THE NEW ARMENIAN MEDICAL JOURNAL
Vol.11 (2017), No 2, p.72-76

EXPERIENCE OF ADMINISTRATION OF L-ORNITHINE-L-ASPARTATE IN THE TREATMENT OF PATIENTS WITH ALCOHOLIC LIVER DISEASE

KIT Z.M.

Department of Family Medicine, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine

Received 11/05/2016;accepted for printing 18/06/2017

ABSTRACT

The study aimed to evaluate the efficacy of hepatoprotective L-ornithine-L-aspartate in complex treatment of patients with alcoholic liver disease.

A total of 35 patients with alcoholic liver disease underwent thorough examination. The age of patients ranged from 42 to 68 years. Disease duration ranged from 8 to 17 years. Patients were hospitalized after alcoholic excess. Alcoholic etiology of liver disease was confirmed by anamnesis vitae and anamnesis morbi, narcological surveillance and different questionnaires. For the first three days after admission all the patients underwent detoxification therapy. Thereafter biochemical parameters were determined reflecting liver function. The drug L-ornithine-L-aspartate ("Hepa-Merz") was prescribed to all patients in the dose of 1 tablet 3 times a day with meals. After the treatment was completed (two weeks on average) repeated examinations were conducted as mentioned above. In addition, the following parameters were used as the performance criteria: the severity of major clinical syndromes (pain, dyspeptic, asthenovegetative, jaundice and occurrence of alcoholic encephalopathy). The statistical data were processed.

As a result of the study it was established that the complex treatment of patients with alcoholic liver disease using "Hepa-Merz" drug leads to regression of pain and asthenovegetative syndromes, a significant reduction of dyspeptic symptoms and virtually no impact on the psychoorganic symptoms caused by alcoholic encephalopathy. It was also revealed that the administration of the hepatoprotector normalizes hepatic biochemical tests (alanine transaminase, aspartate aminotransferase, bilirubin, alkaline phosphatase, thymol test) reflecting cytolysis syndrome and icteric cholestatic syndrome.

Thus, it can be concluded that L-ornithine-L-aspartate may be recommended for wide use in the treatment of alcoholic liver disease patients taking into account the positive clinical effect and absence of side effects.

KEYWORDS: *alcoholic liver disease, hepatoprotector, L-ornithine-L-aspartate.*

INTRODUCTION

Mortality due to alcoholic intoxication ranks third in the structure of mortality, while the share of total alcohol-induced pathologies (alcoholic liver disease, acute and chronic pancreatitis, cardiomyopathy, polyneuro-encephalopathy) accounts for 42.6% of deaths among people who abuse alcohol [*Moiseyev V, 2014*]. According to studies conducted in Canada the increase in alcohol consumption of 1 *liter* per year was accompanied by increased mortality from liver cirrhosis in men by 17%, and in women – by 13%. In the UK, 38% of men and 16% of women aged 16 to 64 years take alcohol in quantities exceeding the allowable dose [*Mishchuk V, 2015*]. At present there is a progressively increasing proportion of alcoholic cirrhosis in the structure of general morbidity of population. The high level of morbidity and mortality, especially among working-age population, the process, which is often in the settings of other diseases, adverse effects on children determine the relevance of the problem of alcoholism [*Samogalskaya O et al., 2015*].

ADDRESS FOR CORRESPONDENCE:
Zoryana M. Kit
69 Pekarska Street, Lviv 79008, Ukraine
Tel.: +38 (098) 331-56-02
E-mail: zoryana.kit27@gmail.com

Liver, together with the pancreas and nervous system are the main targets of the toxic alcohol in its excessive use. There is a direct link between alcohol dependence and liver damage: alcohol abuse leads to the development of alcoholic liver disease, which manifests itself by three major types – steatosis, hepatitis and cirrhosis. Alcoholic liver disease is recognized as the most common among visceral lesions of alcoholic origin [*O'Grady J et al., 2000*; *Bueverov S, 2001*].

Alcoholic liver disease is characterized by the damage to parenchymal cells, activation of stellate cells, inflammation and fibrosis. The clinical course of chronic liver disease is largely dependent on the progression rate, and extent of fibrosis and fibrogenesis can be regarded as an unrestricted process based on the synthesis of connective tissue in activated stellate cells and fibroblasts with epithelial-mesenchymal transformation [*Gressner A et al., 2009; Mishchuk V, 2015*].

Despite the fact that the study of pathogenetic mechanisms of alcohol addiction has been the subject of many publications, a number of issues remain unresolved, as preventive measures and treatment of this disease are not entirely satisfactory. It is known that more than 90% of ingested ethanol is metabolized by the liver causing its damage. However, the liver damage does not develop in all people suffering from alcoholism [*Abittan C, Lieber C, 1999; O'Grady J et al., 2000*].

The metabolism of ethanol causes numerous metabolic disorders. Changes in the ratio of NADH/NAD, which are observed in people who abuse alcohol, lead to significant metabolic disturbances. These patients suffer from lactic acidosis, ketosis, accompanied by metabolic disorders of urate, disturbances in collagen synthesis, steroids and slow down of gluconeogenesis. In addition, produced hydrogen displaces fatty acids as an energy source, leads to the accumulation of triglycerides and fatty liver [*Abittan C, Lieber C, 1999; Moiseyev V, 2014*].

Disturbances in functions of membranes and neurotransmitters in the central nervous system as well as changes in energy metabolism are caused due to the synergistic interaction of ammonia with fatty acids, mercaptans and phenols, which are not neutralized in liver disease [*Sherlock S, Dooley J, 1999*].

Drug therapy in patients with liver disease should primarily be aimed at eliminating the causes of the disease. Taking into account the spectrum of their mechanisms of action hepatoprotectors should be added to causal treatment for faster achievement of clinical effect. Hepatoprotectors are drugs that form the basis of pathogenetic therapy of liver diseases increasing resistance of hepatocytes to pathological effects, enhance their antitoxic function and contribute to the restoration of the disturbed functions of liver cells. Mechanisms of hepatoprotective actions are as follows: increased neutralizing hepatocyte function resulting from the increase of glutathione, taurine, sulfate reserves or increased activity of enzymes involved in the oxidation; inhibition of reactions of excessive lipid peroxidation, binding of lipid peroxidation products and repair of cell membrane structures; anti-inflammatory effect; blockage of fibrogenesis by eliminating hepatocyte necrosis, preventing entry of antigens from the gastrointestinal tract as a result of the translocation of intestinal bacteria and their toxins; being activators of Kupffer cells, stimulation of collagenase activity in the liver and blockade of the enzymes involved in the synthesis of connective tissue components [*Zhuravleva L, Krivonosov E, 2013*].

Unfortunately, the exact mechanisms of action of different hepatoprotectors are only presumptive, which leads to difficulties in determining the indications for their use. Moreover, there are often no reliable scientific data with a high level of evidence (large-scale multicenter randomized placebo-controlled studies), confirming the positive effect of hepatoprotective substances on the human body.

One of advanced hepatoprotective drugs is "Hepa-Merz" (L-ornithine-L-aspartate) manufactured by Merz & Co (Germany). Actually hypoammonemic effect of the drug is due to several mechanisms:

- Ornithine stimulates carbamoyl phosphate synthetase, which is the main enzyme of the urea synthesis, in periportal hepatocytes;
- Aspartate stimulates glutamine synthetase in perivenous hepatocytes, muscles, and brain;
- Ornithine and aspartate are themselves substrates of urea cycle [*Bueverov S, 2001; Vlokh I et al., 2002*].

In addition to the hypoammonemic effect L-ornithine-L-aspartate has a number of other important properties in the treatment of diffuse liver diseases. One of these properties of the drug is its ability to

detect anabolic or anti-catabolic action in the muscle tissue. The mechanism of anabolic action is associated with the ability of the drug to influence the glutamine synthetase. It has also been proven that each of the amino acids that make up the drug has an anabolic effect. Ornithine and aspartate found in the medication act as substrates of ornithine cycle, in which the detoxification of ammonia takes place. Ornithine cycle is associated with the Krebs cycle, which is a major source of human energy. Therefore, the increase of the amount of ornithine and aspartate in the body leads to the increase of energy production in the Krebs cycle. Furthermore, aspartate tends to reduce the dependence of cells to receive energy by glycolysis and increasing energy production through fatty acid oxidation. This reduces the formation of lactic acid and the need for oxygen by increasing the anaerobic oxidation [*Solovieva G, Kvachenyuk E, 2011*].

The study aimed to evaluate the efficacy of hepatoprotective L-ornithine-L-aspartate in complex treatment of patients exclusively with alcoholic liver disease.

Material and methods

The study included 35 patients with alcoholic liver disease (males: 25 with hepatitis, 10 with hepatic cirrhosis). The age of patients ranged from 42 to 68 years (mean age was 48.5±3.2 years). Disease duration ranged from 8 to 17 years. The patients were hospitalized in Lviv City Hospital by ambulance after alcoholic excess. Alcoholic etiology of liver disease was confirmed by anamnesis vitae and anamnesis morbi, narcological surveillance, CAGE, MAST questionnaires, LeGo scale. Alcoholic liver disease was diagnosed taking into account information from clinical history and laboratory instrumental data on the stigma of chronic alcohol intoxication.

All patients underwent detoxification therapy (electrolyte solutions and 5% glucose solution in a volume of 1.5 *l/day*, 30 *ml* of 25% magnesium sulfate) for the first three days after admission. Thereafter biochemical parameters reflecting liver function were determined. All patients received "Hepa-Merz" in the dose of 1 tablet 3 times a day with meals. After the treatment was completed (two weeks on average), repeated examinations were conducted as mentioned above. In addition, the following parameters were used as the performance criteria: the severity of major clinical syndromes (pain, dyspeptic, asthenovegetative, jaundice and occurrence of alcoholic encephalopathy). The study was approved by Institutional Bioethics Committee and conforms to the principles outlined in the Declaration of Helsinki (Br Med J, 1964; p. 177).

Statistical analysis of the results was performed using Statistica and Microsoft Excel, determining the Student's, Pearson's coefficient, and Fisher's ratio test.

Results and discussion

Observation results of patients are presented in table 1, 2.

As it can be seen from table 1, pain syndrome before treatment occurred in every fourth patient, and was absent after treatment. Dyspeptic complaints were expressed by 60.0% of patients before treatment and by every fifth patient – after treatment.

Asthenovegetative syndrome completely disappeared after complex treatment, which was present on admission in all patients without exception. Icteric syndrome was identified in 11 patients (31.4%) before treatment and disappeared after treatment in 2 of them.

Alcoholic encephalopathy manifested itself in these patients almost irreversibly, as evidenced by its unchanged manifestations (disturbances of the intellectual and emotional areas of mental activity) and, despite treatment, only 4 patients had significant improvement.

TABLE 1

General clinical indices after complex treatment of patients with alcoholic liver disease using L-ornithine-L-aspartate

Clinical syndromes	Prior to treatment (n=35)		After treatment (n=35)	
	n	%	n	%
Pain	9	25.7	–	–
Dyspeptic	21	60.0	7	20.0
Asthenovegetative	35	100.0	–	–
Jaundice	11	31.4	9	25.7
Alcoholic encephalopathy	35	100.0	31	88.6

Table 2

Dynamics of biochemical tests after complex treatment using L-ornithine-L-aspartate

Indices	Before treatment	After treatment
Alanine aminotransferase (*mmol/l*)	1.12±0.1	0.5±0.03*
Aspartate aminotransferase (*mmol/l*)	0.78±0.06	0.38±0.02*
Gamma glutaminetransferase (*UI*)	28.8±5.1	24.3±3.9
Bilirubin total	32.8±1.2	20.6±1.2*
Direct	8.0±1.1	5.9±0.7
Indirect	24.6±1.8	15.8±1.1
Alkaline phosphatase (*nmol/s.l*)	3814±105	2074±102*
Total protein (*g/l*)	66.8±2.4	68.0±2.7
Albumin (%)	58.3±0.7	57.9±1.4
Thymol test (*units*)	7.9±0.18	5.9±0.28*

Note: ** – $p<0.05$.*

Thus, complex treatment of patients with alcoholic liver disease using L-ornithine-L-aspartate drug leads to regression of pain and asthenovegetative syndromes significantly reducing dyspeptic syndrome (by 3 times) and virtually does not affect the psycho-organic symptoms caused by alcoholic encephalopathy.

As seen from table 2 the complex drug therapy using L-ornithine-L-aspartate significantly decreased aminotransferase level almost 2 times (alanine aminotransferase: from 0.1±1.12 to 0.5±0.03 *mmol/l*, aspartate aminotransferase: from 0.78±0.06 to 0.38±0.02 *mmol/l)*, bilirubin – 1.6 times (from 32.8±1.2 to 20.6±1.2 *mmol/l*), alkaline phosphatase – 1.8 times (from 3814±105 to 2074±102 *nmol/s.l*) and thymol test – 1.3 times (from 7.9±0.18 to 5.9±0.28 *units*).

Changes in other biochemical parameters were not statistically significant.

Thus, the use of the hepatoprotector normalizes liver biochemical tests (alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase, thymol test) reflecting cytolysis syndrome and icteric cholestatic syndrome.

Thus, complex treatment with the drug L-ornithine-L-aspartate "Hepa-Merz" in patients with alcoholic liver disease is highly effective, both in general clinical tests and the majority of biochemical parameters.

Conclusion

The use of L-ornithine-L-aspartate in complex treatment of patients with alcoholic liver disease effectively eliminates the pain and asthenovegetative syndromes, and virtually has no effect on the psycho-organic symptoms caused by alcoholic encephalopathy.

Normalization of liver biochemical tests (alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase, thymol test) was determined, which reflect cytolysis and icteric cholestatic syndromes.

L-ornithine-L-aspartate can be recommended for extensive use in the treatment of patients with alcoholic liver disease taking into consideration positive clinical effects and absence of its side effects.

REFERENCES

1. *Abittan CS, Lieber CS.* Alcoholic liver disease. Curr Treat Options Gastroenterol. 1999; 2(1): 72-80.
2. *Bueverov SA.* [The role of hepatoprotectors in the treatment of liver diseases] [Published in Russian]. Moscow: Bolezni organov pishchevareniya. 2001; 3(1): 16-18.
3. *Gressner AM, Gao CF, Gressner OA.* Non-invasive biomarkers for monitoring the fibrogenic process in liver: a short survey. World J Gastroenterol. 2009; 15(20): 2433-2440.
4. *Mishchuk VG.* [The level of collagen of IV type and indirect markers of fibrosis in patients with a combination of chronic alcoholic pancreatitis and liver cirrhosis of the class A and B according to the Child-Pugh classification] [Published in Ukrainian]. Modern gastroenterology. Kiev. 2015; 3(83): 15-21.
5. *Moiseyev VS.* [Alcoholic disease, internal organ damage] [Published in Russian]. Moscow: GEOTAR-Media. 2014. 480p.
6. *O'Grady JG, Lake JR, Howdle PD.* Comprehensive Clinical Hepatology. Mosby, London, Sydney, Toronto. 2000. 633p.
7. *Samogalskaya OY, Lobanets NV, Sidorivsky AM.* [Clinical and hemodynamic aspects of alcoholic liver cirrhosis] [Published in Ukrainian]. Modern gastroenterology. Kiev. 2015; 2(82): 37-41.
8. *Sherlock S, Dooley J.* [Diseases of the liver and biliary tract] [Published in Russian]. Practical guidance. Translated from English. Moscow: GEOTAR Medicine, 1999. 468p.
9. *Solovieva GA, Kvachenyuk EL.* [Hepa-Merz in the treatment of alcoholic and non-alcoholic steatohepatitis] [Published in Ukrainian]. Medications of Ukraine. Kiev. 2011; 7(153): 64-70.
10. *Vlokh IY, Kovalchuk YaS, Petrina NYu.* [Comparative characteristics of "Hepa-Merz" and "Essentiale" drugs in the treatment of alcoholic patients with liver disease of alcoholic origin] [Published in Ukrainian]. Ukrainian Bulletin of Psychoneurology. Kharkov. 2002; 10(32): 62-63.
11. *Zhuravleva LV, Krivonosov EM.* [Comparative characteristics of hepatoprotective agents: key to sustainable use] [Published in Ukrainian]. Modern gastroenterology. Kiev. 2013; 4(72): 35-41.