Derivatives of 3-Hydroxypyridine in The Correction of Disorders in The Structural and Functional Properties of Erythrocytes in Experimental Acute Destructive Pancreatitis Due to Chronic Ethanol Intoxication

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Abstract. At present, acute pancreatitis only in some areas is a rather well-studied disease of the abdominal organs, however, the destructive forms of this disease have various developmental patterns, complications and, often unfavorable outcomes. The aim of the research is to establish the possibilities to correct the disorders in the functional and structural features of erythrocytes by 3-hydroxypyridine derivatives in experimental acute destructive pancreatitis due to chronic ethanol intoxication. In experimental acute destructive pancreatitis due to a 60-day ethanol intoxication there was a decrease in the content of proteins (α-, β- spectrin, ankyrin, anion transport protein, actin, gyceraldehyde-3-phosphate dehydrogenase, glutation-S transferase) and lipids (phosphatidylincholine, phosphatidylyethanolamine, phosphatidylserine, phosphatidylinositol, gyceraldehydrolipids, sphingomyelin, phospholipids, triacylglycerol, sum of mono- and diacylglycerol), an elevated level of band 4.1 and 4.5 proteins, pallidin, dematin, tropomyosin and lipids (lysophosphatidylincholine, cholesterol, it’s esters, non-esterified fatty acids), a disorder in intrinsic cellular metabolism of erythrocytes (an increased concentration of lipid peroxidation products, a decreased activity of catalase, superoxide dismutase, degree of stable metabolites of nitrogen oxide and sorption indicators of membrane) in the erythrocyte membrane. The study has revealed that the greatest efficiency in correction of disorders in the functional and structural features of erythrocytes from among the derivatives of 3-hydroxypyridine has a compound ß-hydroxynicotinoylhydrazon 2-methyl-3-hydroxy-4-formyl-5-oxymethylpyrydine dihydrochloride, and the least one - 2-ethyl-6-methyl-3-hydroxypyrdine malate (etoxydol), the administration of 2-ethyl-6-methyl-3-hydroxypyridine succinate (mexidol) has shown an intermediate result.

Keywords: Acute Destructive Pancreatitis, Ethanol, Derivatives of 3-Hydroxypyridine, Erythrocytes.

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1. INTRODUCTION

Despite the existing diagnostic and therapeutic algorithms, the volume and methods of pharmacotherapy aimed at stopping the rise in pancreatic lesions, the development of its individual complications has not been finally resolved. Experimental and clinical studies have shown the development of predominantly destructive forms of acute pancreatitis in close relation to alcohol intake. Destructive pancreatitis of alcoholic etiology is known to be characterized by more severe damages to the nervous, cardiovascular and digestive systems, and primarily the hepatic parenchyma. In presence of chronic alcohol intoxication (CAI) there develop cytolytic, cholestatic, liver cell failure biochemical syndromes of hepatocytes damage, the lipid peroxidation activation (LPO) and blood coagulation processes is observed, a drop in the whole number of circulating erythrocytes and their membrane sorption parameters, the emergence of secondary alcohol-associated immunodeficiency is noted. Pathogenetic mechanisms of tissue damage, due to the growth of oxidative stress, in particular, are also characteristic of acute pancreatitis when LPO processes cause damages not only to pancreatic cells, but also to the hepatocytes membranes, peripheral blood cells, erythrocytes, in particular. In recent decades, various authors in their studies have established a significant role of erythrocytes in the regulation of various elements of homeostasis not only in the normal conditions, but also in pathological conditions, including the diseases of the hepatopancreaticobiliary system. At the same time, there are practically no data on changes in the structural components of the erythrocytes membrane due to the isolated effect of ethanol and acute pancreatitis in presence of alcohol intoxication, and the arising activation of LPO in such a case and damage to cell membranes results in microcirculatory disorders and tissue hypoxia, which negatively affect the processes of reparative regeneration which underlie the infectious complications of destructive pancreatitis. Thus, there is no doubt about the pathogenetic role of changes in the erythrocytes membrane and oxidative disorders in acute pancreatitis, especially in presence of prolonged alcoholization, however, the issues of their correction in many aspects remain open: there are no clear terms and ways of these disorders removal, and preparations with antioxidant effects are often not administered and are not included in the standards of this disease treatment. Multi-year researches have resulted in the synthesis of several compounds and creation of several original domestic medicinal substances, which belong to 3-hydroxypropyridine (3-HOP) class and possess antioxidant, antihypoxic, membrane-protective and other properties: 2-ethyl-6-methyl-3-HOP hydrochloride (emoxipine), 2-ethyl-6-methyl-3-HOP succinate (mexidol, mexicor), 2-ethyl-6-methyl-3-HOP malate (ethoxidol), the compound β-hydroxynicotinoylhydrazone 2-methyl-3-hydroxy-4-formyl-5-hydroxymethylpyridine dihydrochloride. Together with 3-HOP derivatives, they have not been investigated for the possibility to correct the structural and functional properties of erythrocytes in experimental acute destructive pancreatitis (ADP) in presence of chronic ethanol intoxication. The aim of the research is to establish the possibilities to correct the disorders in the functional and structural features of erythrocytes by 3-hydroxypropyridine derivatives in experimental acute destructive pancreatitis due to chronic ethanol intoxication.

2. MATERIALS AND METHODS
immunosorbent assay (ELISA) with the reaction products’ detection at wavelengths ranging from 405 to 630 nm with the aid of ready-made kits to evaluate the action of SOD generated by “Bender Medsystems” (Austria) and to evaluate the action of catalase generated by “Cayman Chemical” (USA). All the ELISA outcomes were registered utilizing a Sunrise microplate photometer (Tecan, Austria). Statistical procedure of the outcomes was performed based on the commonly admitted standards of the variable-bases statistical analysis with the determination of the the mean deviation (m), mean values (M) applying the Microsoft Excel software package, 2010. The importance of the differences was evaluated by Mann-Whitney U test. The differences were deemed significant at p<0.05.

### 3. RESULTS AND DISCUSSION

When modeling ADP in presence of CAI, there was a decrease in the content of α - and β -spectrin, ankyrin, anion transport protein (ATP), actin, glyceraldehyde-3-phosphate dehydrogenase (G-3-PD), glutathione-S-transferase (G-S-T) and an increase in the level of bands 4.1 and 4.5 proteins, pallidin, dematin, tropomyosin. The introduction of ethoxidol normalizes the level of pallidin, the level of band 4.5 protein, corrects the representativeness of the band 4.1 protein, actin, tropomyosin, and G-S-T towards the values of healthy animals. The use of mexidol, compared to ethoxidol, additionally normalizes the content of ATP, dematin, tropomyosin and corrects the level of α -spectrin, ankyrin, G-3-PD. The use of DONAHP, in comparison with mexidol, additionally normalizes the representativeness of the band 4.1 protein and corrects the count of β -spectrin and actin (Table 1).

#### Table 1. Correction of Disorders in Lipids Content of Erythrocyte Membrane with 3-HOP Derivatives in ADP Associated with CAI (M ± m)

| Indicators | 1 | 2 | 3 | 4 | 5 |
|------------|---|---|---|---|---|
| α -spectrin | Control | Introduction of ethoxidol | Introduction of mexidol | Introduction of DONAHP |
| β -spectrin | 108,3±4,2 | 82,1±3,3 | 83,0±2,3 | 95,1±2,8 | 94,1±3,1 |
| Ankyrin | 89,0±3,0 | 70,2±1,6 | 73,8±2,1 | 80,3±1,9 | 83,1±2,2 |
| ATP | 171,6±4,2 | 160,2±3,7 | 161,4±2,7 | 173,9±3,9 | 175,4±3,6 |
| Pallidin | 92,1±4,1 | 100,1±3,2 | 91,3±2,6 | 89,8±3,8 | 88,3±4,1 |
| Dematin | 91,2±3,1 | 104,4±3,5 | 101,3±2,8 | 87,2±3,0 | 86,2±2,9 |
| Actin | 88,1±3,2 | 69,2±2,4 | 72,5±2,2 | 73,9±2,9 | 79,3±2,1 |
| G-3-PD | 54,3±2,0 | 44,0±2,1 | 40,3±2,1 | 49,3±1,8 | 50,0±2,1 |
| Tropomiosine | 63,7±3,1 | 85,0±2,7 | 69,3±2,1 | 65,3±1,7 | 64,1±2,2 |
| G-S-T | 61,2±2,5 | 42,4±1,4 | 54,9±2,0 | 57,1±2,5 | 56,8±2,3 |

Note: asterisk (*) marks significant differences in medians (p<0.05).

When simulating ADP associated with chronic alcoholization in animals, there was a decrease in phosphatidylcholine (PC), phosphatidylethanolamine(PE), phosphatidylserine(PS), phosphatidylinositol (PI), glycerophospholipids (GPL is the sum of PC, LPC, PE, PS and PI), sphingomyelin (SM), phospholipids (PL - the sum of GPL and SM), triacylglycerols (TAG), the sum of mono- and diacylglycerols (DAG, MAG) in the rise of the degree of lysophosphatidylcholine (LPC), cholesterol (C) and its esters (CE), and nonesterified fatty acids (NEFA) in the erythrocyte membrane. The introduction of ethoxidol normalizes the EC content and corrects, but not the control values, the representativeness of PC, PI, SM, PL, NEFA. The use of mexidol, compared to ethoxidol, additionally normalizes the content of PS, PI, GPL, MAG+DAG, brings the representativeness of LPC, FE, PL, C and NEFA closer to the healthy animals’ values. The administration of DONAHP compared to mexidol additionally normalizes the level of PC, PE, GPL, PL, C, NEFA and corrects the content of SM (Table 2).

#### Table 2. Correction of Disorders in Lipids Content of Erythrocyte Membrane with 3-HOP Derivatives in ADP Associated with CAI (M ± m)

| Indicators | 1 | 2 | 3 | 4 | 5 |
|------------|---|---|---|---|---|
| Control | 24,0±0,7 | 20,1±0,2 | 21,7±0,6 | 22,3±0,4 | 25,8±1,3 |
| LPC | 3,9±0,05 | 6,2±0,1 | 6,0±0,1 | 5,2±0,04 | 5,1±0,06 |
| PE | 24,6±1,0 | 19,6±1,0 | 19,2±1,1 | 22,4±0,8 | 24,7±1,4 |
| PS | 19,7±0,7 | 18,3±0,4 | 18,1±0,5 | 19,4±0,3 | 19,5±0,6 |
| PI | 4,6±0,05 | 3,3±0,04 | 3,7±0,03 | 4,5±0,08 | 4,7±0,2 |
| GPL | 76,8±2,2 | 67,5±1,3 | 68,7±1,8 | 73,8±1,4 | 79,8±2,2 |
| SM | 12,2±0,5 | 7,3±0,4 | 9,4±0,2 | 9,1±0,3 | 10,9±0,3 |
| PL | 89,0±2,0 | 74,8±1,7 | 78,1±2,1 | 82,9±1,9 | 90,7±1,5 |
| C | 44,8±2,1 | 61,8±0,6 | 60,6±1,4 | 57,4±1,2 | 48,5±2,1 |
| CE | 40,0±2,2 | 44,1±1,2 | 41,7±1,3 | 41,4±1,2 | 40,4±2,1 |
When assessing the parameters of erythrocytes metabolism, it has been established that in presence of ADP and CAI, the concentration of LPO products (MDA, AHP) in the red blood cells increases, the activity of catalase, SOD, the level of SM<sub>ND</sub> and the sorption parameters of erythrocyte membrane (SCE and SCG) decrease. The introduction of ethoxidol brings all the studied metabolic parameters of erythrocytes closer to the control values<sup>2,9,14</sup>. The use of mexidol additionally normalizes the activity of catalase and increases, but not to the parameters of the norm, the concentration of SM<sub>NO</sub>. The use of DONAHP, in comparison with mexidol, additionally normalizes the level of LPO products, SM<sub>NO</sub> and corrects SOD activity (Table 3).
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