Modern opportunities of pharmacotherapy of chronic pancreatitis

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The pancreas is beautiful and calm, like a sleeping black panther... But wake her up and she will show you her insidious temper.

A.I. Apricot (1875-1955)

Key words: chronic pancreatitis, etiology and pathogenesis, clinical manifestations, diagnosis, treatment

Definition. Chronic pancreatitis - CP is a multifactorial group of pancreatic diseases, mainly of inflammatory nature, characterized by a phase-progressive course with episodes of acute pancreatitis responsible for recurrent pain, with focal, segmental and / or diffuse lesions (necrosis) Its parenchyma (acinar and islet cells), followed by their replacement with connective (fibrous) tissue, changes in the duct system of the pancreas, the formation of cysts, pseudocysts, calcium ifikatov and stones and development for a number of years of progressive exocrine and endocrine pancreatic insufficiency [8, 11].

Prevalence. The frequency of CP is difficult to establish, since in the initial stages it can proceed little or even latently. According to various data, its frequency varies from 0.2 to 0.68% (45.5 per 100,000 of the population among men and 12.4 per 100,000 from women). At autopsy CP detected in 0,04-5% dead [4].

The clinical course of CP - is steadily progressing. Mortality was 20% in the first 10 years and 20-25 years reaches 50% [20].

The etiology and pathogenesis of CP different variety. According to the International Classification of Diseases and Related Health Problems, the WHO 10th revision (ICD-10, 1995) distinguishes between alcoholic etiology (code K86.0) and other cases of unspecified etiology (cipher K86.1).

In 2001 it was published etiologic classification of CP, designated the abbreviation «TIGAR-O" - the initial letters of the etiological factors allocated by it [22].

T (toxic-metabolic) - toxic-metabolic KP.

I (idiopathic) - idiopathic CP.

G (genetic) - hereditary CP.

A (aytoimmuna) - autoimmune KP.

R (recurrent and severe acute) - KP recurrent and severe acute pancreatitis.

About (obstructive) - obstructive CP due to violation of the outflow of pancreatic juice.

In 2007, a group of German pancreatology developed and published a new International Classification of CP named «M-ANNHEIM system" - also on the initial letters of the main etiologic (or pathogenic) factors [33].

M (multiple) - indicates a multiplicity of etiologic factors.

A (alcohol) - alcoholic KP.

N (nicotine) - KP caused by smoking tobacco abuse.

N (nutrition) - KP due nutritional factors.

H (heredity) - hereditary KP.

E (efferent pancreatic duct factors) - KP induced pancreatic ductal patency violation.

I (immunological factors) - KP caused by immunological factors.

M (metabolic factors and miscellaneous) - CP associated with metabolic and other risk factors. **Clinical symptoms of CP.** The main and most painful for patients with CP is abdominal pain syndrome - recurrent or

(rarely) permanent, which significantly reduces the quality of life. In intensity, it does not concede pain in acute pancreatitis, it is localized in the epigastric region with irradiation predominantly posterior to the spine (in 71.2% of cases), less often in the form of a left-sided half-belt (16.8%) or shingles (12 %).

As the precipitating factors of pain often perform: receiving abundant fatty meal (34%), alcoholic drinks and carbonated (19%) [4, 11, 20].

Dyspeptic syndrome is characterized by nausea and vomiting (56.8%), decrease of appetite, anorexia up to (B X Vasilenko:.. «Anorexia pancreatica» [2]) - 27.3%, flatulence (29.5%) and progressive siruyuschim weight loss (19%) [18, 28].

Developing in the late stages of progression of CP, exocrine pancreatic insufficiency is manifested by syndromes of maldigestia and malabsorption, diarrhea, steatorrhea, and growing weight loss.

Basic CP complications formation of retention cysts and pseudocysts postnecrotic RV calcifications (often with alcohol and hereditary CP associated with a mutation of the gene PRSS1, as well as tropical CP - kwashiorkor); The formation of concrements (especially often localized in the main - the Virsunga - duct) and adenocarcinoma of the prostate that develops most often with hereditary CP from the epithelium of the protocol.

Diagnosis is based on the use of **CP,** in addition to clinical symptomatology, imaging prostate instrumental and laboratory functional tests and histological study of prostate tissue obtained by sighting needle biopsy (diameter 25G needle) under ultrasound (EUS).

For visualization of the prostate are used: ultrasonography (US), preferably endoscopic ultrasonography (EUS) using Rosemont criteria [35], computed tomography (CT), magnetic resonance imaging (MRI T), including the stimulation ekzosekretsii pancreas secretin, Allowing to determine quantitatively the secretion of the prostate; Magnetic resonance cholangiopancreatography (MR-CPH) facilitates visualization of the pancreatic duct and endoscopic retrograde cholangiopancreatography (ERCP), and other instrumental methods of diagnosis [9, 23].

From *laboratory functional tests* are most useful: secretin-pankreaziminovy test Direct determination of the duodenum amount of pancreatic juice, bicarbonate alkalinity, and its enzymatic activity fasting and in response to stimulation of the secretin and cholecystokinin-pancreozymin (CCK-PZ); determination of fecal elastase-1 and serum trypsin [9, 23].

When *endocrine* pancreatic *insufficiency* in patients with CP reduced insulin production and hyperglycemia develops.

Thus, *instrumental pancreatic imaging techniques* in CP allow detailed consideration caused change in the prostate tissue and its ductal system, including the presence of ductal adenocarcinoma, detect retention cysts and Postnecrotic pseudocyst, strictures, calculi and calcifications, although their level of sensitivity and especially - not specifically Always high enough.

Laboratory tests allowed to assess the condition of specimens o- and endocrine pancreatic function in CP determine hydrochloric bicarbonate alkalinity and enzymatic activity of pancreatic juice [9, 23, 25, 37].

Pathogenesis of pain in CP. Until recently, the main cause of the onset of pain in patients with CP was considered to be increased pressure in the pancreatic duct system (intraductive hypertension), both due to their obstruction (stricture, calculus) and ischemia, which develops as a result of the formation of inflammatory infiltrates in the prostate tissue accompanied by edema and impaired Microcirculation.

An important role in increasing the pressure in the pancreatic ducts also belongs excessive formation of pancreatic secretion rich in enzymes and bicarbonates (secretory voltage RV), mainly in the initial stages of the CP [4, 11, 23].

Recently, however, hyperalgesia in CP are associated with exposure of the pathological process in the pancreas on nociceptive neurons localized in pancreatic tissues that undergo sensitization under the influence of surrounding inflammatory infiltrates, interact with nociceptive neurons of the spinal cord in violation of their functions, and then with nociceptive neurons in the brain involving the limbic system and somato-sensory formations, causing the patients perception of pain and the emotional response (suffering) [23, 28]. Therefore, the treatment of pain syndrome in CP should not be limited to reducing hypertension in the pancreatic duct system, but also combined with the impact on the nociception system at different levels.

Treatment of CP. *Pharmacotherapy CP patients* differs fundamentally in its initial stage, characterized by hypersecretion of pancreatic juice with a high content of bicarbonate and enzymes, where the clinical picture is dominated by intense abdominal pain syndrome, and in the final stage, when prevalent symptoms copies o- and endocrine pancreatic insufficiency, and pain often absent.

To begin treatment it is necessary with a full refusal from the use of any alcoholic drinks, including beer, and the cessation of smoking of tobacco. This is a prerequisite for the effectiveness of treatment, a sustained pro gressirova Nia disease, prevents the development of complications of CP and prolongs life.

The most important task of pharmacotherapy CP - pain relief or significant reduction of its intensity. It is the pain syndrome that causes the most pronounced decrease in the social function of patients, the quality of their life and work capacity.

With moderate pain syndrome can be achieved obezboliva guide effect without the use of analgesics.

2 treating method it has been proposed that provide *functional rest pancreatic ductal and reducing hypertension (secretory voltage RV).*

1. Ingestion of high doses of encapsulated formulations of modern multienzyme GIZH containing enteric minimicrospheres with high enzymatic activity (lipase - 10-25 thousand ED Ph Eur, amylase -... 8-18 thousand ED, protease -. 1000-1600 ED), - *preparations. Creo n, ermital, pantsitrat, pankre aza, ultresa* et al Proceeding from the stomach into the duodenum, they cause a depression ekzosekretsii RV due to the reverse braking phenomenon (this - duodeno-pancreatic autoregulatory loop) and fracture releasing peptides responsible for Obra mations intestinal hormone secretin and CCK-PZ stimulating active ekzosekretsiyu pancreas, and thereby reduce the volume of pancreatic juice and intraductal hypertension [12, 25, 37].
2. *Use of inhibitors of protonic Pump (IPP) - omeprazole, rabeprazole, esomeprazole* and etc. in order to maximize the suppression of acid secretion in the stomach, since it is the hydrochloric acid of the gastric juice entering the duodenum, secretin stimulates the formation and CCK-PZ, causing the formation of amplification pancreatic secretion and enhancing its ductal hypertension system [12, 29].
3. We propose another method of treatment of moderate pain in CP - appointment *of octreotide* - synthetic somatostatin analogue that inhibits the formation of intestinal hormone secretin and CCK-PZ, which stimulate the pancreas ekzosekretsiyu. In addition, octreotide enhances the formation *of endogenous morphine - Endorphin and enkephalin* possessing analgesic properties and have a positive influence on the general adaptation syndrome [12, 14, 23, 34].

With the lack of effectiveness of the analgesic effect of these treatments *there is a need in the use of analgesics, usually from the group of opioids.* Thus the risk of abuse of drugs reaches 20%, it being borne in mind that most prone to drug CP patients previously abuse alcohol and smoking [23, 27].

According to our observations, when analgesia KP best achieved appointment *tramadol hydrochloride (Tramal)* - non-selective agonist of the mu, delta and kappa opioid receptors. Tramadol is administered parenterally, orally, as well as in the form of rectal suppositories in doses: tab. 150-200 mg twice a day; Solution for injection - in amp. 2 ml (100 mg) subcutaneously, intramuscularly or intravenously; Rectal suppositories - 100 mg each. Sometimes anesthesia require higher doses of tramadol [12, 23, 30].

Other analgesic same group - *FORTRAN* (pentazocine) is an agonist of a kappa opioid receptor and an antagonist of mu receptors. It is prescribed in a dose of 30-60 mg intramuscularly. Unlike morphine, these opioid analgesics do not inhibit the respiratory center and less often cause drug dependence.

Recently it has been proposed combined analgesics: *Zaldiar,* further comprising *paracetamol* (37.5 mg tramadol + 3.25 mg paracetamol) and *betamethasone* (diprospan), which further included *prednisolone* providing peripheral pain blockade mechanism that breaks *"vicious circle": "pain - muscle spasm - pain"* [1, 3].

To increase the analgesic effect of *adjuvant* used *(support) therapy,* complementary effect of opioid analgesics:

1. Tricyclic, bicyclic and monocyclic antidepressants;
2. antioxidants, and - *gabapentoidy* [11, 12, 23].

From antidepressants - selective serotonin reuptake inhibitors - used most often *tsipramil* (citalopram) 20 mg / day. in one portion, and *fluvoxamine* (Luvox) - 12.5 mg / day.

Pain vysokokomorbidna with mental depression. There was even a proposal to allocate a single syndrome "pain - depression," because in the formation of pain are involved, in addition to peripheral painful stimuli, psychological factors: anxiety and depression [6, 13].

Antioxidants can reduce the intensity of pain, reducing the activity of free radical oxidation of lipids (SROL) and enhancing the antioxidant activity (AOA) of blood [15, 24, 32, 36]. Thus, according to GD Costano data [36] and P. Bhard way et al. [32] marked analgesic effect is distinct complex antioxidants (Betamore drug), which comprises: organic selenium (600 mg) + ascorbic acid (0.54 g) + β - carotene (9000 ME) + α - tocopherol (270 ME) + L- methionine (2 g). Taken daily for a long time.

It may also be assigned *ANTIOXICAPS* antioxidant containing organic selenium (15 mg) + ascorbic acid (100 mg) + α-tocopherol acetate (30 mg) + β-carotene (20 mg). It is taken 1 caps / day after meals for 2-3 months. Particularly effective antioxidants when pain syndrome in patients with CP who do not consume alcoholic beverages and non-smokers [24].

From the newest means of pain relief in CP should be called *gabapentoidy* affecting nociceptive neurons at different levels - local, regional and central [23]. Of this group farmakopreparatov in the treatment of pain in CP patients was studied in a randomized, controlled trial only *pregabalin* received an oral dose of 300 mg of 2 times / day. long. It effectively suppresses the pain and can significantly reduce the dose of opioid analgesics [31]. Of the side effects of pregabalin point of dizziness and *a kind of "feeling drunk"* [23, 31]. Regarding its mechanism of action, it is established that it inhibits the predominantly central sensitization somatosensory brain formations [31].

For potentiating the analgesic effect is provided, in addition, *clonidine*, stimulating postsynaptic (α_1 adrenoceptor (agonist is α_1 -adrenoceptor), which acts on the central mechanisms of pain perception [1, 3, 6]. It is administered in a dose of 150 mg intramuscularly or Intravenously with the transition to oral administration - 37.5-75 mcg 3 times / day.

Using these farmakopreparatov with pain syndrome in patients with CP allows it to stop or reduce its intensity.

Exocrine pancreatic insufficiency usually develops after 5 - 10 years after the beginning of the CP and proceeds with syndromes *maldigestion* and *s small* absorption, characterized by diarrhea, steatorrhea with copious stool gray brilliant containing a large amount of fat and a very unpleasant smell (so-called *"Pancreatic* chair"). In patients with impaired bone metabolism with the development of osteoporosis, as well as develop mineral and vitamin deficiency; progressively reduced body weight.

The severity of exocrine pancreatic insufficiency determined by laboratory tests X: level fecal stasis ela-1 (<200 ug / g of faeces) and / or of serum trypsin (<20 ng / ml). In addition, the body mass index is determined (it progressively decreases); clinical and biochemical laboratory parameters (leukocytosis and a left shift in leukocyte formula, erythrocyte sedimentation rate increasing; hypoalbuminemia, hypocalcemia, deficiency of fat-soluble vitamins: A, D, K and E).

The main method of treatment of exocrine pancreatic insufficiency in patients with CP is a replacement therapy *polyfermental farmakopreparatami* containing pork pancreatin. Of the drugs in this group received the highest recognition *kreon* discharged in the form of enteric capsule containing mini - microspheres with basic enzymes of pancreatic juice - lipases, amylases and proteases. *Calculation of the dosage normally produce lipase content* which must be not less than 40 - 50 thousand. USP (90 th. USP) at every meal. Creon should be taken at the time and after the meal.

Besides Creon may be used and other polyenzyme preparations : *ermital, mikrazim, pankreaza, ultresa* and others.

About *the effectiveness of substitution treatment* is judged on the basis of reduction of diarrhea, steatorrhea, build-up weight of the body.

As an *adjuvant (auxiliary) treatment* is used *tseruletid-decapeptide* in dose 2 ng / kg weight body / min - intravenous drip in over 1 - 3 hours, which stimulates ekzosekretsiyu preserved tissue pancreas [11, 12].

Complication KP osteoporosis, boosting the risk of fracture of bones, necessary appointment preparations, containing calcium and fat-soluble vitamin D. It is possible to recommend acceptance *kaltsiya- D* $_3$ *- Nycomed,* regulating calcium and phosphorous exchange. It contains 200 ME kolekaltsiferola and 1.25 g of calcium carbo nata. Kaltsiya- D $_3$ - nikomed increases the density of the bone tissue and compensates deficiency of calcium and vitamin D 3 in the body. Dose: 1 tab. morning and evening, during a meal, for a long time.

When the development of *endocrine insufficiency of the pancreas* in patients with CP observed clinical symptoms of diabetes mellitus, and there is *a need for insulin therapy*. When it is marked not only the deficiency of insulin, but and glucagon, as well as pancreatic polypeptide. Complication KP sugar diabetes increases the risk of pancreatic cancer [10, 19].

In milder cases are diagnosed impaired glucose tolerance. Recognize diabetes based on increase in blood glucose n atoschak (> 126 mg / dl), and also the two-hour test on tolerance to glucose (> 200 mg / dl).

Treatment of diabetes in patients with CP should be carried out under the supervision of an endocrinologist, since during insulin therapy is a risk of hypoglycemic states [19].

Recently there was a treatment recommendation complement CP purpose prebiotic formulation *eubikor* - 2 sachet 3 times a day (6 g / day) in over 4 - x weeks, which provides corrected disorders microbial-tissue complex and normalization functions intestine [5].

It requires a special approach for treating autoimmune CP. To distinguish between 2 serolo cal type of autoimmune CP :

1. *limfoplaz motsitarny sclerosing pancreatitis* (IDL) or autoimmune pancreatitis without granulocyte epithelial damage (GEO), which is characterized by a dense lymphoplasmacytic yn filtration localized predominantly in periductular zones pancreas, and specific moire forme sclerosis and Lim foplazmotsitarnym venulitom with obliteration affected veins and a significant increase in the number (more than 10 in view) IgG4-transitivity of plasma cells;

2. *idiopathic proto kovo-concentric pancreatitis* (IPKP), or idiopathic ductal pancreatitis (IPP) with granulocyte- epithelial lesions (GEO) [7, 16, 26].

Clinically 1- th type - a systemic disease process, which often occurs with obstructive jaundice, and with the involvement of other organs pathological process (bile duct, lung, kidney, salivary glands). The second type of autoimmune CP - a specific disease, occurring without vnepankreaticheskim lesions [16].

Effective treatment of both autoimmune KP types are *corticosteroids*, particularly *prednisone* at a dose of 0.6-1.0 mg / kg body weight / day. You can also use metipred and budesonide. When time begun treatment, they are able to prevent the development of exo-and endocrine pancreatic insufficiency [7, 17, 23].

In case of insufficient effectiveness of the pharmacotherapy KP using *endoscopic therapy and / or surgical treatment.*

Endoscopic therapy allows to eliminate the obstruction in the ductal system of the pancreas at CP, caused by stricture of the main (Wirsung) pankreaticheskog of the duct or calculus, races put in the pancreatic head. For this purpose, use pancreatic and biliary *sphincterotomy* ; *stenting* main duct pancreas, as well as *extraction of the concretion* and *extracorporeal shockwave lithotripsy*, which is effective in 69 % of cases [21]. After fragmentation to onkrementov via litotrip these their small fragments are removed from the duct with the help of ERCP.

Another method of endoscopic therapy: pharmacological blockade of the nerves to the pancreas under EUS control tissue using anesthetics and corticosteroids, administered in the pancreas [21].

CP patients who do not respond to pharmacotherapy and endoscopic treatment *are subject to various* embodiments of the surgical intervention, but they represent only a limited number of patients.

Despite some advances pharmacotherapy, CP still remains steadily progressing and so far incurable disease.

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Modern opportunities of pharmacotherapy of chronic pancreatitis

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Key words: chronic pancreatitis, etiology and pathogenesis, clinical manifestations, diagnosis, treatment

The lecture presents the current definition and classification of chronic pancreatitis, its prevalence, etiology and pathogenesis, clinical picture, diagnostics. Special attention is paid to the treatment, particularly medical one. Pain relief, principles of enzyme therapy, treatment of pancreatogenic diabetes are discussed in details. Indications for endoscopic and surgical interventions are noted.