{a + 2b + 3c}{a + b + c + d}$$

ASR — average severity rate of clinical manifestations;

a —number of patients with symptoms at 1 point;

b — number of patients with symptoms at 2 points;

c — number of patients with symptoms at 3 points;

d — number of patients with no symptoms.

Before and after the treatment we studied blood levels of total lipids, low density lipoproteins (LDL), high density lipoproteins (HDL), very low density lipoproteins (VLDL), triglyceride, cholesterol, α-cholesterol, glucose levels, C-peptide immunoreactive activity, ALT, AST, alkaline phosphatase, γ-glutamyl transpeptidase. Furthermore, we studied bilirubin and its fractions, total protein, proteinogram, NO metabolites in blood. To identify the phenomenon of "deviation" of pancreatic enzymes in the blood and assess the exocrine pancreatic function, we analyzed α-amylase activity, P-isoamylase in blood and urine, blood lipase. We analyzed uroamilase debits (D), and induction of endogenous pancreozymin coefficients (K), fasting (D1), in 30 (D2 and K1) and in 60 (D3 and K2) min after a standard load of food (100 g of white bread, 20 g of butter, 100 g of curd, 200 ml of tea with 5 g of sugar). Direct (probe) examination of exocrine pancreatic function was carried out. For this purpose, two-channel probe and gastroduodenal eufillin-

calcium test were used [2]. In the obtained duodenal contents we studied its volume, flow rate, debit-hour of α-amylase, P-isoamylase, bicarbonates. Duodenal intubation was performed only once — after treatment (to avoid amplifying pancreatic pain upon admission of patients to the clinic). In addition, because of the presence of IHD, arterial hypertension, this study didn't include all the patients (performed in 36 patients).

Activity of α-amylase and P-isoamylase in blood, urine and duodenal contents were examined on biochemical analyzer Vitalab Flexor-2000 (Netherlands) with the use of kits Lachema (Czech Republic). Indices of blood lipase and duodenal contents were studied by kinetic colorimetric method with the use of kits Sentinell (Italy) on the same analyzer. Level of bicarbonates in the duodenal contents was determined by back-titration [1].

Immunoreactive C-peptide levels were measured with the use of kits CIS (France) on the counter "Gamma-12" of Kiev factory of medical equipment.

To determine the blood level of nitrates/nitrites, we used kits R&D Systems (USA). Used method is indirect and is based on the definition of stable metabolites of NO — nitrate (NO_3^-) and nitrite (NO_2^-). The method involves the reduction of nitrate to nitrite using nitrate reductase, further Griess reaction is carried out. The results were evaluated according photocolorimetry absorbance upon wavelength of 540-570 nm. Healthy levels of NO metabolites in blood were 44.2±3.5 mmol/L.

The remaining biochemical parameters were studied by conventional methods using the standard sets on the above mentioned biochemical analyzer.

Results. Before treatment pain syndrome was severe in 22 (36.7%) patients, moderate — in 26 (43.3%) patients and slight — in 12 (20.0%) patients. Thus, ASR of pain syndrome upon admission of patients to the clinic was 2.17. After treatment of pain syndrome was severe in 4 (6.7%) patients, moderate — in 18 (30.0%) patients, slight — in 27 (45.0%) patients and pain disappeared in 11 (18.3%) patients. Thus, as a result of treatment with a combination of Essentialle N and Glutargin ASR of pain syndrome decreased significantly — up to 1.25 (Fig. 1).

Marked improvement was observed in respect of dyspeptic manifestations. Before treatment they were severe in 24 (40.0%) patients, moderate — in 25 (41.7%) patients and slight — in 11 (18.3%) patients. ASR of dyspeptic syndrome was 2.22. As a result of therapy, severe dyspepsia was indicated in only 7 (11.7%) patients, moderate — in 17 (28.3%) patients, slight — in 8 (13.3%) patients, dyspepsia was not detected at all in 28 (46.7%) patients. ASR of dyspeptic syndrome by the end of treatment was 1.05.

Upon auscultation, there was a systolic murmur 2-4 cm below the xiphoid process in the midline in 12 (20.0%) patients. In 7 (11.7%) patients there was a murmur 1-2 cm above the navel. In the first case auscultative data indicated a preferential lesion of abdominal aortic atherosclerosis and/or celiac trunk, in the second one — a predominant involvement of the superior mesenteric artery. In 8 (13.3%) patients we determined the tenderness in palpating the abdominal aorta. After treatment frequency of auscultation and palpable evidence for AIS decreased very slightly. Thus, the mumur below the xiphoid process was in 11 (18.3%) patients, above the navel — in 7 (11.7%) patients. Palpation pain occurred in 6 (10.0%) patients.

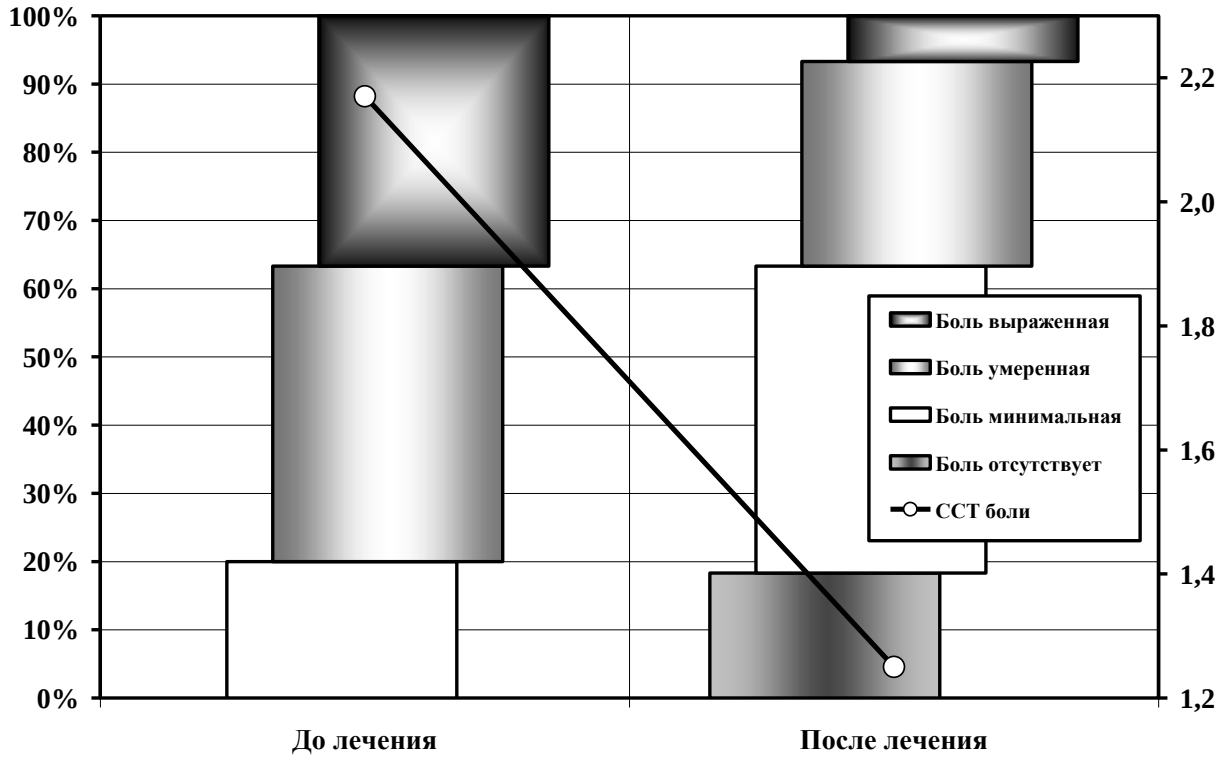

Fig. 1. Frequency of varying pain severity and its ASR during treatment with a combination of Essentialle N and Glutargin.

Body mass index before treatment was 21,3±1,2 kg/m^2, after treatment — 24,6±1,1 kg/m^2 ($p<0,05$). As mentioned above, loss of body weight is one of the important diagnostic manifestations of AIS, so increasing mass during the treatment course indicates efficacy. However, in our view, increased body weight in the patients can't be explained only by the combination of Essentialle N and Glutargin, because patients also had Creon. In the healthy body mass index was 25,7±1,4 kg/m^2.

Treatment contributed to significant improvements in lipid metabolism. Thus, the total cholesterol level decreased from 9,62±0,26 mmol/L to 7,16±0,29 mmol/L ($p<0,05$), LDL (β-lipoprotein) — from 52,3±1,4% to 41,3±0,9% ($p<0,05$); VLDL (pre-β-lipoprotein) — from 36,4±1,5% to 25,3±1,2% ($p<0,05$); HDL (α-lipoprotein) increased from 23,2±1,3% to 30,0±0,7% ($p<0,05$). Atherogenic index decreased from 5,25±0,61 to 3,60±0,54 ($p<0,05$) (Fig. 2).

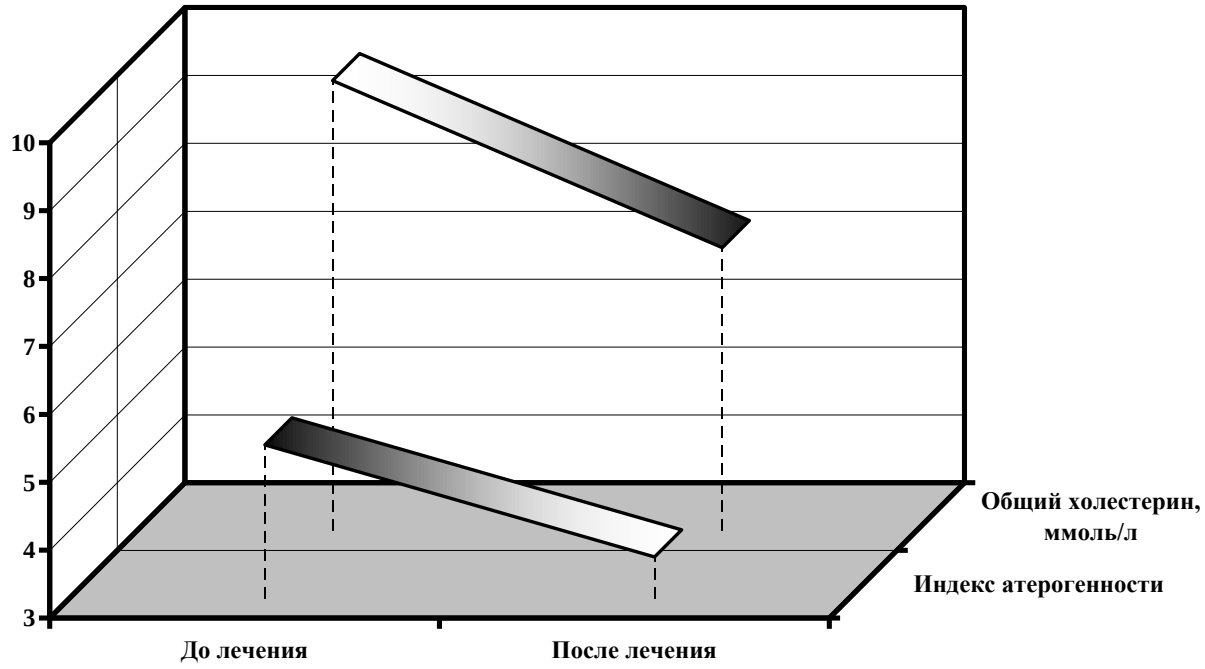

Fig. 2. Dynamics of total cholesterol level and atherogenic index of blood during treatment.

The content of total lipids in the blood decreased during treatment from 9,2±0,6 g/L to 7,6±0,5 g/L ($p<0,05$). Triglycerides indices decreased from 2,32±0,14 mmol/L to 1,86±0,17 mmol/L ($p<0,05$). Level of α-cholesterol increased from 1,26±0,11 mmol/L to 1,79±0,13 mmol/L ($p<0,05$). It is important that the indices of total lipids, triglycerides, LDL, VLDL, HDL, α-cholesterol, atherogenic index after treatment were within in the normal range. Only total cholesterol levels in blood remained elevated.

In the healthy level of total lipids was 5,4±0,5 g/L, total cholesterol — 5,2±1,8 mmol/L, triglycerides — 1,26±0,21 mmol/L, α-cholesterol — 1,89±0,16 mmol/L, LDL — 47,3±2,1%, VLDL — 27,8±2,1%, HDL — 32,1±1,7%. Atherogenic index was 3,12±0,74. The data presented in Table 1 show that AIS patients examined upon admission to hospital had several indices of increased ALT, AST, alkaline phosphatase, γ-glutamyl transpeptidase, total and direct bilirubin, γ-globulin in the blood. Treatment contributed to a significant reduction in all these indices. This is the

result of hepatoprotective properties of Glutargin and Essentialle N, reflecting improved protein-synthesis liver function during treatment.

Table 1

Results of the functional state of the liver examination

Indices	AIS patients, n=60		Healthy, n=30
	before treatment	*after treatment*	
ALT, U/L	43,6±2,1*	35,1±1,9**	26,5±2,1
AST, U/L	39,3±2,7*	26,9±1,3**	21,4±2,3
ALP, U/L	314,9±9,4*	206,1±8,8**	187,8±9,2
γ-glutamyl transpeptidase, U/L	78,8±4,1*	53,2±3,4**	40,5±3,6
Total bilirubin, mcmmol/L	36,8±2,4*	18,1±1,8**	16,4±2,0
Conjugated bilirubin, mcmmol /L	5,1±0,6*	3,1±0,5**	2,8±0,4
Total protein, g/L	72±3	77±5	69±4
Albumins, %	59,7±4,3	55,3±3,8	54,3±3,6
Globulins, %			
α_1-globulins,%	3,6±0,7	3,1±0,4	2,9±0,5
α_2-globulins,%	9,7±0,6	8,4±0,3	8,2±0,8
β-globulins,%	16,1±1,6	15,3±1,3	14,4±1,3
γ-globulins,%	34,8±2,3*	24,3±1,8**	20,7±2,1

Notes: * — index of patients was significantly different from the indices of the healthy;

** — dynamics of the indicator in the treatment process is reliable.

One of the most important indicators in the examination of our patients we considered the level of NO metabolites in the blood. As expected, it was reduced to 33,1±2,8 mcmmol/L (healthy — 44,2±3,5 mcmmol/L, $p<0,05$). Treatment promoted a significant increase in the content of nitrates/nitrites in the blood up to 41,3±1,7 mcmmol/l ($p<0,05$), the index reaching the lower limit of normal (Fig. 3).

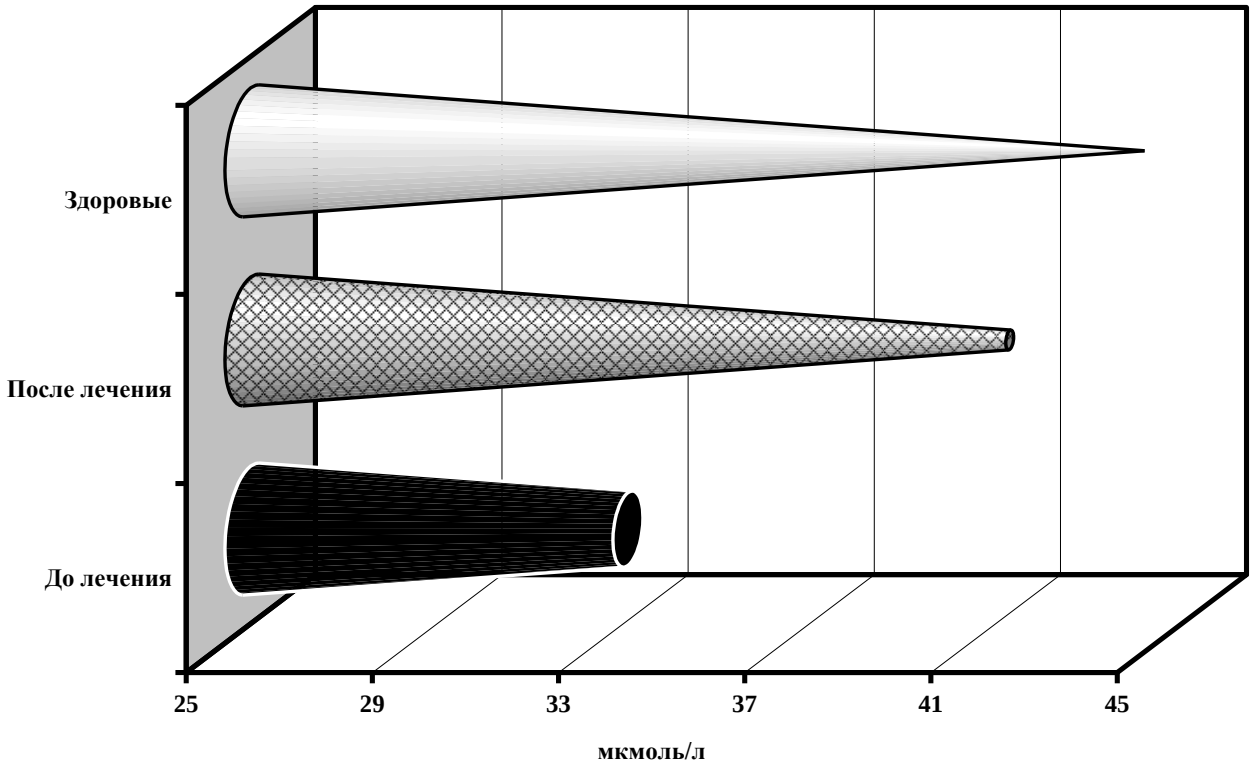

Fig. 3. Influence of treatment on the level of NO metabolites in the blood of patients with AIS.

To study the violations of the pancreas and to assess its functional status in patients with AIS before and after treatment, we studied activity of α-amylase, P-isoamylase, blood lipase, α-amylase, urine P-isoamylase and calculated uroamilase debits before and after food load (D1, D2, D3), the induction of endogenous pancreozymin coefficients (K1, K2). Furthermore, we conducted the probe examination of external pancreatic secretion at the end of treatment. Results of the tubeless tests are shown in Table 2.

AIS patients on admission to the clinic had significantly reduced indices of P-isoamylase in blood and urine, while the activity of α-amylase in blood and urine, as well as blood lipase before treatment had no significant difference from the normal data, but only insignificant trend towards reduction. This is because the α-amylase and lipase enzymes are not pancreatospecific, and their level in the blood (urine) is defined by sufficient production (out-pancreatic) in other sources (salivary isoamylase, gastric lipase, etc.). That is, even with a decrease in production of amylase and lipase by the pancreas, their indices in biological fluids are usually

normal, and that occurred in the examined patients (Table 2). It should be noted that as a significant decline in P-isoamylase in blood and urine, and the tendency to reduce the activity of α-amylase in blood and urine, blood lipase indicate pancreatic hypofunction and, specifically, to reduction of its external secretion (is a reflection of the chronic pancreatic ischemia on the background of which organ's atrophy and parenchymal fibrosis occur gradually). In the course of treatment with a combination of Essentialle N and Glutargin we revealed a significant increase in P-isoamylase production by the pancreas, which was reflected in a significant increase in the activity of enzymes in the blood and urine. Such data are likely due to improved blood supply of the pancreas under the influence of therapy and improved protein-synthesis liver function during treatment (Table 1), the positive effect of Glutargin on the protein metabolism. It is important that the indices of pancreatic enzymes in blood and urine after treatment had no significant differences from that of healthy persons. This indicates, first, that the patients examined had no heavy irreversible changes in pancreatic secretion, and secondly, the possibility of effective improvement of exocrine pancreatic function by inclusion of Essentialle N and Glutargin in combined AIS therapy.

Moderate pancreatic hypofunction in the examined patients is also confirmed by the significant reduction in uroamilase debits and the induction of endogenous pancreozymin coefficients in 30 and 60 min after taking the standard food load (Table 2). D1 was not significantly decreased, i.e. basal pancreatic secretion did not significantly suffer upon AIS, and only upon presentation of higher requirements to the pancreas, upon the need for increasing external secretion in response to food stimulation, we detected decline in the functional abilities of organ. It is important that in patients with AIS upon the admission to the hospital there was a right balance D2>D3 and K1>K2, which indirectly indicated the absence of evident violations of outflow of pancreatic secret, which are typical for obstructive chronic pancreatitis. This confirms the data on the pathogenesis of the organ upon AIS with the predominant primary violation not of the secret outflow (which is typical, for

example, for biliary pancreatitis), but of the organ's parenchyma with progressive fading of its functions.

During treatment we achieved a significant increase in D2, D3, K1 and K2. This as well as the growth of P-isoamylase indices influenced by the therapy reflects the improvement of exocrine pancreatic function. However, since the conditions of food stimulation, as said above, put out high demands for production of pancreatic enzymes, D3 index after treatment stayed significantly reduced as compared to norm (Table 2). The lower limit of norm was reached only by D1, D2, K1 and K2. Indeed, according to the literature, conditions of the blood supply to the abdominal organs especially upon AIS get worse after functional, i.e. food load, after which the appearance of ischemic abdominal pain becomes probable, worsening of dopplerography is observed, as well as worsening of functional disorders not only in the pancreas, but also in other organs of digestion [4].

The results of a probe examination of exocrine pancreatic function are presented in Table 3.

Table 2

Results of tubeless methods of examination of exocrine pancreatic function

Indices	AIS patients, n = 60		Healthy, n = 30
	Before treatment	*After treatment*	
α-amylase in blood, mkkat/L	1,01±0,17	1,12±0,10	1,16±0,45
P-isoamylase in blood, mkkat/L	0,24±0,05*	0,42±0,05**	0,52±0,12
α-amylase in urine, mkkat/L	4,38±0,54	4,82±0,63	5,08±0,68
P-isoamylase in urine, mkkat/L	3,12±0,34*	3,90±0,12**	4,29±0,42
Blood lipase, U/L	18,0±5,0	19,0±2,0	24,0±8,0
Uroamilase debits, mkkat/L			
D_1	20,75±1,21	22,26±1,03	24,63±1,98
D_2	23,12±1,36*	31,15±1,04**	33,82±1,76
D_3	22,16±1,23*	28,23±1,08*/**	31,99±1,32
Pancreozymin induction coefficients			
K_1	1,10±0,04*	1,35±0,06**	1,36±0,09
K_2	1,07±0,06*	1,33±0,10**	1,31±0,07

Notes: * — significant difference between indices of patients and healthy ($p<0,05$);

** — significant difference between indices of patients before and after treatment ($p<0,05$).

Table 3

Results of the direct probe examination of exocrine pancreatic secretion (aminophylline-calcium test)

Indices	AIS patients n = 36	Healthy n = 30
Basal secretion		
Volume, ml/15 min	13,5±3,6	18,0±1,3
Bicarbonates debit, mg-eqv/15 min	0,34±0,13	0,57±0,07
α-amylase debit, mkkat/L/15 min	628±75	777±37
P-isoamylase debit, mkkat/L/15 min	610±63	758±40
Lipase debit, U/L/15 min	9844±1420	11780±1420
Stimulated secretion		
Volume, ml/h	118,9±23,3	158,6±18,4
Bicarbonates debit, mg-eqv/h	5,28±0,39*	8,01±0,92
α-amylase debit, mkkat/L/h	7970±1286	10703±955
P-isoamylase debit, mkkat/L/h	7434±512*	10251±957
Lipase debit, U/L/h	83760±3950*	120800±4640

Note: * — significant difference between indices of patients and healthy.

Basal pancreatic secretion had no significant differences in patients with AIS and healthy, indices of patients were only insignificantly directed downward (Table 3). Study of stimulated exocrine pancreatic function was more informative. So, debits of bicarbonates, P-isoamylase and lipase in the examined patients were significantly reduced, which was a direct evidence of significant reduction of exocrine pancreatic function. Volume of stimulated secretion in the examined patients was not significantly reduced, which again confirms the lack of a clear obstructive component in the pathogenesis of ischemic lesion of the pancreas. Debit of α-amylase also had only slight downward trend than reiterated the lesser clinical significance of the indices of this enzyme as compared to P-isoamylase (Table 3, Fig. 4).

Obtained results of the study of exocrine pancreatic function according to probe and tubeless research methods were appropriate to the types of pancreatic secretion. AIS patients more often had hyposecretory type of pancreatic secretion — in 28 (77.8%) patients; upper obstructive type of pancreatic secretion was detected in 6 (16.7%) patients and lower obstructive type — in 2 (5.5%) patients. These data

suggest that a small number of examined patients (8 patients), besides ischemic injury of pancreatic parenchyma, which, as indicated above, is characterized by a gradual fading of organ functions and the subsequent development of hyposecretory type of pancreatic secretion, had other variants of lesions. These variants are reflected in the development of the upper and lower obstructive types of secretion. It is most likely that the upper obstructive type of secretion is associated with alcohol-induced pancreatic lesion (it was confirmed by in-depth clarification of history), and the lower obstructive type of secretion — with a combination of ischemic organ's lesion along with biliary pancreatitis (both patients with this type of secretion had cholelithiasis). It is important that the examined patients didn't have hypersecretion and normal pancreatic secretion at all. Frequency of different types of exocrine secretion in patients with AIS after treatment is shown in Fig. 5.

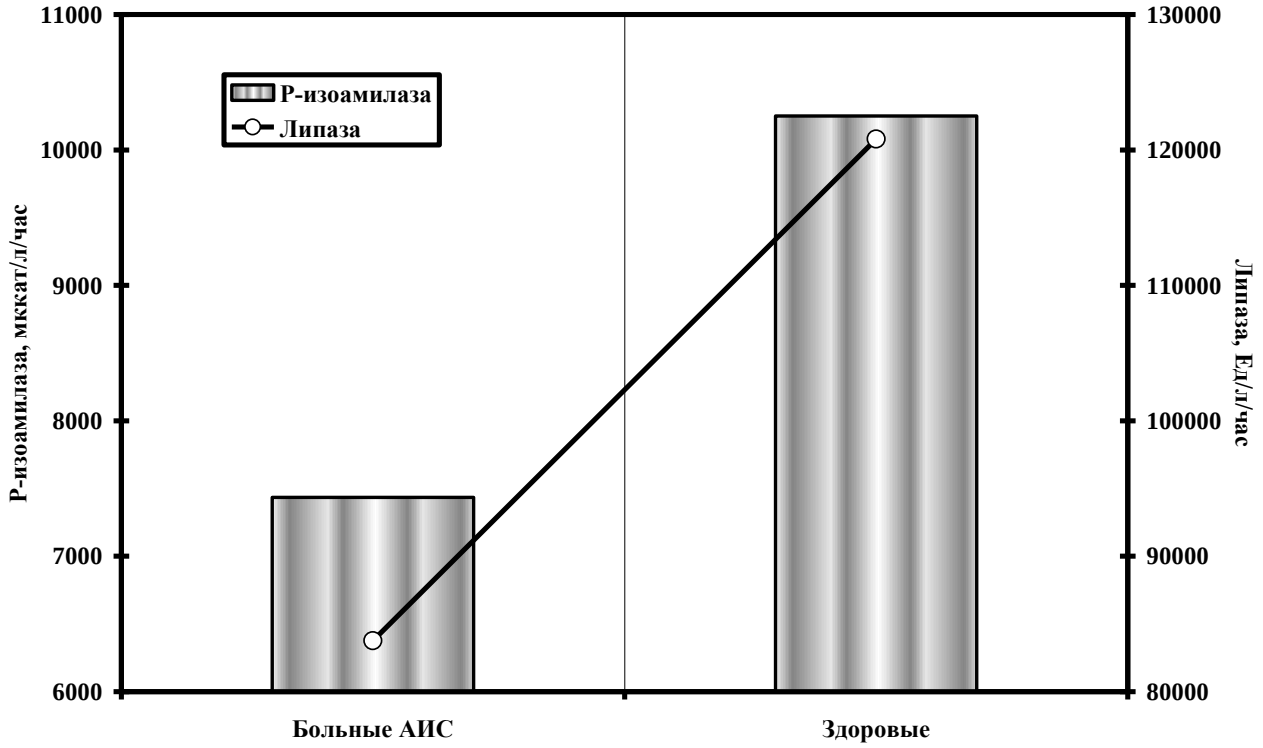

Fig. 4. Lipase and P-isoamylase debit-hour (after stimulation) in the examined AIS patients after treatment.

To assess the endocrine function of the pancreas, we evaluated the dynamics of glucose and C-peptide levels. Blood glucose level before treatment was elevated in 9

(15.0%) patients (type II diabetes was diagnosed). After treatment, index returned to norm in 7 (11.7%) of these patients, however, it should be noted that they had additional tableted hypoglycemic preparations.

Level of C-peptide in the blood of patients before treatment was significantly decreased and was 0,42±0,06 pmol/ml upon norm of 0,69±0,09 pmol/ml. During the treatment significant increase of C-peptide production to 0,58±0,05 pmol/ml ($p<0,05$) was registered.

In accordance with a decrease in pain and dyspeptic syndromes, improving the functional state of the liver and pancreas, improving blood flow in the abdominal aorta and its branches, patients noted improvement in psychosomatic status, i.e. health, activity and mood (based on questionnaire SAN) (Fig. 6).

Common outcome, confirming the effectiveness of the combination of Essentialle N and Glutargin in the treatment of AIS was the improvement of the quality of life of patients (Fig. 7).

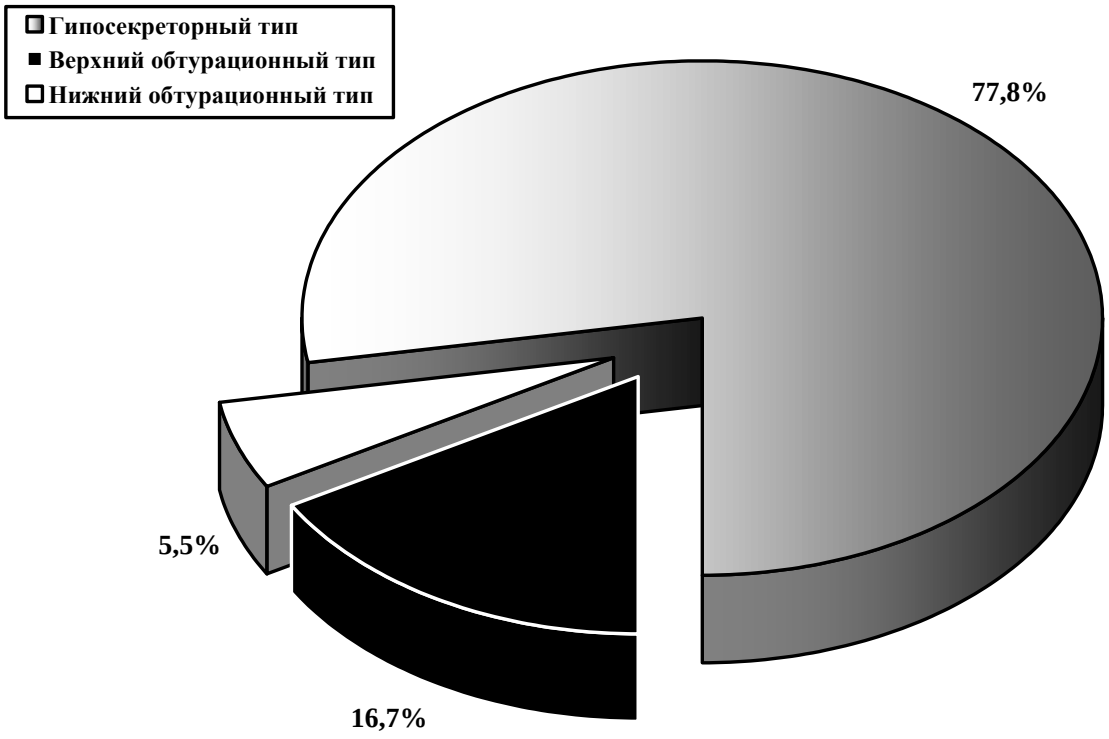

Fig. 5. Types of pancreatic secretion in patients with AIS after treatment according to the results of the probe examination.

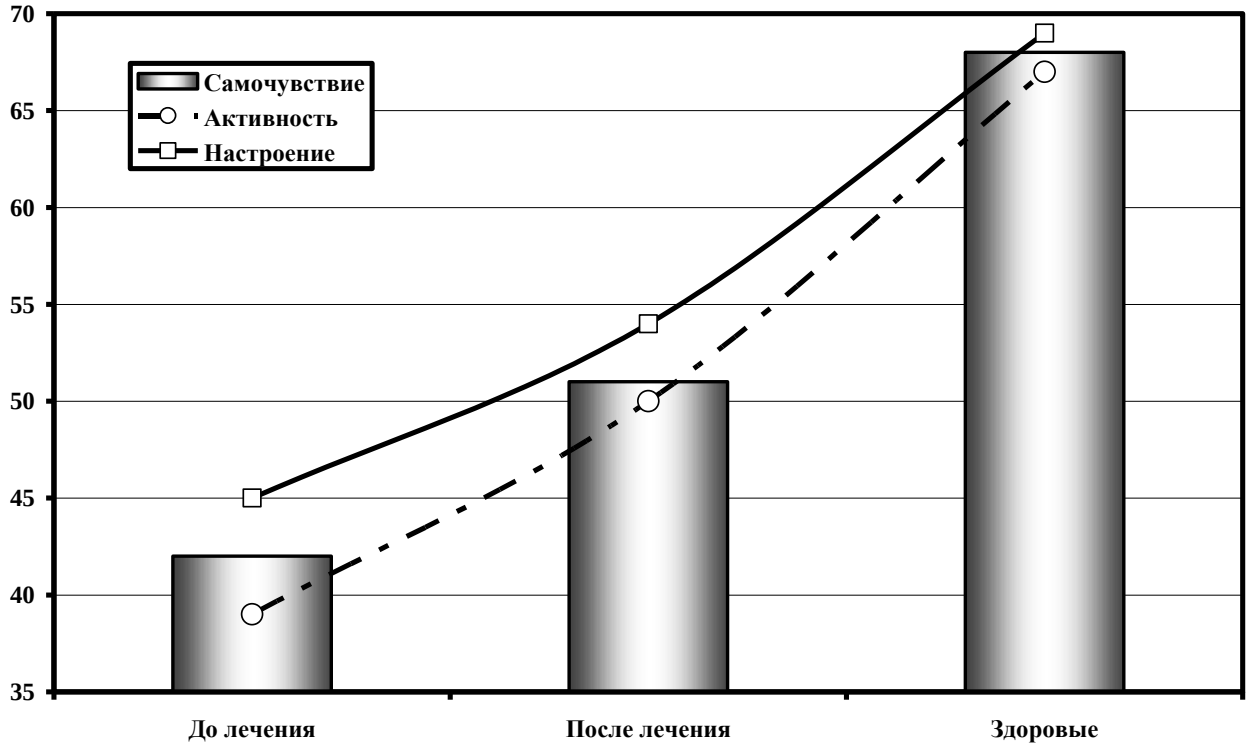

Fig. 6. Improving psychosomatic status of patients under the influence of treatment (based on a questionnaire SAN).

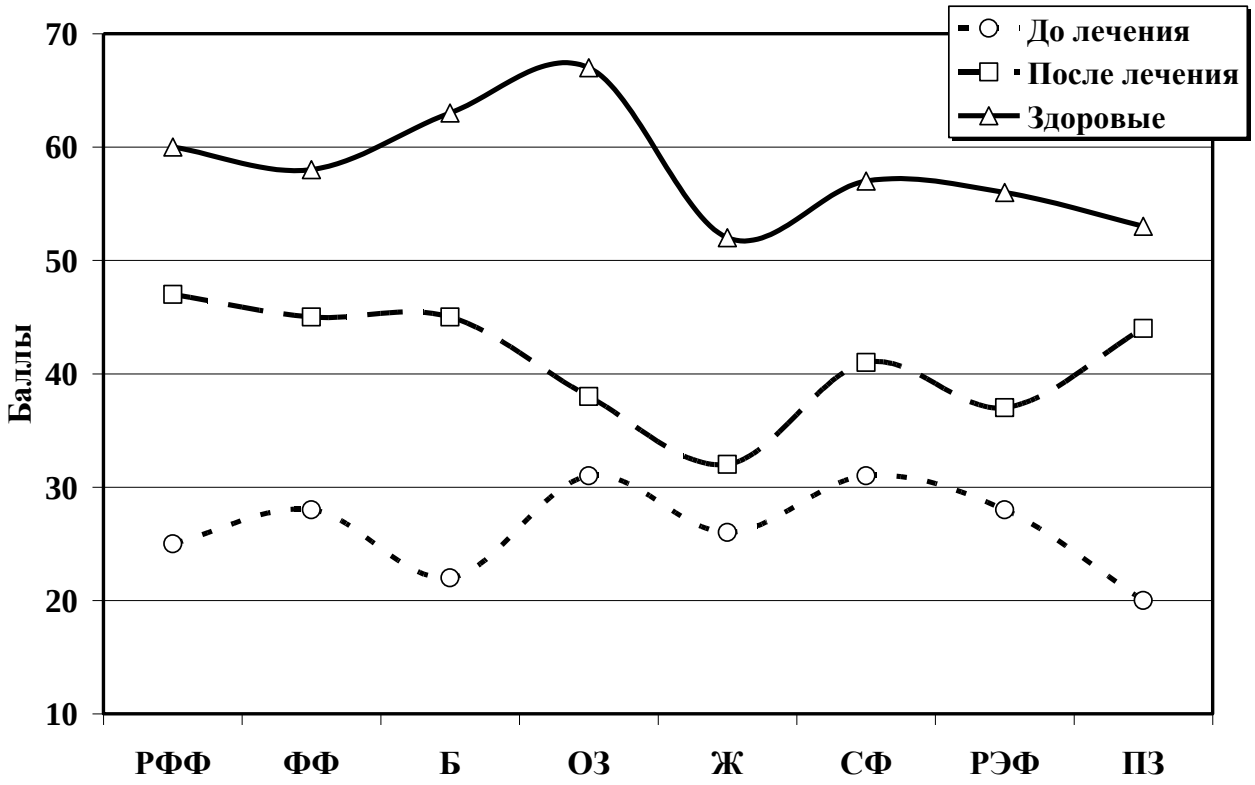

Fig. 7. Indicators of quality of life of patients with AIS before and after treatment (according to the SF-36). РФФ — role physical functioning scale; ФФ — physical functioning scale; Б — pain scale; ОЗ — general health scale; Ж — vitality scale; СФ — social functioning scale; РЭФ —role emotional functioning scale; ПЗ — psychological health scale.

Conclusions:

1. Severity of clinical manifestations of disease is significantly reduced under the influence of combined AIS therapy with Essentialle N and Glutargin H.
2. Inclusion of Essentialle N and Glutargin in the complex AIS treatment promotes correction of blood lipid spectrum, improves liver and pancreas functional state, increases levels of NO metabolites in the blood.
3. Essentialle N in combination with Glutargin improves psychosomatic status and quality of life in patients with AIS.

Prospects of research are to study the effectiveness of the combination of Essentialle N and Glutargin in treatment of digestive diseases in elderly patients, patients with lipid distress-syndrome and metabolic syndrome.

References

1. Богер М. М. Методы исследования поджелудочной железы / М. М. Богер. — Новосибирск : Наука, 1982. — 240 с.
2. Губергриц Н. Б. Клиническая панкреатология / Н. Б. Губергриц, Т. Н. Христич. — Донецк : Лебедь, 2000. — 416 с.
3. Лазебник Л. Б. Заболевания органов пищеварения у пожилых / Л. Б. Лазебник. — М. : Анахарсис, 2003. — 208 с.
4. Лазебник Л. Б. Хроническая ишемическая болезнь органов пищеварения / Л. Б. Лазебник, Л. А. Звенигородская.— М. : Анахарсис, 2003.— 136 с.

Clinical effectiveness of Essentialle N N and Glutargin combination in chronic abdominal ischemic syndrome

N. B. Gubergrits, N. G. Agapova

Donetsk National Medical University n. a. M. Gorky, Ukraine

Key words: abdominal ischemic syndrome, functional state of liver and pancreas, nitric oxide, Essentialle N, Glutargin

Authors explicitly studied an influence of Essentialle N N and Glutargin combination on manifestations of abdominal ischemic syndrome. They proved the efficacy of combined therapy regarding the decrease of clinical intensity, correction of blood lipid profile, improvement of liver and pancreas functional state. During treatment with the combination of Essentialle N and Glutargin significant increase in the level of nitric oxide metabolites in blood was reached, patients' psychosomatic status and quality of life were improved.