Central Asian Journal of Medicine

Volume 2019 | Issue 4 Article 7

12-3-2019

HEPATOPROTECTION IN THE INTENSIVE CARE OF PATIENTS WITH PURULENT-SEPTIC INFECTION

V.E. Avakov
Tashkent Medical Academy, Tashkent, 100109, Uzbekistan

N.K. Ibragimov
Tashkent Medical Academy, Tashkent, 100109, Uzbekistan

T.M. Isomov
Tashkent Medical Academy, Tashkent, 100109, Uzbekistan

Central Asian Journal of Medicine

HEPATOPROTECTION IN THE INTENSIVE CARE OF PATIENTS WITH PURULENT-SEPTIC INFECTION

Avakov V.E., Ibragimov N.K., Isomov T.M.

Department of Anesthesiology and Resuscitation, Tashkent Medical Academy, Tashkent, Uzbekistan.

Objective: Prevention, early detection and timely correction of functional liver disorders in patients with purulent-septic infection.
Materials and Methods: We studied 38 patients with severe purulent-septic infection associated with diabetic foot syndrome (20), acute peritonitis (18) of appendicular origin (8), acute destructive pancreatitis (7) and blunt abdominal trauma with a rupture of the small intestine (3). All the patients described had generalization of the infectious onset with development of sepsis (30 patients) and sepsis syndrome (8 patients). All the patients had generalization of infectious origin with the development of sepsis (30) and sepsis syndrome (8). **Results**: In the process of intensive therapy, the hemostatic parameters studied are already improved from the 3rd day, the most pronounced in patients of the 2nd group, who received the hepatoprotector jetepar. **Conclusions**: The obtained data confirm the hepatoprotective and detoxifying role of jetepar drug in severe purulent-septic infection. The drug can be used in the complex therapy of such critical conditions for the prevention and assistive therapy of developing hepatic complications.
Key words: liver, hepatic insufficiency, endotoxemia, hepatoprotection, hemostasis.

INTRODUCTION

Recently there has been a steady increase in the number of patients with acute and chronic liver diseases. Every year, more than 2 million people worldwide die from liver failure (LF), in which there are gross mismatches between the needs of the body and the functional capabilities of the liver [1]. In the Republic of Uzbekistan, liver pathology is a regional problem. Abstracting from the main most common causes liver failure (viruses, alcohol, poisoning with hepatotropic poisons), it should be noted that significant impairment of liver function is a frequent occurrence in emergency surgery [2, 3]. In ICU patients, critical conditions are often accompanied by the development of multiple organ failure syndrome (MOFS), which significantly worsens forecast. One of the often-affected organs in this case is the liver, which accounts for a lot of pathologically affecting factors in critically ill patients. The etiopathogenesis of liver damage in critically ill patients consists of many components [4, 5]. The cause of liver damage, first of all, can be the conditions themselves, which determined the admission of patients to the ICU, especially with severe purulent-septic infection. In addition, the need to use a large number of drugs (usually polypharmacy) in patients in the intensive care unit causes a variety of toxic drug lesions of the liver. According to the literature, drug liver damage (DLD) accounts for 10% of all adverse reactions of drugs [6, 7, 8]. However, the true prevalence of LPP seems to be higher than 3.6]. Up to 40% of all cases of diagnosed hepatitis are caused by drugs, and among patients older than 40 years, more than 50% of cases of hepatitis are drug-induced [9, 10]. The data of many researchers confirm the presence in all critically ill patients of impaired liver function, as well as diffuse or focal lesions [11, 12]. Thus, in 11% of ICU patients,

acute liver failure develops within the first 48 hours after admission to the department, and subsequently it progresses, increasing by 2 times the nosocomial mortality [13]. The use of strictly differentiated intensive care based on pathogenetic features of the development of hepatic, hepatic and renal failure, early diagnosis of liver involvement in the pathological process, assisting correction of its impaired functions, can reduce the progression of the disease as a whole and the development of severe forms of liver failure [14]. Prevention and early detection of functional liver disorders in patients with purulent-septic infection, as well as their timely correction.

MATERIAL AND METHODS

During 2017, 38 patients (18 women, 20 men) with severe purulent-septic infection associated with diabetic foot syndrome (20 bx), acute diffuse peritonitis (18) of appendicular origin were treated in the TMA infected intensive care unit (8) (8) associated with acute destructive pancreatitis (7) and blunt trauma of the abdomen with a rupture of the small intestine (3). All patients had a generalization of the infectious onset with the development of sepsis (30 bx) and sepsis syndrome (8). Patients were aged 21 years and 47 years (mean age 36.7±4.1 years). All patients were operated on to eliminate the main source of infection or to fully drain it (in cases of destructive pancreatitis). All patients had DIC without its manifestation. In the pre- and postoperative period, all patients received intensive therapy: correction of the functions of vital organs, antibiotics, infusion-transfusion therapy, and detoxification. In addition, they had a fight against DIC, adequate analgesia, debridement of the surgical wound, diuretics, and symptomatic therapy were prescribed.

Patients we were divided into two groups of 19 patients: in patients of the 1st group, which was the control, studied the archive data. Patients of the 2nd group (under study) received Jetepar hepatoprotector (Jetepar, manufacturer of Popular Chemical Works (PvT) Ztd, G-km Sheikhupura Road, Zahore, Pakistan, MediSina ZZP) on the background of basic therapy. The drug was administered intravenously in a drop of 30 ml per day in order to maintain the functional state of hepatocytes with a pronounced effect of numerous hepatotoxic factors on the liver (purulent-septic infection, intoxication, surgical interventions, medications). The number of pharmacological agents prescribed for each of the patients totaled 14-23 items, on average 18 ± 2 (antibiotics, analgesics, NSAIDs, parenteral nutrition, metabolism, hormones, antifungal drugs, vasopressors, infusion media, etc.). 18 patients with peritonitis received complete parenteral nutrition. The remaining patients were on mixed artificial nutrition at the rate of: protein - 2 g / kg, carbohydrates - 3 g / kg, fats - 1-2 g / kg. Protein calories were not counted in the total calorie content. In both groups, in order to normalize protein metabolism, the specialized Akumin-Hep amino acid mixture containing branched chain amino acids (42%) and a significant reduction in aromatic amino acids was administered intravenously.

According to the instructions, the drug Jetepar has a hepatoprotective and antitoxic effect due to the betaine glucuronate (glucometamine) and diethanolaglucuronate (glucodiamine) included in its composition. The criterion for not including patients in this study was fatal cases and serious complications (bleeding, pneumonia, pulmonary embolism, noncupable peritonitis, etc.). Patient groups were almost randomized in all respects, which enabled us to compare the data obtained. Clinical laboratory tests of blood and urine, biochemical studies (bilirubin, nitrogenous slags, total protein, protein fractions by electrophoresis), determination of fibrinogen level (according to Rutberg), enzymes AST, ALT (Wrightman-Frenkel method), bilirubin (according to Iendrashek) and its fractions, blood electrolytes, and also average molecular peptides in the blood (in optical units) .If necessary, ultrasound, CT of the abdominal organs were performed, ECG monitoring, duplex examination of the deep veins of the lower extremities and pelvis were performed to exclude their thrombosis.

Stages of the study: upon admission and every day the patients are in ICU. All data obtained were subjected to statistical analysis using standard methods of variation statistics.

RESULTS AND DISCUSSION

In admission to both groups, a serious condition associated with the main pathology, purulent-septic intoxication, hypovolemia, organ and systemic disorders caused by generalization of the process was noted upon admission. Almost all patients had enlarged liver sizes. Patients complained of weakness, dyspeptic symptoms (21 b), skin itching (13), jaundice (4), pain and a feeling of heaviness in the right hypochondrium (29). Clinical and laboratory studies revealed anemia, hypoproteinemia with a decrease in the level of albumin in the blood moderate thrombocytopenia. The content of nitrogenous toxins in the blood, serum transaminases, and bilirubin did not go beyond the physiological value, but were at the level of the upper limits of the norm.

Table 1

Clinical and laboratory data of patients at admission, n = 38

Showing	**1st group**	**2nd group**
Hemoglobin, g / l	94.7 ± 2.4	91.3 ± 1.9
Red blood cells, 1012 / L	2.9 ± 0.2	2.8 ± 0.1
White blood cells, 109 / L	11.4 ± 0.9	12.0 ± 0.5
Lymphocytes,%	13.7 ± 1.1	14.1 ± 0.9
Total protein, g / l	56.3 ± 3.4	54.4 ± 2.7
Albumin,%	41.1 ± 1.0	39.8 ± 1.3
Globulins,%	59.9 ± 2.4	60.2 ± 1.4
Fibrinogen, g / l	3.5 ± 0.3	3.6 ± 0.4
Creatinine, μmol / L	145.9 ± 3.7	151.7 ± 4.0
Urea, mmol / L	13.4 ± 0.9	13.8 ± 1.2
AST, μmol / (ppm)	0.51 ± 0.04	0.49 ± 0.02
ALT, μmol / (ppm)	0.78 ± 0.05	0.76 ± 0.06
The level of average molecules	0.78 ± 0.04	0.80 ± 0.04
Glucose, mmol / L	11.2 ± 1.1	10.7 ± 0.9
Potassium, mmol / L	5.4 ± 0.3	5.2 ± 0.4
Sodium, mmol / L	146.0 ± 1.1	142.9 ± 1.6
Bilirubin, μmol / L	14.7 ± 2.1	16.9 ± 1.7
Direct bilirubin, μmol / L	3.1 ± 0.4	4.4 ± 0.3
Indirect bilirubin, μmol / L	11.6 ± 1.7	12.5 ± 1.4

As can be seen from table 1, in patients of both groups, upon admission, in addition to anemia, hypoproteinemia, a decrease in A / G coefficient (068, 0.66, respectively), an increase in the level of nitrogenous slags in the blood was observed, indicating kidney dysfunction, lymphopenia, which is indirect indicates a decrease in the immune response of patients to purulent-septic infection. The increased activity of transaminases in the blood of patients of both groups indicates necrobiotic processes in the body and, above all, in the kidneys and liver, as indicated by hypoalbuminemia and a high level of average molecular peptides in the blood. Elevated blood sugar (average group data) is entirely due to such in patients with diabetes. In patients without diabetes mellitus, the average values of blood glucose at admission were within 3-4 mmol / L. In order to verify DIC, determine its stage and assess the degree of impaired hepatic function associated with hemostasis, coagulogram data were analyzed in all patients upon admission (table. 2).

Table 2

Indices of hemostasis upon admission in patients, n=38

Indicator	**Group**			
	1st, n=19		**2nd, n=19**	
Blood coagulation time according to Sukharev, min	beginning	5.3 ± 0.2	beginning	5.7 ± 0.3
	end	6.7 ± 0.4	end	6.9 ± 0.3
International normalized ratio	1.52 ± 0.2		1.56 ± 0.2	
Plasma recalcification time, s	167.9 ± 4.4		170.1 ± 4.2	
Plasma tolerance to heparin, min	17.7 ± 1.8		18.4 ± 0.9	
Prothrombin index,%	67.6 ± 2.4		65.9 ± 3.0	
Platelets. thousand in mm3	182.7 ± 3.9		186.0 ± 2.7	
Thrombotest. degree	3.7 ± 0.3		3.6 ± 0.2	
Fibrinogen (colorimetric method), g / l	3.2 ± 0.4		3.4 ± 0.4	
Fibrinolytic plasma activity, min	407.6 ± 10.1		413.3 ± 7.6	
Fibrin degradation products (FDP)	+		+	
Activated partial thromboplastin time, s	61.9 ± 4.3		60.7 ± 3.9	

The data presented indicate the presence of DIC, as evidenced by the positive reaction of FDP. Changes in the plasma and platelet parameters of hemostasis with relatively normal values of fibrinogen indicate a transition from stage II to stage III - the stage of hypocoagulation, directly or indirectly indicating the involvement of the liver in hemostatic disorders. Our data on primary liver damage in patients with purulent-septic infection after surgical interventions (they had no history of impaired liver function) are quite consistent with the determination of the causes of liver failure by consensus of the Asia-Pacific Association for the Study of the Liver (APASL, 2014) and the opinion of T.V. Ermolova et al. (2009). Traumatic surgeries, infection, endotoxemia, and drugs are among the factors in the development of acute liver failure in ICU

patients. It was this set of factors that exerted hepato-nephro- and cerebro-toxic effects that occurred in the patients we observed. Clinical and laboratory parameters that were determined in patients during the standard intensive care adopted in our clinic, as well as in patients who additionally received hepatoprotector JetiPar company MediSina ZZP are presented in table 3.

Table 3

Clinical and laboratory parameters of patients of the 1st (numerator) and 2nd (denominator) groups

Indicator	The terms of the study after surgery, days		
	1st	3rd	5th
Hemoglobin, g / l	87.2 ± 0.2 82.6 ± 0.3	93.1 ± 1.3 ab 98.4 ± 1.5b	96.6 ± 1.4ab 99.8 ± 0.7b
White blood cells, 109 / L	13.7 ± 0.6 12.4 ± 0.4	11.8 ± 0.7 12.6 ± 0.8	10.8 ± 0.4ab 10.8 ± 0.3ab
Lymphocytes,%	11.6 ± 0.3 9.4 ± 0.4	13.3 ± 0.4ab 17.9 ± 0.7b	18.7 ± 1.0ab 24.0 ± 2.1b
Total protein, g / l	52.9 ± 2.7 53.7 ± 3.0	59.7 ± 1.4b 63.4 ± 2.0b	62.0 ± 0.7ab 65.9 ± 1.9b
Albumin,%	39.8 ± 2.7 40.4 ± 3.1	42.1 ± 1.4a 49.9 ± 1.6b	44.3 ± 1.1a 57.7 ± 2.3b
Creatinine, μmol / L	160.4 ± 4.1 157.9 ± 3.3	119.4 ± 3.7ab 103.6 ± 2.9 *	99.8 ± 1.4ab 90.1 ± 1.2b
Urea, mmol / L	12.7 ± 1.2 10.9 ± 0.8	10.6 ± 0.9 9.4 ± 0.4	9.8 ± 0.7 8.4 ± 0.4
AST, μmol / (ppm)	0.54 ± 0.05 0.56 ± 0.03	0.41 ± 0.02ab 0.33 ± 0.02b	0.35 ± 0.02b 0.30 ± 0.01b
ALT, μmol / (ppm)	0.63 ± 0.05 0.66 ± 0.04	0.60 ± 0.02 0.55 ± 0.03b	0.52 ± 0.02b 0.50 ± 0.03b
The level of secondary molecules, opt. units	0.80 ± 0.03 0.79 ± 0.04	0.62 ± 0.02ab 0.54 ± 0.03b	0.49 ± 0.03ab 0.41 ± 0.02
Potassium, mmol / L	5.0 ± 0.4 5.2 ± 0.3	4.6 ± 0.3 4.8 ± 0.2	4.3 ± 0.2b 4.1 ± 0.3
Sodium, mmol / L	149.1 ± 1.3 145.3 ± 1.1	146.9 ± 1.7 144.4 ± 1.0	147.0 ± 1.6 142.3 ± 1.4
Bilirubin, μmol / L	16.9 ± 2.3 21.7 ± 2.7	13.1 ± 1.7 12.8 ± 0.9b	11.1 ± 0.7b 10.6 ± 0.7b
Glucose, mmol / L	12.3 ± 0.9 10.7 ± 0.7	9.5 ± 0.9b 8.6 ± 0.4b	8.2 ± 0.6b 7.8 ± 0.3b

Note. p <0.05: a - differences between groups of patients on the day of the study; b - compared with the 1st day of the study.

The data presented indicate a positive effect of intensive care on the studied clinical and biochemical blood parameters of patients of both groups, which corresponded to clinical manifestations. A detailed analysis of the results demonstrates more pronounced positive changes in patients of the 2nd group, which already have 3rd and especially on the 5th day, practically all the studied blood indices improved. The increase in the concentration of total protein in the blood on the 5th day after the operation occurred mainly due to the growth of albumin. A decrease in the content of medium-molecular peptides - predictors of endotoxemia, transaminase activity, and normalization of the level of azotemia by the 5th day indicates an improvement in the functional state of the liver and kidneys. Regardless of the causes of the deficiency, in previous manuals, patients were advised to prescribe organic proteins. In our actions, we were guided by the recommendations of the ESPEN Guidelines on Parenteral

Nutrition: Hepatology [14]. To maintain the nitrogen balance, we used a specialized set of amino acids, the dose of which was 1.2-2.0 g / kg / day. In addition, in the review E.Yu. Plotnikova (2013) showed that in patients with acute liver failure with excessive protein restriction as a result of activation of muscle catabolism, the level of ammonia in the blood increases [10,14]. However, when comparing the data obtained by groups, it can be noted that the restoration of these blood parameters in patients Group 2 occurs a little earlier (from the 3rd day) and is more pronounced, which, all other things being equal, indicates a positive effect of the hepatoprotector Jetepar. So, if by the 5th day the concentration of total protein in the blood of patients of the 1st group increased by 17.2%, then in the 2nd group this growth was 22.7%, and the level of albumin increased by 11.3 and 42, respectively. 8%, which clearly indicates the restoration of the protein synthesizing function of the liver against the background of a significant decrease in necrobiotic processes in the liver, as indicated by ALT and AST, which by the 5th day decreased by 17.5 and 24.3, respectively; 35.2 and 46.5%. The decrease in the level of medium molecules on the 5th day was 38.8 and 48.2%, respectively, which may also indicate an improvement in the detoxification function of the liver and the functional state of the kidneys. Positive dynamics are also noted in the indicators of the hemostatic system (Table 4).

Table 4

Indicators of hemostasis in patients of the 1st (numerator) and 2nd (denominator) groups

Indicator	Research period after surgery, days			
	1st		2nd	3rd
Coagulation time according to Sukharev, min	beginning	5.47 ± 0.4	5.51 ± 0.4	6.01 ± 0.3
		5.35 ± 0.4	5.40 ± 0.3	5.58 ± 0.4
	end	6.30 ± 0.3	6.32 ± 0.4	6.46 ± 0.4
		5.55 ± 0.4	6.01 ± 0.3	6.08 ± 0.4
Plasma recalcification time, s	152.4 ± 3.9		146.9 ± 2.1	137.8 ± 3.1
	156.1 ± 4.0		132.2 ± 3.0	112.0 ± 2.0
Plasma tolerance to heparin, min	18.0 ± 0.3		17.5 ± 0.4	17.0 ± 0.3
	17.9 ± 0.2		15.6 ± 0.3	14.4 ± 0.2
Prothrombin index, %	59.2 ± 1.9		62.4 ± 1.5	70.8 ± 1.9
	58.4 ± 2.1		65.2 ± 1.3	71.2 ± 2.1
Platelets, 109 / mm3	167.4 ± 4.1		172.0 ± 4.2	188.1 ± 4.0
	170.1 ± 3.6		186.6 ± 3.9	204.6 ± 3.9
Thrombotest (degree)	3.6 ± 0.2		3.8 ± 0.2	4.0 ± 0.3
	3.4 ± 0.1		4.1 ± 0.3	6.1 ± 0.3
Fibrinogen g / l	346.6 ± 2.7		335.5 ± 4.0	296.5 ± 3.6
	349.7 ± 4.3		313.1 ± 3.7	287.1 ± 2.9
Fibrinolytic plasma activity, min	377.9 ± 8.4		341.0 ± 6.2	311.2 ± 4.7
	390.1 ± 9.2		297.1 ± 5.1	224.8 ± 3.9
APTT, s	57.9 ± 2.7		56.6 ± 3.0	56.2 ± 3.1
	60.1 ± 2.5		50.4 ± 2.7	47.0 ± 2.2
INR	1.5 ± 0.3		1.4 ± 0.2	1.1 ± 0.1
	1.4 ± 0.2		1.1 ± 0.1	0.9 ± 0.2

The data presented in table 4 indicate that on the 1st day after surgery the level of plasma and platelet factors shifted to the side of hypocoagulation, which indirectly indicated a deficiency of hepatic factors of hemostasis. hemostasis in patients of both groups, however, in

patients of the 2nd group, positive changes are more pronounced, which also indicates the positive role of the hepatoprotector jetepar. A more pronounced and earlier decrease in the level of average molecular peptides in patients of the 2nd group may indicate a detoxifying effect of the drug. The pathogenetic mechanisms of liver damage are very diverse. But they are all characterized by damage to hepatocytes, accompanied by inflammation, cytolysis and the development of fibrosis. The basis of pathogenetic therapy in these cases is drugs that affect the structure and function of hepatocytes. It is these funds that relate to hepatoprotectors. They are representatives of various groups of drugs. The hepatoprotector Jetepar used by us in the complex therapy of patients with purulent-septic infection contributed to an increase in the resistance of hepatocytes (a decrease in the activity of transaminases) to pathological influences, restored their neutralizing function (decrease in the level of average molecular peptides, an improvement in the urea-synthesizing function), and helped restore the protein synthesizing function of hepatocytes and their hemostatic system. The results of our studies are consistent with the literature on the positive effect of hepatoprotectors in the prevention of impaired liver function in critically ill patients [11-13,15,19]. Our observations confirm the hepatoprotective and detoxifying role of MediSina ZZP Jetepar in severe purulent-septic infection. The drug should be used in the complex treatment of patients in similar critical conditions, with the aim of preventing and assisting the treatment of developing liver complications.

CONCLUSIONS

1. In ICU patients with purulent-septic infection, one of the leading places in organ and systemic dysfunction is occupied by functional liver disorders due to numerous pathological factors affecting hepatocytes: infection, intoxication, surgical intervention, and numerous medications.
2. The most common hepatic impairment is a disorder of detoxifying, protein synthesizing function and hemostasis.
3. Prevention and early correction of conditions that occur when hepatocytes are damaged require a complex effect on the pathogenetic mechanisms of the development of functional liver disorders.
4. The use of drugs that reduce the level of toxic load and affect the mechanisms of hepatoprotection is an effective way to correct hepatic dysfunction.
5. The drug Jetepar has a hepatoprotective and detoxifying effect, acting on hepatocytes, reducing dystrophic changes in them (as evidenced by the normalization of transaminase activity indicators and a decrease in the level of average molecular peptides in the blood) and increasing their resistance to damaging factors.

REFERENCES

1. Baykova I.E., Nikitin I.G. Medicinal lesions of the liver // Gastroenterology. - 2013. - No. 2. - p. 7-15.

2. Dibirov M.D., Briskin B.S. and others. Hepatorenal syndrome and the problem of correction of protein-energy metabolism in emergency surgery of the abdominal organs // Expert. and wedge. gastroenterol. - 2009. Volume 2. - p. 83-87.

3. Eremina E.Yu. drug damage to the liver // Gastroenterology. - 2012. Volume 1. - p 16-23.

4. Ermolova T.V. Study of the effectiveness of L-ornithine-L-aspartate (Hepa-Merz) in the prevention of postoperative complications in patients with chronic liver diseases // Gastroenterology. - 2009. Volume 5. p 26-32.

5. Ermolova Yu.V. Heptral for liver damage in critically ill patients // Ukrainian honey. journal - 2011. Volume 4. p 84-85.

6. Israilova V.K., Aitkonoin G.K. Modern ideas about liver failure and treatment methods // Tomsk State University Journal. KazNMU. - 2012. - No. 4. - S. 27-28.

7. Kucheryavy Yu.A. Hepatoprotectors: rational aspects of application: Textbook. allowance for doctors. - M., 2002. - 36 p.

8. Plotnikova E.Yu., Role of L-ornithine-L-spartate in the complex treatment of patients with hyperammonemia // Clin. Prospects for gastroenterol. and hepatol. - 2013. Volume 2. p 41-49.

9. Praunyan L.M. Comparative effectiveness of hepatoprotectors and exercise with dysfunctions and liver diseases // Tomsk State University Journal. morphol. - 2015. Volume 2. p. 286-288.

10. Sorokina E.Yu. Acute liver dysfunction in patients of the intensive care unit and metabolic therapy methods // Honey. emergency conditions. - 2015. - No. 8. - p. 35-45.

11. Khazanov A.I., Rumyantsev O.N. and other Features of medicinal and viral medicinal lesions of the liver // Kremlin medicine. - 2000. - No. 1. - S. 44-47.12. Acute or chronic liver failure: consensus recommendations of the Asian Pacific Associations for the Study of the Liver // Hepatol. Int. – 2014. – Vol. 8. – P. 453-471.

13. Andrade R.J., Agundeg J.A. et al. Pharmase genomics on drug induced liver in juri // Curr. Drug Metabol. – 2009. – Vol. 10, Issue 9. – p. 956-970.

14. ESPEN Guidelines on parenteral Nutrition // Hepatol. Clin. Nutr. – 2009. – Vol. 28. – p. 436-444.

15. Kim T.Y., Kim D.Z. Acute – on chronic liver failure // Clin. Mol. Hepatol. – 2013. – Vol. 19 (34). – p. 349-359

16. Mullen K.D., Prakash R.K. Management of covert hepatic encephalopathy // Clin. Ziver Dis. – 2012. – Vol. 16, №1. – P. 91-93.

17. Wright Y et al. Management of hepatic encephalopathy // Hepatology. – 2011. – Vol. 12. – P. 84-89.

18. Zevis J.H. Drug inclucad liver disease // Med. Clin. North Amer. – 2000. – Vol. 84. – P. 1275-1311.

19. Zucena M. J., Kaplovitz N. et al. Recurrent Drug – Induced Liver Injury // J. Hepatol. – 2013. – Vol. 4. – P. 820-827.