ORIGINAL ARTICLE

An Analysis of the use of Tiocetam in Hepatic Encephalopathy

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Abstract

Aim and Scope: Hepatic encephalopathy in liver cirrhosis affects up to 40% of patients. It is important that the hepatic encephalopathy has a potentially reversible nature on the initial stages and is irreversible on the final stages. Therefore, the application of an effective treatment is important for the prognosis of the disease. In the treatment of hepatic encephalopathy, it is important to have a protein restriction diet and drugs that reduce the level of ammonia in the body. Along with this, there is still an insufficiently studied influence of hepatic encephalopathy medications with cerebroprotective capabilities on the clinical symptoms. Taking into account, the multifactorial effects of piracetam and thiotriazoline on metabolic and bioenergetic mechanisms in the body, a combined drug was developed – tiocetam, which consists of 0.2 g of piracetam and 0.05 g of thiotriazoline. In recent years, clinical trials have been conducted on the effectiveness of the use of tiocetam in neurology, which have shown its positive effects on the functional state of the central nervous system, and taking into account, the known hepatoprotective properties of thiotriazoline, it makes sense to study its possible effectiveness in the treatment of hepatic encephalopathy. Therefore, the purpose of our work was to study the effectiveness of tiocetam in patients with hepatic encephalopathy due to liver cirrhosis. **Materials and Methods:** For the study, 62 patients with liver cirrhosis, Class B (Child–Pugh score) with the signs of hepatic encephalopathy of Grades I and II, were selected. All of them underwent 2 weeks of common treatment, which included milk thistle, S-adenosylmethionine, diuretics, enzyme replacement therapy, and systemic enzyme therapy. All patients were divided into two groups, randomized by age, sex, and severity of manifestations of liver cirrhosis and hepatic encephalopathy: The comparison group – 20 patients, who continued the above course of common treatment; the main group – 42 patients, who were additionally prescribed tiocetamin 2 tablets 3 times/day for 1 month. The control group consisted of 20 healthy individuals. To assess treatment results, the dynamics of clinical manifestations of liver cirrhosis was studied. The degree of sleep disturbance was expressed in points: Mild – 1 point, moderate – 2 points, and severe (lethargy) – 3 points. The state of cognitive function was evaluated using the 10 words memory test; the severity of depression was evaluated applying Hamilton Depression Scale and Beck Depression Inventory. **Results and Discussion:** An assessment of the general condition of patients 1 month after the beginning of the study revealed a positive dynamics of clinical symptoms in 90.5% of patients in the main group and in 65.0% of patients in the comparison group; furthermore, there was a marked improvement of several biochemical parameters in both treatment groups relative to the control group and to the levels before treatment. There was also an improvement in the quality of sleep, the state of cognitive function, and the severity of depression in the main group relative to the comparison group and to the levels before treatment. **Conclusion:** The analysis of the results of the use of a combined drug – tiocetam, which consists of 0.2 g of piracetam and 0.05 g of thiotriazoline, in the treatment of hepatic encephalopathy of Grades I and II in patients with subcompensated liver cirrhosis, showed significant clinical effect, namely: Reliable improvement of general condition, several key biochemical parameters, sleep disturbances, cognitive function, and also resulted in a reduction of manifestations of depression, all of which improved the quality of life of patients.

Key words: Hepatic encephalopathy, liver cirrhosis, piracetam, thiotriazoline, tiocetam

INTRODUCTION

The pathology of the liver, which is accompanied by a decrease in its function, leads to significant changes in the functioning of other organs and systems of the human body. In particular, the disturbance of the detoxification function of the liver and blood seen in liver cirrhosis, regardless

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of the etiology of the process, leads to the accumulation of endogenous neurotoxins and amino acid imbalance, which causes changes in the functioning of the brain, and along with this, an increased level of bilirubin causes direct toxic effects on the tissue, the brain. Therefore, hepatic encephalopathy develops – a neuropsychiatric syndrome with a disorder of intelligence, consciousness, and other neurological disorders, which is one of the clinical manifestations of cirrhosis of the liver of various etiologies.[1-3] Patients with hepatic encephalopathy have decreased cognitive function – memory, attention, state of consciousness, intelligence, and behavior flexibility, which greatly affects the quality of life and work performance. Hepatic encephalopathy in liver cirrhosis affects up to 40% of such patients.[4] It is important that the hepatic encephalopathy has a potentially reversible nature on the initial stages and is irreversible on the final stages. Therefore, the application of an effective treatment is important for the prognosis of the disease.[5,6]

In the treatment of hepatic encephalopathy, it is important to have a protein restriction diet and drugs that reduce the level of ammonia in the body.[5] Along with this, there is still an insufficiently studied influence of hepatic encephalopathy medications with cerebroprotective capabilities on the clinical symptoms.

In experimental studies, it was proved that thiotriazoline increases the resistance of brain tissues to various stressful influences, especially hypoxia. In particular, it was found that in the case of experimental cerebral ischemia, the drug exhibits significant cerebroprotective properties, which were realized due to positive effects on ischemic disorders of bioenergetic processes (glycolysis, Krebs cycle oxidation, energy balance, and activation of the antioxidant system).[7]

In neurological practice, the drug piracetam is widely used, which has the properties of a psychostimulant, improves the intellectual function, perception, especially in the visual system, ability to focus attention, and stimulates the speech function,[8] all of which are important in the treatment of hepatic encephalopathy.

Taking into account, the multifactorial effects of piracetam and thiotriazoline on metabolic and bioenergetic mechanisms in the body, a combined drug was developed – tiocetam, which consists of 0.2 g of piracetam and 0.05 g of thiotriazoline. A number of studies were conducted on topic of the chemical and pharmacological interactions of these two drugs, which proved the safety and feasibility of the use of this dosage form.[9]

Experimental studies in animals have shown that tiocetam has an antioxidant effect by inhibiting the formation of active forms of oxygen in bioenergetic systems of neurons and by increasing the activity of antioxidant enzymes, especially superoxide dismutase. Anti-ischemic action is realized through the intensification of anaerobic and, especially, aerobic pathways of glucose oxidation, adenosine triphosphate synthesis, protein and mitochondria synthesis, and improvement of cerebral hemodynamics. Its nootropic properties are a result of inhibition of oxidative modification of proteins in the brain, elevation of neurotrophic factor levels, and activation of gamma-aminobutyric acid-ergic neurotransmission.[10]

In recent years, clinical trials have been conducted on the effectiveness of the use of tiocetam in neurology, which have shown its positive effects on the functional state of the central nervous system, and taking into account, the known hepatoprotective properties of thiotriazoline, it makes sense to study its possible effectiveness in the treatment of hepatic encephalopathy. Therefore, the purpose of our work was to study the effectiveness of tiocetam in patients with hepatic encephalopathy due to liver cirrhosis.

MATERIALS AND METHODS

For the study, 62 patients with liver cirrhosis, Class B (Child–Pugh score) with the signs of hepatic encephalopathy of Grades I and II, were selected. All of them underwent 2 weeks of common treatment, which included milk thistle, S-adenosyl methionine, diuretics, enzyme replacement therapy, and systemic enzyme therapy.

Criteria for the inclusion of patients in the study

Among criteria for the inclusion of patients in the study there were: an age from 18 to 65 years; an established diagnosis of liver cirrhosis with hepatic encephalopathy; an ability to cooperate with the physician and a written consent for research participation.

Criteria for the exclusion of patients in the study

Among criteria for the exclusion of patients from the study there were: an age less than 18 years or more than 65 years; an increased sensitivity to the components of the drug; a presence of an uncontrolled disease condition, including decompensated concomitant diseases or acute illness that could affect the results of the present study; an alcohol abuse during the last year before the study, pregnancy, drug abuse history; an inability of the patient to adequately cooperate with the physician, refusal to participate in the study.

Before the beginning of the study, voluntary written consent was obtained from each patient under study. We examined 62 patients with liver cirrhosis, the average age was 51.9 ± 4.7 years, that is, persons were mainly of working age. Men comprised 63.5% of all patients and women – 36.5%. The duration of the disease (from the initial diagnosis of liver cirrhosis) was 1.8 ± 0.3 years. On the initial examination, asthenic and dyspeptic symptoms were found in 100% of patients, abdominal pain

– in 87.10%, jaundice – in 54.83%, edema and/or ascites – in 88.71%, cytolytic syndrome was detected in 79.03% of patients, cholestatic syndrome – in 38.71%, and hypersplenism – in 17.74%. On abdominal ultrasonography, in all patients, a hepatomegaly of varying degrees and severity with signs of fibrosis was seen; in 74.19% of patients also, a splenomegaly was present. Also the distension of the portal vein was detected in 85.48% of patients. Grade I of hepatic encephalopathy (West-Haven classification of mental condition in hepatic encephalopathy)[11] was diagnosed in 40.5% of patients and Grade II – in 59.7%. The degree of sleep disturbance was expressed in points: Mild – 1 point, moderate – 2 points, and severe (lethargy) – 3 points. The state of cognitive function was evaluated using the 10 words memory test; the severity of depression was evaluated applying Hamilton Depression Scale and Beck Depression Inventory.[12]

All patients were divided into two groups, randomized by age, sex, and severity of manifestations of liver cirrhosis and hepatic encephalopathy: The comparison group – 20 patients, who continued the above course of common treatment and the main group – 42 patients, who were additionally prescribed tiocetamin 2 tablets 3 times/day for 1 month. The control group consisted of 20 healthy individuals.

The investigation of blood biochemical indicators was carried out in a certified laboratory of Ternopil State Medical University using automated biochemical analyzers. This work was approved by the ethical committee of Ternopil State Medical University.

Statistically significant differences between the results of various groups were determined using the non-parametric Mann–Whitney *U*-test criterion with a generally accepted level of significance $P < 0.05$. Statistically significant differences between the results of the same group before and after treatment were determined using the non-parametric Wilcoxon signed-ranked test with a generally accepted level of significance $P < 0.05$.

RESULTS AND DISCUSSION

An assessment of the general condition of patients 1 month after the beginning of the study revealed a more pronounced positive dynamics of clinical symptom change in patients of the main group, and improvement was found in 90.5% of patients in the main group compared with 65.0% of those in the comparison group. Patients in both treatment groups had a significant difference in major biochemical indicator levels in comparison to the control group and to those levels that were present before the treatment began ($P < 0.05$), but there were no significant differences between the main and the comparison group results after the treatment [Table 1].

Attention was paid to the analysis of the change in hepatic encephalopathy manifestations under the influence of tiocetam. After treatment in patients within the main group, normalization of sleep was observed in all 17 (100%) patients with Grade I hepatic encephalopathy, but within the comparison group only in 3 (37.5%) patients. Among patients with Grade II hepatic encephalopathy, sleep disturbance decreased from average level of 2.3 points to 1.3 points in the main group and to 2.0 points in the comparison group. Assessment of the state of cognitive function through 10 words memory test showed significant difference in the tiocetam-administered group relative to the comparison group and to those levels that were present before the treatment began ($P < 0.05$), while in the comparison group, there was only a trend toward improvement ($P > 0.05$) [Table 2].

The estimation of the severity of depression on the Hamilton Depression Scale showed a significant difference in the main group relative to the comparison group and to those levels that were present before the treatment began ($P < 0.05$), while the changes in the comparison group relative to levels before treatment were insignificant [Table 3].

According to the data obtained, the use of tiocetam allowed to reduce the severity of depression on the Hamilton scale by 1.5 times in the presence of both Grades I and II of hepatic encephalopathy.

Similar results were seen after the estimation of the severity of depression using Beck Depression Inventory. The analysis of the dynamics of depression rates on the Beck scale showed a significant decrease of depression severity in patients within the main group, namely, in the presence of Grade I of hepatic

Table 1: Changes of biochemical indicator levels in the process of liver cirrhosis treatment

Indicator	Control group (*n*=20)	Comparison group (*n*=20)		Main group (*n*=42)	
		Before treatment	After treatment	Before treatment	After treatment
Bilirubin total, μmol/L	16±0.91	83.21±4.31*	26.14±1.24†	84.16±1.2*	23.36±1.33†
Alanine aminotransferase, μmol/L	0.52±0.05	1.49±0.18*	0.76±0.15†	1.47±0.24*	0.68±0.07†
Aspartate aminotransferase, μmol/L	0.41±0.02	1.17±0.23*	0.61±0.07†	1.18±0.21*	0.52±0.04†

*Statistical significance of difference relative to control group ($P<0.05$). †Statistical significance of difference relative to levels before treatment ($P<0.05$)

Table 2: Changes in the cognitive function state in the process of liver cirrhosis treatment

Grade of hepatic encephalopathy	Number of recalled words before treatment (*n*=62)	Number of recalled words after treatment	
		Comparison group (*n*=20)	Main group (*n*=42)
I	5.1±0.5	5.7±0.1	7.0±0.3*
II	4.0±0.2	4.5±0.2	6.1±0.2*

*Statistical significance of difference relative to numbers before treatment (P<0.05)

Table 3: Changes in the severity of depression in the process of liver cirrhosis treatment

Grade of hepatic encephalopathy	Depression severity, score in points		
	Before treatment (*n*=62)	After treatment	
		Comparison group (*n*=20)	Main group (*n*=42)
I	31.3±2.8	28.5±3.1	20.8±1.7*
II	38.6±2.2	32.3±4.1	25.1±2.4*

*Statistical significance of difference relative to score before treatment (P<0.05)

encephalopathy, it changed from 19.4 ± 2.3 to 10.3 ± 1.7 points ($P < 0.05$), of Grade II of hepatic encephalopathy – from 22.8 ± 3.1 to 13.1 ± 1.2 points ($P < 0.05$), while the changes within the comparison group relative to levels before treatment remained insignificant. It should be noted that the decrease of the severity of depression significantly improved the well-being of patients, their behavior flexibility, and attitude toward others.

Thus, the data obtained confirm some well-known experimental studies.[10] Beneficial effects of tiocetam on the state of patients with hepatic encephalopathy can be explained by the fact that thiotriazoline enhances the resistance of brain tissues to various influences, especially hypoxia, that is, it exhibits cerebroprotective properties, namely, due to positive effects on ischemic disorders of bioenergetic processes (glycolysis, Krebs cycle oxidation, and energy balance retention), as well as also being able to induce activation in the cellular antioxidant systems.[7]

Thus, the obtained results indicate the expediency of the use of combined preparation of thiotriazoline and piracetam in the treatment of patients with liver cirrhosis with manifestations of hepatic encephalopathy.

CONCLUSION

The analysis of the results of the use of a combined drug – tiocetam, which consists of 0.2 g of piracetam and 0.05 g of thiotriazoline, in the treatment of hepatic encephalopathy of Grades I and II in patients with subcompensated liver cirrhosis, showed significant clinical effect, namely, reliable improvement of general condition, several key biochemical parameters, sleep disturbances, cognitive function, and also resulted in a reduction of manifestations of depression, all of which improved the quality of life of patients.

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