EFFICIENCY OF TRIMEBUTINE MALEAT IN COMPLEX TREATMENT OF CHRONIC PANCREATITIS IN CHILDREN

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Introduction. Nowadays investigators all over the world focus their attention on diagnostics and therapy of pancreatic diseases not only in adults but in children and adolescents too [1]. It is explained by increased rate of overweight adolescents, prevalence of harmful habits and non-cured diseases of upper abdomen.

In Europe spread of chronic pancreatitis in children, due to researcher's data, varies from 2 to 9 incidences per 100 000 people, aalthough in Russia it occurs only in 5 to 42 cases per 100 000 children accordingly [1]. At the same time there is a problem of differential approaches to treatment because of clinical features of pathology, condition of exocrine pancreatic function and complex mechanisms of neuro-hormonal regulation [1, 5]. In several scientific papers are mentioned neuro-remodeling qualities of vasointestinal polypeptide being implicated in control of circadian rhythm of the organism, and particularly, condition of «sleep-awakening» [6].

Hypersensitivity of m-, δ- and k-opiate receptors of encephalins makes impact in manifestation of abdominal pain syndrome in chronic pancreatitis [3]. Usage of complex spasmolytic medicine trimebutine maleat, which could cooperate with these receptors, belongs to one of appropriate ways for decrease of this hypersensitivity. However, efficiency of this medicine in modern pediatrics remains unclear [2, 4, 7].

Objectives of the research work — to study clinical and laboratory features of chronic pancreatitis in children and to estimate efficiency of the complex therapy with usage of trimebutine maleat.

Materials and methods. We have thoroughly examined 100 children aged from 7 to 18 with chronic pancreatitis. They were treated in Ivano-Frankivsk regional

children's hospital for the last three years. Diagnosis of the chronic pancreatitis is confirmed according to protocol of diagnostics and treatment, confirmed by Ministry of public health of Ukraine (Oder № 59 from 29.01.2013). 30 healthy children of the same age make a group of comparison with a purpose to study level of fecal elastase-I.

Plan of investigation includes review of anamnesis and clinical data, palpation of the pancreas by Grott (in modification, offered by Gudzenko G.P. 1980), estimation of levels of fecal elastase-I and vasoitestinal polypeptide, sonography of the abdomen with exact visualization of the pancreas. Also fibroesophagogastroduodenoscopy of the upper abdomen is preferable (apparatus Olympus, Japan).

Palpation of the pancreas, according to a method offered by Grott, is based on estimation of sizes and elasticity of the organ than the patient lies down on his back. For correct conduction of the procedure doctor uses his left hand for supporting of patient's lumbar area in such a way that his fingers are penetrating in the area between big curve of the stomach and transversal colon, reaching the spinal column. Then he slips them in from the top to deep for palpation of pancreas.

Hereby, we are able to differentiate pathology of the pancreas from other somatic diseases and avoid mistakes in clinical diagnostics.

Fecal elastase-I we detect by ELISA method (Schebo-Tech, Gissen, Germany) [40]. Normally activity of this enzyme in feces is 200 мkg/gr.

Level of vasointestinal polypeptide (VIP) hs been estimated by immunoassay method (Peninsula Laboratories. PEPTIDE ENZYME IMUNNOASSAY (EIA), USA), protocol №4 (Std.AbON.Bt)). Normal value of this polypeptide due to ths method is from 4 to 70 ng/L.

It is well known, that basic therapy of the chronic pancreatitis includes: strict diet (refuse of water and tea for 2 or 3 days, gradually application of thin gruels, soups with mucus, boiled vegetables and fruits, stewed cutlets), providing of maximal physical and psychological comfort. Broaden of the meal is undertaken 1 month later by usage of increased amount of the protein (130% from physiological needs) ad

decreased amount of the fats (80% from physiological needs). Stimulative therapy includes: antisecretory medicines (H_2-blockers) in dose from 2 to 4 mg/kg 2-3 times per day, complex antacidic medicines in dose 5 up to 15 ml 2-3 times per day in 1.5-2 hours after meal, priphinium bromide (Riabal) in dose 1 мg/kg per day. In 4-6 days, after decrease of symptoms of abdominal pain, enzymes in minimicrospheres (Creon, Pangrol) are given to the patients. Dose of these enzymes is 1 capsule 2-3 times per day after meal, and it might be given since signs of pancreatic insufficiency should disappear.

According to objectives of investigations, sick children were distributed in two groups. Patients of the main group (50 children) received in complex therapy of chronic pancreatitis medicine Tribudat (trimebutine maleat), «Amoun Pharmaceutical Co. SAE» Egypt (Registration certificate № UA/9496/03/01) in dose 40 мg (2 teaspoons) 3 times daily per os. The course of therapy is 1 month.

50 children of comparison received only basic therapy of the chronic pancreatitis according to modern protocol.

Statistic data, particularly Pearson correlation coefficients, middle arithmetical mean were obtained by usage of computer program Statistic 7.0.

Results and its discussion.

Prevalence of girls is noticed among examined children (75.0% and 25.0%, $p<0.05$). Duration of the disease, before admission to the hospital, is from 1 to 5 years. At the same time, only 30% of he patients were treated in a hospital before. Mainly they accepted enzymes, antacids and painkillers by themselves, without supervision of medical personnel. Moderate to severe course of the disease is confirmed in 65.0% of the patients, and severe course is verified in 35.0% of the sick children accordingly.

During acquiring the anamnesis, we have improved prominent risk factors of chronic pancreatitis in children, such as: disorders of the diet (68.0%), exacerbation of the chronic cholecystitis and dysfunction of Oddi's sphincter, pancreatic type (65.0% and 50.0% of incidences, $p>0.05$), rarely -obesity and low physical activity (40.0% and 35.0% incidences, $p>0.05$). Viral infections, first of all, virus of the

chicken pox and rubella, are noticed in anamnesis of 10.0% of children with chronic pancreatitis.

Among the features of chronic pancreatitis there are: attacks of spastic abdominal pain like «half of the belt» (78.0 %), nausea, which do not depend on food consumption (65.0 %), vomit with admixtures of the bile without subsequent relief (45.0 %), also stool violations, like diarrhea (30.0 %) or constipation (15.0 %).

Significant features of the abdominal pain syndrome are as follows: frequent attacks (with duration few hours per day), which could have intensive character with irradiation to the back. In 80.0% of cases, few nutritive factors like consumption of stewed cabbage, preserved food and sweets with cream, contribute into intensity of abdominal pain. In 25.0% of the patients with peak attacks of abdominal pain at the background of the hyperacidity, are observed.

In patients under our supervision we do not see somatic abdominal pain. It could be explained by compensatory capacities of the pancreatic functions in children's age and more late involvement of peritoneum in pathological process.

In majority of examined children with pancreatic pathology are seen signs of asthenia: general weakness (90.0%), increased fatigue and headache (85.0% and 78.0% of cases, $p>0.05$). Violations of sleep pattern, especially fall into sleep (65.0%), as a result of expressed abdominal pain, are seen also.

Among concomitant pathology in children with chronic pancreatitis there are: chronic cholecystitis, without gall stones, and gastroesophageal reflux disease (85.0 % and 75,0 % of cases, $p>0.05$).

Making complete physical examination, we have noticed that painful symptoms in certain specific pancreatic zones are present. For instance, pain in Shoffar-Ruvje zone is observed in 44.8% of cases, expressed positive symptoms of Mayo-Robson and De Garden are noticed less common (in 37.9 % and 34.5% of cases accordingly, $p>0.05$). Extreme tenderness of the abdominal muscles ("locus minoris resistencia") is not seen at all, which indicates late development of the complications and enough capacity qualities of the pancreatic gland as it was confirmed earlier.

Functional state of exocrine pancreatic insufficiency in children with chronic pancreatitis we have studied by detection of organic-specific enzyme — fecal elastase-I, presented in table 1.

Table 1

Levels of fecal elastase-I in children with chronic pancreatitis, depending on course of the disease, n=100 (M±m)

Course of the chronic pancreatitis/number of the patients	**Content of fecal elastase-I, мkg/g**
Moderate to severe course, n=65	166,0±0,2*
Severe course, n=35	135,0±0,1*
Healthy children, n=30	199,0±0,1

Note: * — significant difference between indexes of the fecal elastase-I in children with chronic pancreatitis and in healthy ones, $p<0.05$

Analysis of received data exposed presence of expressed exocrine insufficiency of the pancreas in children with severe course of the chronic pancreatitis, compared to healthy ones (135.0±0.1 and 199.0±0.1 mkg/gr), $p<0.05$.

Results of sonographic examination of the pancreatic gland in 70.0% of cases revealed presence of slight hyperechogeny like spots and triangles of fibrosis underneath parenchyma. Also mild enlargement of the main pancreatic duct in children with chronic pancreatitis in comparison with normal values is verified in 50.0% of cases.

Diagnosis of concomitant pathology we determined due to typical ultrasound symptoms of the diseases: presence of biliary sludge at the cavity of the gall-bladder (75.0 %), echo-positive admixtures in tissues nearby (68.0 %), Thickening of the walls of the gall-bladder and biliary tract up to 2 or 5 mm (45.0 %).

Appearance of the reflux is indicated by endoscopic data: bile admixture in content of the stomach (68.0%), increased retrograde peristalsis (60.0%), signs of erosive esophagitis (50.0%), prolapsed cardiac sphincter (45.0%).

Symptoms of erosive duodenitis are seen in 5.0% of cases, edema of the duodenal sphincter and several leaks of greenish bile because of ceased flow of the bile are noticed (30.0%).

We found out level of vasointestinal polypeptide and its dependence on the functional condition of the gastrointestinal tract, which is represented in table 2.

Table 2

Level of vasointestinal polypeptide in children with chronic pancreatitis due to endoscopic data, n=100

Endoscopic changes	**Number of patients Absolute number/percentage**	**Level of vasointestinal polypeptide, ng/l**	
		M	**±m**
Superficial changes of upper abdomen	30 (30,0%)	4,40	0,1
Erosive changes of upper abdomen	50 (50,0%)	2,15	0,3
Duodenitis	45 (45,0%)	1,22	0,1
Hypertrophic changes	20 (20,0%)	4,48	0,2
Content of the stomach and esophagus			
Pus with bile	68 (68,0%)	4, 35	0,2
Mucus with chloric acid	32 (32,0%)	2,27	0,1
Prolapsed cardiac sphincter	13 (26,5%)	2,29	0,2
Increased retrograde peristalses	60 (60,0%)	2,22	0,1
From the esophagus to the stomach	12 (25,5%)	3,43	0,1
From the duodenum to the stomach	14 (28,6%)	1,28	0,1
Prolonged spasm of the duodenal sphincter	23 (46,9%)	1,32	0,1

Results of the investigation verify decreased level of the VIP in children with erosive changes in upper abdomen (2.15±0.3 ng/l), also in children with insufficiency of the cardiac sphincter of the esophagus (2.29±0.2 ng/l). Direct correlation link is found between level of VIP and superficial changes of the upper abdomen (r=+0.5818), as well as indirect correlation link between level of VIP and erosive changes of the stomach — r=-0.6098.

We must admit that the deficit of the VIP is the promoted trigger factor for the development of hyperacidic “aggression”.

In 25.0% of the patients with chronic pancreatitis and violations of the sleep pattern we found out decreased level of vasointestinal polypeptide: from the 4,61±0,1 of the predicted values up to 2.01±0.1ng/l, $p<0.05$).

In a matter of fact, levels of neuropeptide and fecal elastase-I are decreased: level of VIP is 2.49±0.1 ng/l and level of fecal elastase-I remains 166.0±0.2 мkg/gr., which reveals inhibition of secretine-like effect of neuropeptide in children with chronic pancreatitis (r=-0.088±0.15).

Efficiency of the proposed therapy we estimated according to positive dynamics of the clinical symptoms, mainly of abdominal pain syndrome (fig.1).

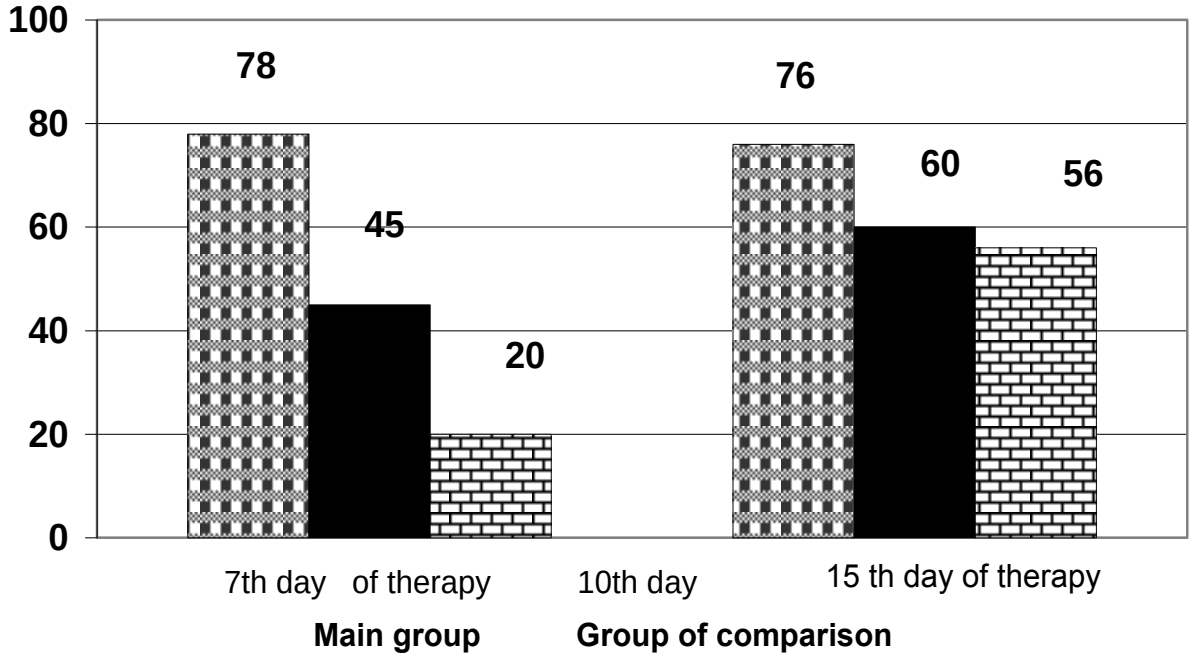

Fig.1 Dynamics of the clinical displays of the abdominal pain in children with chronic pancreatitis under proposed therapeutic scheme, n=100.

Data fixed on a figure above improves diminished signs of the abdominal syndrome in a main group up to the 7 th day of therapy. Results of the investigation showed presence of discomfort in upper abdomen in 25.0% of the patients.

In comparison to the data of control group signs of abdominal pain are registered in 60.0% of cases during first week of hospital treatment with tendency to decrease.

Dynamics of the dyspeptic symptoms is represented on figure 2.

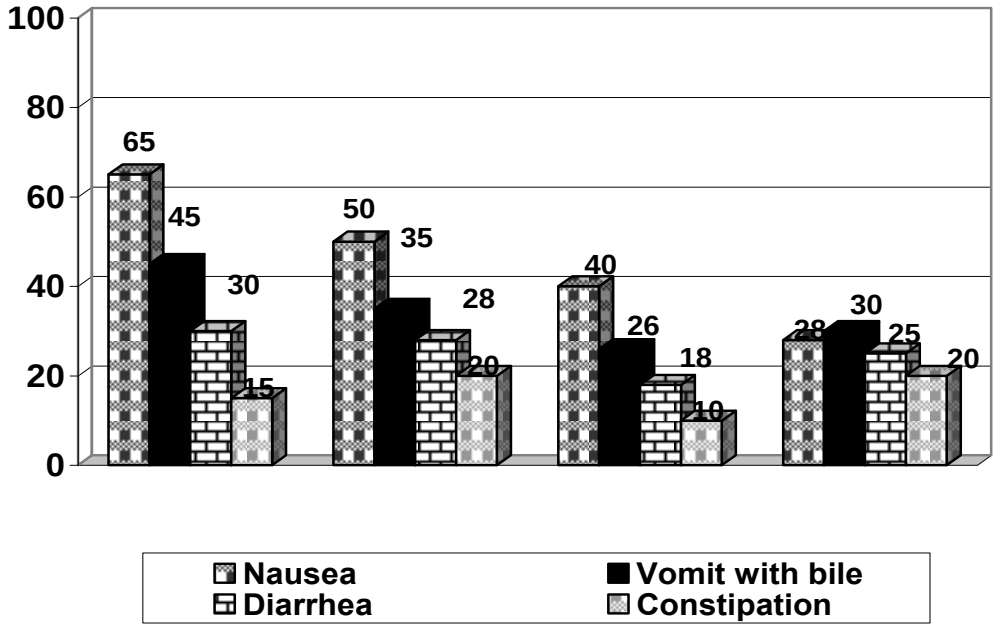

Fig. 2. Dynamics of clinical displays of dyspeptic syndrome in patients with chronic pancreatitis under the proposed therapeutic scheme, n=100.

Data, represented above, shows improved decrease of the main abdominal symptoms of the pancreatic pathology during first 10 days of treatment in a hospital, although in patients of control group this dynamics is seen on 14^{th} day of therapy accordingly.

In 30.0% of cases few dyspeptic symptoms, for example, vomit with bile admixtures, are still common even at the second week of the therapy in a hospital.

In 70.0% of children with chronic pancreatitis with violations of the sleep patterns, besides diminished symptoms of the abdominal pain, general physical condition and self-feeling became better as well. Thus nobody among children, who receives only traditional medicines, manifests with improvement of his health, mainly in a response to painful feelings in the area of the pancreas.

Improved process of falling asleep in children of the main group with chronic pancreatitis is also accompanied by increased level of VIP (from 2.01±0.1 ng/l to 4.02±0.3 ng/l, $p<0.05$).

It is a known fact that VIP creates associative connections between cells of the brain at this area of suprachiasmatic nuclei, which are responsible for regulation of the circle «Sleep-awakening» [6]. From the other point of view, in our investigation we didn't find exact correlation between level of VIP and changes in qualities of the sleep pattern. Represented dynamics of the level of neuropeptide much over is explained by regress of the intensive abdominal pain, which has moderate impact on the sleeping pattern also.

Due to our investigation, level of vasointestinal polypeptide in patients of the main group with erosive changes in upper parts of the digestive tract, up to the end of the first week became higher than recently (from 2.15±0.2 up to 4.05±0.1 ng/l, $p<0,05$). Suppressed retrograde peristalsis is accompanied by increased level of VIP (from 2.22±0.1 up to 3. 45±0.1 ng/l, $p<0,05$).

In general, we have to consider, that during clinical examination of the patients, positive compliance between patients and their doctor is achieved. No side-effects or unlike actions of trimebutine maleat in children with chronic pancreatitis are not present.

Conclusions. All mentioned above improves high therapeutic efficiency of trimebutine maleat in complex treatment of neuro-hormonal disorders, which are seen in children with chronic pancreatitis. Application of the medicine in therapeutic scheme facilitates more quick recovery, normalization of fecal elastase-I and vasointestinal polypeptide levels, making shorter terms of hospitalization. In such a matter, medicine could be used in complex treatment of chronic pancreatitis in children.

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In the article clinical picture and laboratory findings of chronic pancreatitis in children, and its correction with application of trimebutine maleat are described. It is proved that prominent risk factors of development of chronic pancreatitis due to anamnesis include: violations of diet (68.0%), exacerbations of chronic cholecystitis and dysfunction of Oddi's sphincters of pancreatic type (65.0% and 50.0% accordingly), rarer — obesity (40.0%) and low physical activity (35.0%). Among main clinical symptoms of chronic pancreatitis there are the following ones: attacks of spastic abdominal pain like a «half belt» (78.0%), nausea (65.0%), vomit with bile admixtures, which don't relief patient's state (45.0%), general weakness (90.0%), fatigue (85.0%), and headache (78.0%). Pancreatic insufficiency in patients with moderate to severe and severe course of the disease is estimated. Level of vasointestinal polypeptide is decreased upon erosive lesions of upper abdomen (2.15±0.3 ng/l) and insufficiency of cardiac sphincter in gullet (2.29±0.2 ng/l). Connection between decreased levels of vasointestinal polypeptide and fecal elastase-1 is found. Usage in therapeutic scheme of trimebutine maleat, like a regulator of motility function of the stomach, implicates regress of clinical manifestations of the disease and normalization of paraclinical indexes being able to improve quality of life of patients.