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# The Significance of Hepatoprotectors in Thetreatment of Chronic Liver Diseases (Review)

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This article talks about the role and importance of hepatoprotectors in the pathogenetic treatment of chronic liver diseases, that is, in the treatment of chronic liver diseases. The following literature review presents current concepts and opinions on the classification, mechanisms of action and clinical effects of hepatotropic drugs in the treatment of chronic liver diseases.

Chronic viral hepatitis is one of the widespread current social and medical problems. The reason for this is that due to the lack of effective treatment, as the consequences are unpredictable, it is formed from early childhood and is common. Chronic viral hepatitis is an urgent problem not only among children, but also among adults, the prevalence of hepatotropic viral infection and severe clinical course lead to a number of chronic processes ending with cirrhosis, early disability and limitation of life expectancy; lack of high efficiency and adequate treatment [V.F.Uchaykin, 2001; N.I. Nisevich, 2001; B.S. Kaganov, 1998; K.P. Mayer, 1999].

Complex treatment of liver diseases includes two main directions: etiotropic and pathogenetic therapy. Etiotropic therapy is used in parenterally transmitted viral hepatitis to stop the replication of viruses, to stop them from causing the disease, and to ensure the elimination of viruses (Kotovich M.M. 2003; Kramaryov S.A. 2009).

Yakovenko E.P. (2008) determined that pathogenetic therapy is important in any chronic liver disease, and one of its main components is hepatoprotectors. These drugs increase the resistance of hepatocytes to pathological effects; restores the impaired functions of liver cells and causes an increase in antitoxic function. The author defines the main factors affecting the choice of hepatoprotectors: the cause of the disease; the presence of cholestasis (increased levels of alkaline phosphatase and y-glutamyltranspeptidase in the blood); the level of activity of the pathological process; the need for continuous antifibrotic therapy; that there is an autoimmune reaction in the pathogenesis of hepatocyte necrosis.

Today, there is no generally accepted classification of hepatoprotectors. Depending on the origin and chemical structure of the drug, several groups of hepatoprotectors are distinguished (Okovityy S.V. 2002; Mubarakshina O.A. 2008; Tkach S.M. 2009):

1. Preparations containing natural or semi-synthetic flavonoids of the asparagus plant are primarily silymarin (karsil, hepabene, legalon, hepatofalk planta, etc.).
2. Preparations preserving natural or semi-synthetic flavonoids of other plants (khofitol, LIV-52, hepaliv, etc.)
3. Organopreparations obtained from animals (sirepar, hepatosan).
4. Phospholipids essential preservative preparations (FES) (essentiale, fosfogliv, etc.).
5. Drugs of various groups: nonsteroid anabolics, vitamins and vitamin-like substances (V, E, S lipoic acid), ursodeoxycholic acid, amino acids and their products (ademetionine - heptral, ornithine).

The mechanism of action of hepatoprotectors includes [Yakovenko E.P. 2008]:

- Increases the activity of enzymes involved in oxidation or increases their detoxification function as a result of increasing the accumulation of glutathione, taurine, sulfates in the hepatocyte;

Reparation of cell membrane structures and binding of products of free radical oxidation of lipids (hydrogen peroxide, O++ and H+, etc.), inhibition of excess oxidation of lipids by free radical formation;

- Anti-inflammatory effect;

Blocking of fibrogenesis at the expense of: elimination of necrosis of hepatocytes; - prevention of antigens from the gastrointestinal tract as a result of the translocation of bacteria and their toxins from the intestines due to the activation of copper cells; blocking enzymes involved in the synthesis of connective tissue components and stimulation of collagenase activity in the liver.

From the above, it can be concluded that currently many drugs have hepatoprotective activity.

**Natural or semi-synthetic flavonoid preservatives of other plants (khofitol).** Khofitol is a medicinal preparation obtained by grinding artichoke leaves from plants and has wide clinical significance. Due to the multifaceted effects of Khofitol and its main biologically active components (caffeol and citric acid, flavonoids, sesquiterpenlactone, vitamins A, V1, V2, C and a number of important trace elements), its therapeutic potential is used. The drug has choleretic and cholekinetic, hepatoprotective, antioxidant, antitoxic, hypoazotemic and diuretic properties, besides, it stimulates the biosynthesis of phospholipids, proteins and hepatocyte regeneration.

All the authors who studied Khofitol in clinical conditions determined the positive effect of the drug during course treatment: it reduces or eliminates asthenic and dyspeptic syndromes that develop as a result of exogenous and endogenous intoxication in chronic hepatitis. This drug inhibits cholesterol synthesis, has an antioxidant effect, increases the formation of bile (choleretic effect), protects the cell membrane from damage [Grigorev P.Ya. 2003; Dogtyareva P.I., Kharchenko N.V. 2003; Minushkin O.N. 2003; Perederiy V.G. et al., 2004; Potapov A.S. et al., Mubarakshina O.A 2008].

Belyaev N.M. and all. (2004) used Khofitol drug in complex treatment of viral hepatitis. The results of the analysis provide information about the clinical effectiveness of Khofitol in the complex treatment of acute viral hepatitis, mainly in the cholestatic form of viral hepatitis A, as well as biliary dyskinesia. In many patients who received Khofitol, good signs were achieved in the dynamics with mesenchymal-inflammatory, cytolytic and cholestatic (hypokinetic type) syndromes, which allows recommending its use in cases of compensated cirrhosis due to viral hepatitis and chronic hepatitis of various etiologies against the background of antiviral treatment.

Minushkin O.N. and all. (2004) used xofitol in the treatment of chronic hepatitis. The obtained results show that Khofitol drug is an effective tool in the treatment of chronic hepatitis of various etiologies with weak or moderate activity. In this case, the aggravation of the cytolytic and mostly cholestatic syndrome decreases, the intensity of clinical symptoms significantly decreases or disappears, and the antitoxic function of the liver improves, testifying to the hepatoprotective effect of the drug. According to the known properties of Khofitol, hepatoprotective, antitoxic and hypocholesterolemic effects were confirmed in this investigation, which allows the drug to be widely used in clinical practice.

**Aminoacids and their products (ademetionine-heptral).** Ademethionine (S-adenosyl-L-methionine) is a product of L-methionine and adenosine triphosphoric acids synthesized in the liver and is a natural substance. Ademetionine is widespread

in all biological systems of the body and covers various metabolic processes [Frezza M., Terpin M. 1992]. It is involved in three important metabolic processes: transmethylation, transsulfuration and aminopropylation. In this reaction, it sometimes participates as a methyl group donor and sometimes as an enzyme inducer.

Many biological effects of ademetionine are determined depending on the significant amount of the biochemical cascade that affects the listed reactions [Kolomoets A.V., Usenko L.V., Kobelyatsky Yu.Yu., Mosentsev N.F., 2008].

The mechanism of hepatoprotective action of ademethionine (heptral) occurs due to the following effects [Podymova S.D., Nadinskaya M.Yu. 1998]:

1. Ademetionine (heptral) participates in the transmethylation reaction due to the property of biosynthesizing phospholipids, which are the main building block of the cell membrane;
2. Ademetionine (heptral) participates in the synthesis of polyamines such as putrescine, spermidine and spermine, and they play an important role in the regeneration process of hepatocytes and the formation of ribosome structures;
3. Ademetionine (heptral) shows antifibrotic activity in the experiment;
4. Ademetionine (heptral) has the property of forming glutathione, the main antioxidant of the cell, which neutralizes a number of exo- and endotoxins.
5. Ademetionine (heptral) is a sulfur-preserving peptide - it participates in keeping the content of glutathione in sufficient quantity, and it has the property of protecting liver cells from the toxic effects of free radicals;
6. Ademetionine (heptral) participates in the sulfation reaction, plays an important role in the detoxification of a number of metabolites. For example, it converts toxic bile acids into sulfates, which do not have a damaging effect on cells;

Ademetionine (heptral) in high concentration affects the process of transmethylation in nervous tissue. This is an important link in the metabolism of catecholamine (adrenaline, noradrenaline), indolamine (serotonin, melatonin) and histamine, which is the main neurotransmitter due to its antidepressant effect on the MNS [Perederiy V.G., Chernyavsky V.V., Shipulin V.P., 2008]. If ademetionine was added to the complex treatment of patients with chronic hepatitis C and ribavirin combined with interferon therapy, then virological results were achieved in 71% of these patients. Ademetionine was also accompanied by a biochemical response in all patients included in the trial. It is appropriate to prescribe ademetionine to eliminate intrahepatic cholestasis syndrome developed against the background of interferon treatment of patients with chronic hepatitis C [Podymova S.D., Nadinskaya M.Yu. 2008]. Carrying out a full course of interferon therapy allows to eliminate cholestasis in such patients. Ademetionine increases the commitment to antiviral treatment of patients with chronic hepatitis C, and its antidepressant effect is also commendable. Various diseases of the liver with ademetionine intrahepatic cholestasis are chronic viral hepatitis, toxic hepatitis, alcoholic hepatitis, biliary cirrhosis, liver encephalopathy [Kolomoets A.V., Usenko L.V., Kobelyatsky Yu.Yu., Mosentsev N.F., 2008] will be an instruction for .

Unfortunately, until now, there is no information on the use of ademetionine (heptral) in pediatric practice, especially for the treatment of chronic viral hepatitis in children.

In the last 10 years, progress has been made in the use of ursodeoxycholic acid (UDXC) in hepatology. UDXK is a hydrophilic non-toxic tertiary bile acid, which is formed from 7-ketolithocholic acid under the action of a bacterial enzyme and enters the small intestine from the liver. It is 4% in human natural bile acid [Bueverov A.O.

2005].UDXK hepatoprotective action mechanism due to the following effects [Kharchenko N.V. 2002; Bueverov A.O. 2005].

1. Membranostabilizing effect:

- reduces the circulation of hydrophobic bile acids and prevents their toxic effect on bile duct epithelium and hepatocyte membrane;
- normalizes the HLA-DR antigen expression on the surface of the cell membrane, stops the production of immunoglobulins, weakens their autoimmunity and reduces the indirect immunosuppression of cholestasis;
- placing UDXK in the phospholipid layer of cholangiocyte and hepatocyte cell membrane restores their structure and increases resistance to damaging factors (viruses, toxins, alcohol);

2. Choleretic effect:

- receptors in the ileum squeeze out toxic hydrophobic bile acids due to the coverage of their competitors;
- reduces the concentration of hydrophobic bile acids in hepatocytes, leads to stimulation of exocytosis by activating Sa-dependent α-protein kinases;
- increases the release of hydrophobic bile acids into the intestine and induces bicarbonate choleresis;

3. Antiapoptotic and antifibrotic effects: cholangiocyte and hepatocyte apoptosis and caspase activity are blocked in place, leading to the prevention of cytochrome C release from mitochondria, reducing the concentration of ionized Ca in the cell;

4. Antioxidant effect: Kupfer reduces the oxidizing activity of hydrophobic bile acid in cells, activates glutamine-regenerating enzyme;

5. Anti-inflammatory effect: reduces the expression of HLA class II molecules on cholangiocytes and HLA class I molecules on hepatocytes, reduces the production of anti-inflammatory cytokines (interleukin 1,2,6, α - tumor necrosis factor, α - interleukin);

6. Litholytic effect - due to the formation of liquid crystal with cholesterol molecule, UDXK reduces the lithogenicity of bile fluid, and also dissolves cholesterol stones and prevents the formation of cholesterol stones.

In addition to litholytic and choleretic effects, UDXK also has hepatoprotective, antioxidant and immunomodulatory properties. It can be seen that it allows to use UDXK as a pathogenetic agent in the treatment of various clinical forms and variants of viral hepatitis in children. Lapenna D called the UDXK a great "scavenger" of free radicals. UDXK is known to have a hypocholesterolemic effect, in addition, it has a good effect on one more important link in the pathogenesis of chronic viral hepatitis D - steatosis (decreased absorption of cholesterol in the intestines, synthesis in the liver and secretion of bile fluid) [F.I. Inoyatov et al., 2006] .

F.I. Inoyatov et al., (2006) used UDXK to treat children infected with chronic viral hepatitis D. After 3, 6, and 12 months of use of UDXK for the treatment of children with chronic viral hepatitis D, improvements in liver function tests were observed, and good results were achieved in all patients. During the treatment with UDXK, it was found that the children had chronic viral hepatitis with delta cholestasis syndrome, and clinical and biochemical effects occurred after UDXK was prescribed.

It was also found that 3 months after the start of treatment, it had a good effect on the condition of liver tissue and gall bladder.According to the data of this investigation, in the treatment of UDXK, a repeated course of treatment should be prescribed to prevent relapse of the disease. The drug is prescribed to children at a dose of 10-12 mg/kg of body weight per day before going to bed.

Uchaykin V.F. et al. (2003), in the treatment of chronic hepatitis, UDXK is often used simultaneously with interferon therapy. In the treatment of acute and chronic liver diseases [Avezov S.A., Mansurova F.Kh., 2004] suggested using ursodeoxycholic acid (UDXK) and heptral in a combined form. This combination is the main moment of the pathogenesis of the disease and improves the clinical-biochemical and immunological indicators of the disease due to its immunomodulatory, antiapoptotic, antioxidant and choleretic effects.

Reyzis A.R. and others (2001) suggested the use of UDXK drug in all forms of acute and chronic hepatitis of any etiology, toxic hepatitis of various genesis, and chronic viral hepatitis: in the non-replication phase - as monotherapy, and in the replication phase - in combination with an antiviral drug.

In conclusion, we wanted to highlight the selection algorithm for prescribing hepatoprotectors in chronic liver diseases [E.P. Yakovenko 2008].

1. Presence or absence of cholestasis. If patients have cholestasis (only γ-glutamate transpeptidase increases), ademetionine or UDXK is prescribed. If the levels of γ-glutamate transpeptidase and alkaline phosphatase increase, the patient's treatment begins with the appointment of UDXK drug.

2. If there is an active inflammatory process in the liver (increased levels of ALT, AST). When the inflammatory process is accompanied by cholestasis, demethionine together with UDXK is prescribed intravenously at a dose of 15 mg/kg per day for 10-15 days, then the reception of UDXK is continued until the signs of cytolysis and cholestasis disappear. If the activity of the process is moderate and cholestasis is not observed (the amount of ALT, AST increases up to 5 times compared to the norm), EFL or ademetionine (or α-lipoic acid) is used parenterally for the course of treatment until the enzyme indicators are normalized. It is recommended to stop the course of treatment with hepatoprotectors after 1 month after the signs of cytolytic syndrome have subsided.

3. Organization of etiological factors. When the liver is infected with viruses, when it is not possible to carry out anti-viral therapy, a course of UDXK drug is prescribed for no less than 6 months.

4. Achieving an antifibrotic effect. To achieve this goal, the UDXK course is prescribed for a period of not less than 6 months.

5. UDXK drug is used to improve the process of digestion and when diseases of the biliary system are combined.

Thus, from the above data it can be concluded that until now there is no ideal hepatoprotector.

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