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Increasing the Effectiveness of Treatment of Intrahepatic Cholestasis Syndrome

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Abstract: Despite the improvement of preventive and therapeutic diagnostic methods, liver diseases continue to be a common cause of complications and deaths. In recent years, a number of international and national recommendations have been published aimed at optimizing the pharmacotherapy of liver diseases. The introduction of patients with chronic liver diseases (CLD) with intrahepatic cholestasis syndromes requires significant material costs - this is not only payment for treatment, but also indirect costs with temporary and permanent disability of the patient. This fact necessitates the use by doctors of modern and effective methods for diagnosing the prevention and treatment of CLD.

Keywords: chronic liver diseases (CLD), Ursodeoxycholic acid (UDCA), intrahepatic cholestasis (IHC), alkaline phosphatase (AP), gamma-glutamyl transpeptidase (GGTP), total bilirubin (TB).

The foregoing indicates that the study of the current situation with the introduction of CLD patients will allow not only to assess the state of diagnosis and treatment of patients with intrahepatic cholestasis, but also to make adjustments in the algorithm for the introduction of patients with this pathology. An increase in the cost of medical care for patients with CLD with limited funding opportunities determines the need to look for ways to rationalize medical expenses while maintaining the quality of medical care and its preventive focus.

Ursodeoxycholic acid (UDCA) remains the only approved drug for the treatment of intrahepatic cholestasis (IHC) syndrome caused by various liver diseases. Among UDCA preparations, ursofalk, ursodiol, ursosan became the most popular due to their clinical effect.

The study used ursosan, which has various positive effects: cholelytic, hepatoprotective, antioxidant, membrane-stabilizing, etc. To date, various approaches have been developed in choosing the optimal dose of ursopreparations. Known methods for the treatment of cholestatic liver diseases with ursosan, where the criterion for selecting a daily dose are: body weight (mg/kg) or type of pathology. Duration of taking Ursosan ranges from several months to 2.5 years. However, the clinical efficacy of these regimens often remains ambiguous due to the long-term persistence of cholestatic syndrome, despite ursosan therapy and an unreduced risk of complications. Therefore, the search for opportunities to enhance the effectiveness of ursotherapy continues to be relevant in modern hepatology.

The purpose of the work: Development of a method for increasing the effectiveness of therapy for intrahepatic cholestasis syndrome

Material and methods of research: A method for increasing the effectiveness of therapy for intrahepatic cholestasis syndrome caused by various liver diseases, based on optimizing the daily dose of ursodeoxycholic acid. An open randomized study in parallel groups was conducted to compare the therapeutic efficacy and safety of UDCA - ursosan in liver diseases accompanied by intrahepatic cholestasis, in accordance with the main provisions of the ethical requirements of the Declaration of Helsinki. The study included 50 patients (26 men, 24 women) with a diagnosis of chronic hepatitis of viral or toxic etiology and 15 patients with a diagnosis of liver cirrhosis of viral or unclear etiology, Child-Pugh class A or B. Those included in the survey were divided into 2 main groups: the control

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group - those who took ursosan according to the traditional scheme, at a dose of 8-12 mg/kg/day, the experimental group - those who took the same drug according to an alternative (implemented) scheme, where the daily dose was optimized taking into account the severity of the clinical - biochemical manifestations of intrahepatic cholestasis.

Each of these main groups was subdivided into the following subgroups: patients with chronic hepatitis of various etiologies (viral or toxic), respectively, with mild and moderate severity of CPH, patients with cirrhosis of the liver developed on the basis of previous hepatitis or of unclear etiology, class A or B according to Child's classification - I drink, respectively, with mild, moderate and severe IHC.

The criteria for inclusion of patients in the study group should be: the presence of IHC, which manifests itself in the form of pruritus and an increase in at least one of the following laboratory parameters of total (mainly due to its direct fraction) bilirubin (OB) > 20.5 μmol/l, alkaline phosphatase (AP) > 306 IU/l, J - glutamyl transpeptidase (GTPP) > 60 IU/l, no concomitant pathology of the kidneys, cardiovascular system.

Criteria for not inclusion in the study: concomitant chronic liver disease without clinical and biochemical signs of HC; clinically pronounced cholelithiasis; cardiovascular diseases in the stage of decompensation, refusal of the patient to participate in the study; gastrointestinal bleeding (bleeding from the upper gastrointestinal tract (GIT) not caused by esophageal varices; bleeding from esophageal varices; bleeding from the small and large intestine); skin diseases; allergic reactions; hypersensitivity or individual intolerance to the components of the drug; active tuberculosis; the patient has a mental illness that does not allow for an assessment of the effectiveness of therapy; alcoholism and drug addiction at present or in history; patients suffering from a malignant neoplasm of any localization, which was known at the time of inclusion in the study.

Results:

Schemes for the use of UDCA (ursosan), PRO.MED.CSPrahaa.s., in capsules of 250 mg. The initial dosages of ursosan are selected in the inpatient conditions of the gastroenterological department of the Bukhara multidisciplinary medical center, where patients receive treatment for 10-15 days, then examination and therapy continue on an outpatient basis for 5.5 months. The total observation period lasts for 6 months.

In the control group, according to the traditional scheme, ursosan was prescribed depending on the severity of intrahepatic cholestasis (8-10 mg/kg for mild, 10-12 mg/kg for moderate and 12-13 mg/kg for severe IHC). Patients received the adjusted dose for 6 months.

In the main group, according to the test scheme, the daily dose of ursosan was optimized depending on the severity of clinical and biochemical manifestations of intrahepatic cholestasis. The assessment of the severity of cholestasis was based on taking into account quantitative changes in the indicators of biochemical indicators of cholestasis: alkaline phosphatase (AP), gamma-glutamyl transpeptidase (GGTP), total bilirubin (TB) and the severity of clinical symptoms, such as pruritus and jaundice, calculated in points . The severity of cholestasis was expressed as mild, moderate and severe, depending on the multiplicity of the increase in total bilirubin in the blood relative to the upper limit of the norm (respectively: 20-40, 40-60 and over 60 mlmol / l. According to this gradation, the initial daily dose of ursosan was determined , equal to 8–10 mg/kg in mild cases, 11–14 mg/kg in moderate cases, and 15–18 mg/kg in severe cases of IHC) depending on the content of bilirubin in the blood before the start of treatment. The study of indicators of biochemical indicators of cholestasis and the severity of clinical symptoms was carried out at the beginning and at the end of each month during the treatment. At the same time, after the first 30 days of treatment, in accordance with the decrease in the content of bilirubin, the daily dose of ursosan also decreased, and when it was subsequently normalized, the drug was canceled.

To assess the effectiveness of treatment, periodically (1, 2, 3 and 6 months after the start of treatment) examinations of clinical and biochemical markers of intrahepatic cholestasis were carried out, which

were also used to identify the severity of cholestasis: alkaline phosphatase (AP), gamma-glutamyl transpeptidase (GGTP), total bilirubin (TB) and the severity of clinical symptoms, such as pruritus and jaundice, calculated in points. At the same time, the clinical manifestations of the intensity of pruritus were expressed according to a quantitative assessment scale (from 1 to 3 points): detectability of pruritus 1-2 times a month - 1 point, 1 time per week - 2 points, if every day - then 3 points.

Analysis of the results of the study shows that the differentiated administration of UDCA, depending on the severity of IHC, allows for a fairly pronounced choleretic effect.

So, in patients with chronic hepatitis and mild IHC during treatment with ursosan according to the traditional scheme at an average daily dose of 10-12 mg / kg. Normalization of clinical symptoms and biochemical parameters (bilirubin and GGTP) was observed by the 90th day of therapy, while with more severe IHC, this picture was achieved only after 6 months of treatment (Table 1).

Table 1 Dynamics of clinical and biochemical parameters of patients with chronic hepatitis in the course of treatment of IHC of varying severity

B/M	Bilirubin µmol/L		GGTP U/l	
Groups	**Control group**	**Main group**	**Control group**	**Main group**
Mild IHC				
Before treatment	39,0 ± 3,1	42,4 ± 3,3	111,8 ± 9,9	97,6 ± 8,7
30 days	32,4 ±2,3	31,1 ± 2,7	99,9 ±7,8	84,1 ± 7,0
60 days	26,8 ± 2,1	26,1 ± 1,9	85,1 ± 7, 7	72,3 ± 5, 9
90 days	21,3 ±1,2	21,5 ± 1,6	71,9 ± 5, 8	60,0 ± 4, 9
180 days	17,1 + 1,1	19 + 1,3	57, 0 + 4, 3	51,2 + 3, 7
The average degree of IHC				
Before treatment	60,2 ± 4,0	61,3 ± 3,6	129,7 ± 11,1	97,7 ±7, 5
30 days	52,4 ± 3,7	46,3 ± 2,9	110,2 ± 9,3	84,2±6,0
60 days	38,7 ± 3,5	32,0 ± 2,7	92,1 ± 7, 7	74,1 ±4, 9
90 days	28,5 ± 2,6	23,0 ± 1,6	73,9 ± 6, 9	59,3 ± 4, 4
180 days	21,1 + 2,2	17,0 + 1,4	62,1 + 4, 6	53,4 + 3, 0
Severe IHC				
Before treatment	107,6 ± 10,8	78,9 ± 8,1	139,5 ± 14, 3	111,7 ± 10, 7
30 days	87,0 ± 8,2	52,5 ± 5,2*	116,2 ± 10,5	91,0 ± 8,2*
60 days	65,6 ± 6,3	36,6 ± 2,7*	93,3 ± 8, 5	77,4 ±4, 9*
90 days	43,0 ± 4,1	23,2 ± 2,8*	76,3 ± 6, 9	60,1 ± 5, 5*
180 days	25,3 + 2,1	17,2 + 1,5*	58,7 + 4, 9	50,6 + 3, 8

Note: * - the difference is significant compared to the control group ($p < 0.05$)

The optimized method of prescribing UDCA suggested adjusting the initial dose of the drug and then every 30 days for the next 3 months based on the results of biochemical studies with discontinuation of the drug after the normalization of indicators. In particular, the initial doses of ursosan for patients with mild, moderate and severe IHC were selected as 8, 14 and 16 mg/kg, respectively, and then they decreased first by 15-20% and then by 1/3. As a result, the effectiveness of treatment turned out to be similar to that in the traditional scheme for patients with mild and moderate IHC, and in severe IHC, it was even significantly better. As a result, the normalization of clinical symptoms and biochemical parameters was observed by the 90th day of therapy, regardless of the severity of IHC.

With a mild degree of IHC in patients with class A liver cirrhosis, according to their initial clinical and biochemical parameters, especially taking into account the content of bilirubin in the blood and GGTP activity, the initial dose of ursosan was selected - 9 mg / kg

In the control group, the appointment of ursosan in patients with liver cirrhosis according to the traditional scheme, i.e. at a stable dose, depending on the severity of CPH, led to the following results:

a decrease in the level of bilirubin and GGTP activity after a 30-day treatment period with complete normalization of these parameters by 90 days. Subsequently, treatment with ursosan was discontinued.

With an alternative (implemented) method, the dose of ursosan was adjusted based on the results of biochemical studies every 30 days and stopped after normalization of the parameters, namely, it decreased after 1 month by 15-20%, and after 2 months by 45-55% of the level of the initial dose. Despite the reduction in the dosage of the drug, the clinical and biochemical parameters of the patients did not undergo significant changes relative to those in the control group, i.e. no statistically significant differences were found between the groups.

Table 2 Dynamics of clinical and biochemical parameters in patients with class A liver cirrhosis and mild CHD

B/M	Bilirubin µmol/L		GGTP U/l	
Groups	**Control group**	**Main group**	**Control group**	**Main group**
Before treatment	36,3± 3,1	33, 6±2,6	96, 2±6, 7	109, 3±7, 0
30 days	29,3± 2,0	28, 1±2,1	84,8±5,0	95,5±6,1
60 days	23,2± 1,7	23,4± 2,0	72, 7±4, 6	80, 7±4, 7
90 days	19,2± 1,6	18,9±1,5	61, 0±4, 4	65, 1±3, 9
180 days	16,1+ 1,3	15,8+ 1,1	56, 4+ 3, 4	60, 3+ 2, 9

Note: * - the difference is significant compared to the control group ($p < 0.05$)

In the remaining patients (with moderate and severe IHC), normalization of the studied parameters was observed at different times, depending on the severity of IHC and the selected dose of ursosan. Thus, in the control group of patients with class B liver cirrhosis who received ursosan according to the traditional scheme at an initial dose of 12 mg / kg, regardless of the severity of IHC, normalization of clinical symptoms and biochemical parameters (bilirubin and GGTP) was observed only after 6 months of treatment.

In the experimental groups, according to an alternative method, the initial dose of ursosan was selected depending on the severity of IHC (12, 14 and 16 mg/kg). Subsequently, the dose of the drug was adjusted based on the results of biochemical studies every 30 days, respectively, by 15-20% and 45-50%, and after 3 months of treatment, ursosan was discontinued due to the normalization of indicators.

Reducing the dosage of the drug in the treatment of class B liver cirrhosis did not lead to significant changes in the clinical and biochemical parameters of patients with an average degree of IHC at an initial dose of UDCA -12 mg / kg relative to those in the control group, i.e. no statistically significant differences were found between the groups. However, with more severe IHC, when it was necessary to increase the initial daily dose of UDCA to 14 mg / kg or 16 mg / kg in the experimental groups, starting from the 2-month treatment period, statistically significant more pronounced decreases in blood bilirubin levels were observed, while normalization this indicator in most patients was detected by the end of the 3rd month of treatment, i.e. almost 90 days earlier than the corresponding control groups.

Table 3 Dynamics of clinical and biochemical parameters of patients with class B liver cirrhosis in the process of treatment of CPH of varying severity

B/M	Bilirubin µmol/L		GGTP U/l	
Groups	**Control group**	**Main group**	**Control group**	**Main group**
Average level of IHC - UDCA in the initial dose of 12 mg/kg				
Before treatment	50,4± 3,8	53, 7± 4,0	122, 1± 8, 5	118, 6±7, 8
30 days	43,1± 3,1	43, 3±2,9	100,7± 7,0	103,0± 7,3
60 days	34,3± 2,8	33,0± 2,4	87, 5± 6, 9	83, 4± 6, 6
90 days	25,5± 2,1	22,9±1,9	73, 4± 5, 4	64, 1± 4, 5
180 days	19,3+ 1,8	18,6+ 1,7	60, 3+ 3, 9	55, 0+ 3, 5

Average level of IHC - UDCA in the initial dose of 14 mg/kg				
Before treatment	61,5± 4,9	66, 7± 5,3	121, 7± 9, 3	129, 8± 9, 7
30 days	54,6± 4,6	50, 6± 3,9	105,7± 7,8	101,3± 8,4
60 days	42,7± 3,4	34,0± 3,2*	88, 6± 7, 3	80, 6± 7, 0
90 days	31,9± 2,4	21,4±1,9*	74, 6± 6, 1	62, 7± 5, 7*
180 days	23,2+ 1,6	17,2+ 1,2*	63, 0+ 3, 9	53, 2+ 4, 0*
Severe IHC - UDCA at an initial dose of 16 mg / kg				
Before treatment	103,0± 8,9	103, 7± 8,8	127, 8± 10, 6	120, 2± 10, 2
30 days	83,9± 6,4	74, 2± 6,2	106,2± 8,8	99,2± 9,3
60 days	65,0± 5,8	42,6± 3,9*	86, 2± 7, 4	80, 7± 6, 6
90 days	45,7± 3,4	27,2± 2,8*	69, 0± 5, 1	64, 0± 5, 0
180 days	24,8+ 1,9	19,6+ 1,7*	53, 5+ 3, 9	54, 9+ 4, 4

Note: * - the difference is significant compared to the control group ($p < 0.05$)

In general, the total course dose of UDCA per patient required for the treatment of IHC in chronic hepatitis was reduced with individualized therapy, relative to the traditional regimen, by 73.4%, 52.6% and 39.7%, respectively, with mild, moderate and severe IHC .

Table 4. The average course dose of UDCA per patient with chronic hepatitis during the treatment of IHC of varying severity

№	Severity of IHC	Control group, in mg/kg	Main group, in mg/kg
1	Mild degree	2088,0 ± 140,7	555,3 ± 35,8*
2	Average degree	1944,1 ± 128,0	921,1 ± 62,7*
3	Severe degree	1953,5 + 133,0	1178,1 + 85,2*

Note: * - the difference is significant in comparison with the indicators of the control group (at $p < 0.05$).

In class A liver cirrhosis, which has a mild severity of IHC (at an initial dose of 9 mg / kg), the total course dose of ursosan required for the treatment of each patient according to the traditional regimen was 873 mg / kg, and with an alternative regimen - 460.8 mg \kg, which was lower than the level of the control group by 47.2%.

A similar result was also obtained in the analysis of course doses of ursosan in patients with class B liver cirrhosis, depending on the severity of IHC and the selected initial dose of the drug. Here, the reduction in course dosages was, respectively, the initial doses of 12, 14 and 16 mg / kg - 60.2%, 56.4% and 44.4%. As can be seen, dose reduction becomes inversely proportional to the severity of CPH.

Table 5 The average course dose of UDCA per patient with class B liver cirrhosis during the treatment of IHC of varying severity (in mg / kg)

№	Groups	Average course dose of UDCA in mg/kg
1	Control group, constant dose 12 mg/kg	2145,4 ± 142,2
2	The main group, the optimal initial dose of 12 mg / kg	855,8± 61,4*
3	Main group, optimal initial dose 14 mg/kg	935,3± 84,5*
4	Main group, optimal initial dose 16 mg/kg	1192,0 ± 95,2*

Note: * - the difference is significant compared to the control group ($p < 0.05$)

Therefore, a clinical result similar to the traditional treatment regimen for IHC with UDCA can be achieved with the use of lower dosages of the drug. All patients tolerated the drug satisfactorily, without side effects.

The assessment of the economic efficiency of the applied medical and diagnostic agents in the process of testing the object of innovation was carried out by calculating the cost of the UDCA drug using in practice the diagnostic and treatment standards approved by the Ministry of Health of the Republic of Uzbekistan with a description of the evaluation criteria and calculation methods. Since it was found

that during the treatment of IHC in inpatient and outpatient conditions according to the traditional and tested (alternative) schemes for the use of UDCA, there was no reduction in the duration of treatment (bed days and time of disability) or a decrease in the use of any medical manipulations, then to assess the economic efficiency of the object innovations, only changes in the course dose per patient were used. This parameter depended only on the severity of IHC and led to savings in the course use of ursosan in mild chronic hepatitis in the amount of 1532.7 mg/kg per patient, and in more severe degrees, respectively, 1023 mg/kg and 775.4 mg/kg per patient. sick. As we see in the individualized treatment of chronic hepatitis, a decrease in the dosage of ursosan becomes inversely proportional to the severity of IHC.

With a mild degree of liver cirrhosis of class A, individualized treatment of IHC with ursosan led to savings in the course use of the drug in the amount of 412.2 mg / kg per patient. In more severe degrees of IHC in patients with class B liver cirrhosis, this indicator turned out to be 1289.6 mg/kg, 1210.1 mg/kg and 953.4 mg/kg per patient, respectively. The median for moderate CHD was 1249.9 mg/kg (out of 1289.6 mg/kg and 1210.1 mg/kg)

If conditionally, we take the weight of one patient as 70 kg (the most common weight), then the amount of the drug saved in the treatment of chronic hepatitis will be, respectively, per patient 107,289 mg (or 429 capsules) with mild IHC, 71,610 mg (287 capsules), with moderate and 54278 mg (or 217 capsules) for severe IHC. In value terms, if each box of Ursosan, containing 100 capsules, is estimated at 150,000 UZS. This savings in the cost of purchasing the drug will be 643,500 UZS, 430,500 UZS and 325,500 UZS for the treatment of each patient with chronic hepatitis, respectively, with mild, moderate and severe IHC.

Similar parameters for the treatment of patients with liver cirrhosis were 28,854 mg (or 116 capsules) in class A, 87,493 mg (350 capsules) in class B for moderate severity and 66,738 mg (or 267 capsules) for severe IHC. Accordingly, the cost of this number of capsules was 174,000 sums, 525,000 sums and 400,500 sums for the treatment of each patient with cirrhosis of the liver, respectively, with mild, moderate and severe IHC.

Discussion and generalized conclusions, therefore, a clinical result similar to the traditional regimen of treatment with ursosan VPH in chronic hepatitis and cirrhosis of the liver can be achieved with the use of lower dosages of the drug. The use of an individualized (alternative) scheme for the use of ursosan for the treatment of CPH based on the results of biochemical studies (bilirubin and GGTP) every 30 days will save money on the purchase of the drug for the course treatment of each patient with chronic hepatitis in the range of 643,500 sums, 430,500 sums and 325,500 soums, respectively, for mild, moderate and severe IHC. And also in the amount of 174,000 sums, 525,000 sums and 400,500 sums for the treatment of each patient with cirrhosis of the liver, respectively, with mild, moderate and severe IHC.

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