ISSN
0975-2366

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH

VOLUME 11, ISSUE 1, JAN - MAR, 2019

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Pharmacological evaluation of the efficacy of metabolic drugs for acute biliary pancreatitis

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Received: 30.03.19, Revised: 30.04.19, Accepted: 30.05.19

Abstract

Rate of acute pancreatitis is up to 40 cases per year per 100,000 adults, while about 10-15% of patients have severe forms of this disease, among which the mortality rate reaches 80%. Aim: to experimentally evaluate the pharmacological efficacy of the combined use of drugs (immunomodulators, antioxidants and membrane protectors) in acute biliary pancreatitis with a high degree of severity. A laboratory rat population was used for the study. 210 animals were divided into 3 groups. Group 1 did not receive any drugs, group 2 received a combination of ferrovir, mexidol and phosphogliv, and group 3 received a combination of polyoxidonium and Essentiale N. Before and after the administration of drugs combination, the indicators of the immunological status and parameters of the oxidative system were evaluated. Combination of ferrovir, mexidol and phosphogliv with mild pancreatitis corrects 12.0% and normalizes 75% of the studied laboratory immune and oxidative indices, respectively. With a moderate degree of pancreatitis, these indicators were 19.2% and 45%, and with a severe degree, corresponding to the control values. For group 3, drug combination leads to normal laboratory values of immune and oxidative status in mild pancreatitis, with moderate severity it normalizes 27% and correlates in 73% of cases, and with severe severe it correlates with all studied results. As established experimentally, mild forms of biliary pancreatitis are completely corrected with different drug combinations. With moderate and severe severity, there are immunometabolic disorders recorded. The combination proposed in this case is neither sufficiently effective nor ineffective. This study has convincingly proved the relevance of drug treatment of mild biliary pancreatitis with drug combination on the example of laboratory animals. At the same time, drug treatment is ineffective for moderate and severe pancreatitis. The study requires the continuation and testing of the resulting drug combination for mild biliary pancreatitis.

Key words: biliary pancreatitis; ferrovir, mexidol, phosphogliv, polyoxidonium, Essentiale N, combination.

INTRODUCTION

Acute pancreatitis (AP) is an enzymatic lesion of the pancreas. This process is autocatalytic and often ends in autocatalysis and organ necrosis. It determines the aseptic inflammation of the demarcation type. The cause is necrobiosis and auto-aggression caused by enzymes. Subsequently, necrotic changes occur with the addition of a secondary purulent infection. This can lead to the fact that clinical phenomena can manifest themselves in the form of minor pain sensations, with variations up to the most severe enzymatic shock (Andersen et al., 2008; Agarwal et al., 2016; Zhuang et al., 2016). The frequency of AP development in the world varies from 20 to 120 cases per 100,000 population; in Ukraine - 102 per 100,000 population (Konopljia et al., 2015; Mikaelyan, 2017). Factors such as the average age and level of alcohol consumption among the population affects the disease
(Bermejo et al., 2008; DiMagno, 2011; Bakker et al., 2012; Goyal et al., 2016). AP mortality percentage remains very high despite modern methods of treatment use: 7–15% in total, 30–40% with destructive forms (Brown et al., 2008; Gardner et al., 2009; van Santvoort et al., 2010; van Brunschot et al., 2014; Chen et al., 2016).

Acute pancreatitis is a diagnosis of up to 230,000 hospitalizations in the United States every year (Fagenholz et al., 2007; Crockett et al., 2018). Although moderate acute pancreatitis reaches a mortality of only <1%, mortality from severe pancreatitis can reach a third of cases (30%) (Freeman et al., 2012; Ermolov, 2016).

Drugs can cause 0.1% -2% of cases of acute pancreatitis (Barkin et al., 2017). Most cases of drug-induced pancreatitis are mild or moderate. However,

serious and even fatal cases may occur. Treatment of acute pancreatitis caused by drugs requires the abolition of violating drugs and supportive therapy. If it is impossible to identify a drug that is an active violating agent, then this can lead to critical delays.
Prevention of drug-induced pancreatitis requires up-to-date knowledge of drugs with strong evidence linking their use to the development of pancreatitis. At the same time, there is an opposite trend - the need to introduce pharmacological methods for the correction and treatment of pancreatitis, using the results of laboratory experiments.

The main factor in the emergence and subsequent AP development are extrahepatic biliary tract diseases, up to 37-45% of all cases of pancreatitis (Krishna et al., 2015; 2017; Lee et al., 2016; Lorenzo et al., 2017; Huh et al., 2018). This is the cause of the development of acute biliary pancreatitis (BP). The pathogenesis of pancreatitis is manifested as a violation of the pancreatic secretory function due to obstruction of the major duodenal papilla (MDP) (Mouli et al, 2013; McNabb-Baltar et al., 2014; Majumder et al., 2015.
Chronic biliary pancreatitis (CBP) is therefore a chronic inflammatory disease of the pancreas. For BP, a combination of the following morphological and histological factors is characteristic as follows: histological changes of different locations in the part of the pancreas associated with excretory-secretory function. Later, this part of the pancreas begins to degenerate, with the result that the gland tissue is replaced by connective tissue cells. At the physiological level, disorders are manifested in the form of the presence of functional insufficiency of various degrees of expression.

The causes of biliary pancreatitis (BP) in most cases (within 35–56%) are pathologies of the biliary tract, namely: cholecystitis, disorders at the morphological level, resulting in a loss or decrease of duodenum and pancreas functions. Thus, BP development is determined by a whole complex of disorders, mainly at the morphological, histological and physiological levels (Phillip et al., 2011; Minkov et al., 2015).

One of the insufficiently studied pharmacotherapy methods is the combined use of immunomodulatory, membrane-protective and antioxidant pharmacotherapy of varying BP severity and etiology. Indicators for the use vary and are associated with impairments in the immune status and oxidative system. They are especially pronounced in severe BP forms. Therefore, it is necessary to compare pharmacological methods of BP treatment or correction depending on its severity - mild, moderate and severe.

Aim: to experimentally evaluate the pharmacological efficacy of the combined drugs use (immunomodulators, antioxidants and membrane protectors) in acute biliary pancreatitis with a high degree of severity.

MATERIALS AND METHODS

All experiments were performed on a population of 210 laboratory rats. The average weight of the animals, taking into account the average error, was 219 ± 41 g. The animals were selected according to the following principles: a) the same age; b) approximately the corresponding weight category; c) the same period of the experiment, 8 am to 12 pm. Gender of the surveyed population was not taken into account.

The size of each experimental group is 70 laboratory rats.

To obtain statistically significant data, the group consisted of 70 animals. Group 1 did not receive any medication, 2 groups of animals were given a combination of the following drugs. Medications were administered once a day. In total, each of the drugs was administered 10 times. The first combination consisted of ferrovir, phosphogliv and meskidol. The first was administered intramuscularly to each of the animals at the rate of 1 kg of body weight at a dose of 15 mg. Meskidol was administered in 3 times larger amount per 1 kg of body weight, but inside the abdominal cavity. Finally, phosphogliv was injected into the oral cavity, as a solution in 1% starch, at the rate of 750 mg per 1 kg of body weight. For the third group of animals, a combination of other drugs was proposed. This polyoxidonium, emoxipin and Essentiale N, 10 times, in different ways. Polyoxidonium, like ferrovir, was also administered intramuscularly at a dose of 0.025 mg. Injection of emoxipin was also carried out intramuscularly as follows: 1.5 ml, 1% solution of emoxipin itself, with the addition of 20 ml of 1% solution of sodium chloride. The resulting solution was administered in an amount of 0.5 ml. Essentiale N, as well as mexidol, is entered into an abdominal cavity, in a dose of 0.05 ml.

In order to simulate a situation occurring in the pancreas with BP of varying severity, we used the following methods. To simulate all BP degrees, operations with animals were carried out 5 days before killing. The choice of this period is due to the fact that the physiological parameters necessary for

the study are observed during this specified period of time.

To simulate a mild severity of BP, the animals underwent a laparotomy. In the future, using liquid nitrogen and a special applicator was applied to one of the lobes of the pancreas. After 3 hours, 85% of the rats developed edematous syndrome BP. Sequential analysis of laboratory results was performed on animals with edematous syndrome BP.

Modeling of moderate and severe types of pancreatitis was carried out by combining surgical intervention (truncating one duct into each of the pancreas) and physiological initiation (administration of prozerin, once every 60 minutes, dose was 0.25 mg per 1 kg of body weight). With this method of modeling, destructive pancreatitis development was detected morphologically. In order to achieve pancreatitis of moderate severity, it is necessary to bandage only one pancreatic duct, and to simulate a severe form, similar actions were performed with two ducts and proserin injection.

Laboratory parameters of the control group are shown on the example of 50 healthy rats.
Rats were immunized by injecting a sheep red blood cells into the abdominal cavity. 110 red blood cells were injected per 1 kg of body weight. Indicators of the humoral immune response after 5 days were recorded on the following grounds: CBC is the number of cells localized in the spleen and producing immune antibodies. Also taken into account is the difference in mass between regional and contralateral lymph nodes (Mass difference MD, Number difference ND).

In the peripheral blood phagocytic index and the number of phagocytes was taken into account. Oxygen indicators were recorded by standard methods (restoration of nitro-synthetic tetrazolium, optical density (NBT test)). The levels of AHP (acyl hydroperoxide) and MDA (dialdehyde malic (malonic) acid) in the blood plasma were taken into account as indicators of the intensity of lipid peroxidation. At the same time, the total antioxidant activity (TAA) was taken into account. All ELISA results were recorded using a photometer (Sunrisemicroplate, Tekan (Austria)).

Experimental studies of the reliability of differences between the results were determined using statistical methods, indicating the data and their errors mean (± m) and the probability of a possible error (p), calculated using the t-test for independent samples. Differences were assessed as significant, prir = 0.05. For the calculations, the statistical analysis program Microsoft Excel 7.0 is used. In addition, the Spearman's rank correlation coefficient was determined.

RESULTS

In rats with a mild degree of PD, there was a decrease in the CBC values in the spleen, whereas in the peripheral blood a decrease in the level of MD and ND. In the immune system, as it was possible to establish the results of NBT test, processes with opposite directivity occurred - a significant decrease in the activity of phagocytes and an increase in the activity of polymorphonuclear-type leukocytes, which is dependent on the oxygen level. These data are presented in Table 1.

Other researchers pointed to the fact that metabolic disturbances can be only with destructive forms of pancreatitis (Krishna et al., 2015; 2017; Lee et al., 2016,; Lorenzo et al., 2017; Huh et al., 2018). Our study allows us to state with confidence that metabolic disorders of varying degrees of severity are also observed with a mild form of PD. According to our data, activation of lipid peroxidation processes was detected (in particular, an increase in MDA and AHP), as well as a slight increase in SMO in the absence of changes in the activity of catalase and TAA (Table 1).

Table 1. Drug therapy of mild biliary pancreatitis on the example of laboratory rats.

Indicator	Units	1	2	3	4
		Control group	Mild BP		
			No drugs	Ferrovir + mex + phosphogliv	Polyoxidonium emoxipin + Essentiale N
AHP	units	0.40± 0.04	0.47±0.04	0.23±0.05	0.37±0.05
MDA	umol/l	1.8±0.8	4.9±0.3	1.75±0.03	1.68±0.02

SM_{NO}	umol/l	1.77±0.8	2.81±0.05	1.93±0.2	1.71±0.09
OAA	%	48.0±0.6	48.2±0.6	42.1±0.3	47.8±0.6

Drugs selected in the experiment, are actively used as an immunomodulator, membrane protector and antioxidant, in particular for violations of the hepatopancreatobiliary system.

Our data showed that in a group of rats with a mild PD, a combination of ferrovir, mexidol and phosphogliv normalized the development of the humoral form of immunity, and also corrected the formation of the cellular (MD, ND) form. Due to the use of this combination, the functional activity of peripheral blood neutrophils and oxidative indices (Table 1) were completely normalized in rats. MDA indices in group 2 significantly decreased 2.5 times as compared with control, AHP indices - by half (Table 1). On the other hand, the introduction of the second group of drugs, namely polyoxidonium, emoxipine and Essentiale N, normalized the parameters of humoral and cellular immune response, the activity of granulocytes in the blood, indicators of the oxidative system.

Simulation of a more pronounced compared with a mild and moderate PD, showed a significantly more pronounced degree of reduction in CBC (localization - the spleen). In addition, indicators of MD and ND, as well as all indicators of phagocytosis, have changed in the direction of decline. For MDA, approximately the same decline was recorded as with the introduction of the first combination of drugs, for AHP - a higher level (Table 1). This means that the processes associated with AHD and MDA with the second combination of drugs are more pronounced.

When modeling PD of moderate severity, the group of laboratory rats showed a more pronounced reduction in the number of antibody-forming cells (AFC) in the spleen compared to the mild form, as well as indicators of MD and ND of regional and contralateral lymph nodes, and indicators of phagocytosis (phagocytic coefficient PC, phagocytic index PI, phagocytes activity index PAI), increase of parameters of oxygen-dependent activity of peripheral blood neutrophils. Revealed a more pronounced activation of the processes of lipid peroxidation (increased AHP, MDA), a decrease in the activity of catalase, OAA. Increasing the level of substances associated with NO also suggests a more significant activation of lipid peroxidation processes (Table 2).

Table 2. Drug therapy of moderate biliary pancreatitis on the example of laboratory rats.

Indicator	Units	1	2	3	4
		Control group	Mild BP		
			No drugs	Ferrovir + Mex + phosphogliv	Polyoxidonium emoxipin + Essentiale N
AHP	units	0.40± 0.04	7.4±0.08	5.5±0.05	1.37±0.05
MDA	umol/l	1.8±0.8	20.9±0.5	16.7±1.0	11. 8±1.9
SM_{NO}	umol/l	1.77±0.8	2.6±0.09	3.1±0.20	3.7±0.07
TAA	%	48.0±0.6	25.2±1.6	27.1±0.9	33.8±1.6
AFC	thousand/splee	26.9±2.3	7.8±1.5	26.8±1.6	26.3±1.4
MD	мг	2.45±0.03	0.26±0.02	0.55±0.05	1.6±0.06

ND	10^6 of lymphocy	1.82±0.04	0.12±0.02	0.14±0.02	0.68±0.07

The first combination of drugs resulted in normal AFC level in rats' spleen, and also corrected the processes of phagocytosis (phagocytic coefficient, phagocytic index, phagocytes activity index), the content of lipid peroxidation products, catalase activity, TAA, increased levels of CNO in plasma. No effect on cellular immunity, oxygen-dependent activity of peripheral blood neutrophils (Table 2) was noted.

The second combination of drugs normalized the following parameters: the number of immune AFC in the spleen, phagocytosis, corrected, but not to normal values, indicators of MD and ND and TAA. The coefficients of the AAFC and SMNO compared with the control decreased by 0.7 and increased 2 times, respectively (Table 2).

In the third experiment, associated with severe BP, the following differences were reliably established. When combining drugs group 1, differences from control were at the level of 1st order, between rats group 1 and group, 2 differences were not significant, while the combination of drugs groups 2 in rats group reduced AHP level by 4 times. Yet this AHP level was 10 times higher than normal. The same pattern is fixed for MDA (Table 3). Opposite processes (decrease) were recorded for SNNO (2 times decrease), TAA and AFC (4-5 times decrease in comparison with the control), as well as MD, ND (decrease by more than 1 order).

Table 3. Drug therapy of severe biliary pancreatitis on the example of laboratory rats.

Indicator	Units	1	2	3	4
		Control group	Severe BP		
			No drugs	Ferrovir + Mex + phosphogliv	Polyoxidonium emoxipin + Essentiale N
AHP	units	0.40± 0.04	17.9±0.9	16.8±0.5	4.7±0.05
MDA	umol/l	1.8±0.8	30.9±3.5	31.7±2.7	18. 2±2.1
SM_{NO}	umol/l	1.77±0.8	0.6±0.4	0.8±0.05	0.85±0.07
TAA	%	48.0±0.6	10.9±1.5	12.1±0.9	17.8±0.9
AFC	thousand/splee	26.9±2.3	5.8±1.4	5.6±1.1	16.3±1.4
MD	мг	2.45±0.03	0.15±0.02	0.11±0.01	0.9±0.02
ND	10^6 of lymphocy	1.82±0.04	0.07±0.02	0.04±0.01	0.12±0.03

Thus, it can be argued that in severe BP, the administration of both groups of drugs 2 and 3 to a group of laboratory animals did not change the parameters of physiological stress, but on the contrary, either reduced them or increased them.

None of the studied immune and oxidative

parameters could not be normalized with the introduction of the second group of drugs. The use of this combination in severe CP corrected, but not to normal indicators of AFC, MD, ND, PC, PAI, the level of MDA and AHP, TAA and SMNO level.

DISCUSSION

Negative correlations were found between the indicators of adaptive forms of the immune response and the processes of phagocytosis. On the other hand, positive, reliable correlations were found between the oxygen-dependent activity of peripheral blood neutrophils and oxidative indicators. In total, between 48 indicators of immunity and oxidative status revealed 48 significant correlations.

In moderately severe PD, the total correlation number was 43. Indicators of humoral, cellular forms of the immune response and lipid peroxidation products (MDA and AHP) showed negative correlation links. Catalase and TAA activity is positive. The metabolic activity of peripheral blood neutrophils showed positive correlations with LPO products and negative with catalase and TAA. The titer of stable NO metabolites did not correlate with the parameters of innate and adaptive immunity.

When modeling severe PD, all indicators of the immune and oxidative systems correlated. 50 significant correlations were found. At the same time, positive correlations were found between the humoral, cellular forms of the immune response, phagocytosis processes and catalase activity, TAA, as well as the level of SMNO. Negative correlations are manifested between antioxidant indices and metabolic activity of peripheral blood neutrophils.
Thus, it can be concluded that in case of mild PD, the changes are minimal and are completely corrected by both combinations of drugs, then the mean and severe forms of PD are more pronounced immunometabolic disorders. These physiological disturbances are not effectively corrected by the proposed combinations. The obtained data on moderate and severe degrees and pharmacological correction of the proposed drug combinations are consistent with the results obtained by other researchers (Brown et al., 2008; Gardner et al., 2009; Peery et al., 2012; Chen et al., 2016; Polyansky, 2017).
The problem of treating biliary pancreatitis is far from being resolved. The choice of surgical tactics, pharmacological therapy or accompaniment, corrections remain controversial (Brown et al., 2008; Samokhvalov et al., 2015; Chen et al., 2016; Ramos et al., 2016; Schmidt et al., 2017).

BP is known to be one of the most difficult diagnoses, often ending with complications or death (Setiawan et al., 2017; Sellers et al., 2018). There are several ways of therapy, but all of them are united by the time factor - it is necessary to start therapy at an early stage, immediately after diagnosis set (Tenner et al., 2013; WorkingGroup, 2013). In the case of the actual medical examination without treatment, various pathologies of the liver and pancreas develop. Pathology manifests itself in the form of hypertension in the ducts, as a result of this - noninfectious jaundice develops, various kinds of inflammatory processes, resulting in necrotic changes in the pancreas (Fagenholz et al., 2007; Wu et al., 2008; Crockett et al., 2018; Vege et al., 2018). At the cellular level, this is manifested as the cessation of hepatocytes functioning, at the system level - in the cessation of the reticuloendothelial system functioning. The physiological level also undergoes significant and fatal changes - endothelium toxicosis occurs, stress from an increased content of free radicals, and other processes. At the macro level, stones form in the pancreas, and as a result, necrosis develops. In this case, even an urgent surgical intervention will not correct the situation.

The urgency of the question remains quite acute today, as it is necessary to develop new methods for detecting and treating PD, their complex application and detailed analysis of preliminary results obtained from laboratory experiments (van Santvoort et al., 2010; van Brunschot et al, 2014).

Pharmacotherapy is one of the ways to treat mild PD, to stabilize the more severe degrees of this disease. The primary issue remains the development and introduction of new methods for monitoring and diagnosing people with BP.

The combination of ferrovir, mexidol, and phosphogliv in mild pancreatitis is 12.0% and normalizes 75% of the studied laboratory immune and oxidative parameters, respectively. With an average degree of pancreatitis, these indicators were 19.2%, 45%, and with a severe degree, it corresponds to the values of the control group.

CONCLUSIONS

This study has convincingly proved the relevance of drug treatment of mild forms of biliary pancreatitis with a combination of drugs on the example of laboratory animals. At the same time, drug treatment is ineffective for moderate to severe pancreatitis. The study requires the continuation and testing of the resulting combination of drugs in patients with mild

biliary pancreatitis.

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