American Journal of Medicine and Medical Sciences 2022, 12(5): 595-598
DOI: 10.5923/j.ajmms.20221205.29

Pharmacological Correction of Cytolytic Syndrome in Isoniazid-Induced Acute Hepatitis

Khudayberdiev Kh. I.

Department of Pharmacology, Tashkent Medical Academy, Tashkent, Uzbekistan

Abstract The comparative hepatoprotective activity of lesbokhol, celagrip, konvaren and legalon was studied in experiments on 30 white outbred male rats weighing 180–200 g. The acute toxic hepatitis was induced by the orally administration of the anti-tuberculosis drug (ATD) - isoniazid at a dose of 70 mg/kg. The effectiveness of the investigated medicines lesbokhol (25 mg/kg), celagrip (25 mg/kg), convaren (50 mg/kg) and legalon (100 mg/kg) in eliminating the cytolytic syndrome was established. The cytolysis markers activity of the alanine aminotransferase (ALT, in IU/l) and aspartate aminotransaminase (AST, in IU/l) was determined in blood. there was an increase in ALT activity by 150.6% and AST by 36.7% under the influence of isoniazid in rats. The activity of ALT in comparison with the control group was lower by 33.5% in the group of animals treated with lesbokhol and by 33% in the group of animals treated with legalon. Along with this, in the groups of animals treated with lesbokhol, celagrip, convaren, and legalon, the activity of AST in the blood serum also decreased compared to the control group by 15.5%, 21.7%, 13.5%, and 11.9%, respectively. With respect to the low toxicity of Celagrip and its higher hepatoprotective activity, we consider the possibility of using it in patients with tuberculosis in the treatment of drug-induced hepatitis.

Keywords Toxic liver damage, Anti-tuberculosis drugs, Lesbokhol, Celagrip, Convaren

1. Introduction

Chronic diseases of the hepatobiliary system are the main causes of death among economically developed countries. Annually, 40 million people die from cirrhosis of the liver and hepatocellular carcinoma in the world [1].

In addition to viruses, some household chemicals, pesticides, alcohol, industrial substances, and a number of drugs also have a hepatotoxic effect [2].

The amount of drugs consumed by the population, the appearance of a new generation of drugs with high pharmacological activity, the irrational use of drugs, medical errors, and the use of counterfeit drugs ultimately lead to liver damage, since the detoxication function of the liver is central to the biotransformation of xenobiotics. About 10–28% of all adverse reactions from the application of pharmaceutics lead to various liver damage, up to fulminant liver failure [3].

In recent years, the number of cases of drug-induced liver damage has increased significantly. This problem is faced by physicians of all specialties, and there are some difficulties in diagnosis and treatment in time [4].

* Corresponding author:
dmcuz@mail.ru (Khudayberdiev Kh. I.)
Received: Apr. 19, 2022; Accepted: May 13, 2022; Published: May 27, 2022
Published online at http://journal.sapub.org/ajmms

It is noted that a good clinical effect is not always achieved with the use of legalon (reference hepatoprotector). A decrease in the permeability of cell membranes under the influence of silymarin is associated with stimulation of protein and phospholipid synthesis, which leads to stabilization of cell membranes. As a result, the loss of cell components, including intracellular enzymes - transaminases, is prevented, which is clinically manifested by a decrease in the cytolytic syndrome. In addition, silymarin prevents the penetration of certain hepatotoxic substances, in particular the poison of *Amanita phalloides*, into the cell. However, the low bioavailability of silymarin when taken orally, the possibility of intensifying the cholestasis syndrome, and proven efficacy only when it is administered intravenously in viral hepatitis C can be attributed to the disadvantages of this group of drugs. [5,6,7]. Therefore, the development of new, effective medicines for the treatment of drug-induced liver damage or the comparative evaluation of known drugs is an urgent problem in pharmacology.

The aim of this work was an experimental study of Celagrip, Lesbokhol, Convaren and Legalon on the course of the cytolytic syndrome in drug-induced liver injury.

2. Material and Methods

2.1. Experiments

The experiment was carried out on 30 outbred male rats in the department of pharmaco-toxicological researches of the Interuniversity Research Laboratory of the Tashkent Medical Academy.

Before the start of the study, the animals were kept in a 10-day quarantine, during which the rats were examined and the body weight, behavior, and general condition of the animals were recorded. The main criteria for the inclusion of animals in the study were body weight (not less than 180–200 g); wool cover (smooth and shiny); behavior and general condition (active dynamics of movement and feed consumption). Before the start of the study, rats meeting the inclusion criteria were randomly divided into several groups. The studies were carried out at room temperature 20-22℃.

An experimental model of liver pathology was created according to the method of G.N. Mozhokina [8] by administering the anti-tuberculosis drug (ATD) isoniazid at a dose of 70 mg/kg intragastrically for 10 days.

In the experiment, the animals were divided into six groups: 1st group — intact rats; 2nd group- control group, animals were received distilled water; 3rd group- rats were received lesbokhol at a dose of 25 mg/kg per os; 4th group- rats were received celagrip at a dose of 25 mg/kg per os; 5th group - rats were received konvaren at a dose of 50 mg/kg; 6th group-rats were received legalon at a dose of 100 mg/kg.

The studied medicines were used intragastrically after a 10-day administration of the anti-tuberculosis drug isoniazid. Control animals received distilled water in the same volume. The above-studied medicines were administered once daily for six days.

Animals were sacrificed by simultaneous decapitation and blood was taken for biochemical studies. The determination of cytolysis markers (activity of the alanine aminotransferase (ALT, in IU/l) and aspartate aminotransaminase (AST, in IU/l) was included in the complex of biochemical studies. Biochemical blood tests were performed on a Mindray semi-automatic biochemical analyzer (China, 2014) using test kits from Human (Germany) and Cypress Diagnostics (Belgium). Experimental studies were carried out in accordance with the "Rules for Conducting Work Using Experimental Animals", as well as the rules adopted by the European Convention for the Protection of Vertebrate Animals used for experimental studies or for other scientific purposes (ETS No. 123), Strasbourg, 18.03.1986.

2.2. Statistical Analysis

The data obtained were processed by the method of variation statistics using the paired Student's test and one-way analysis of variance using the standard software package BIOSTAT 2009 with an assessment of the significance of indicators (M ± Std. error). Differences in the compared groups were considered significant at a significance level of 95% $p < 0.05$.

3. Results and Discussion

The choice of isoniazid as a drug for the study was due to the fact that it belongs to the first-line drugs for the treatment of tuberculosis, as well as data indicating that it causes liver damage in 5.4 to 85.7% of patients who receive it for the treatment of tuberculosis [8].

The cytolytic syndrome is one of the main reasons leading to the death of hepatocytes or the development of hyperenzymemia. In clinical practice, a biochemical study of the activity of ALT and AST enzymes in blood serum is often used for the evaluation of the level of this syndrome [5].

The results of the studies showed that there was an increase in ALT activity by 150.6% and AST by 36.7% under the influence of isoniazid in rats (table 1). An increase in the concentration of these enzymes in the blood indicates a significant increase in the permeability of cell membranes and necrosis of hepatocytes.

Table 1. Comparative study of the effect of some new medicines on the activity of ALT and AST in blood serum in rats with isoniazid-induced toxic hepatitis (M ± Std. error, n=6)

Indicators / Groups	ALT, IU/l	AST, IU/l
Intact	57,24 ± 2,17	110,70 ± 8,07
Control	143,47 ± 7,10*	151,37 ± 8,28*
ADIH + Lesbokhol	95,34 ± 6,81*#	127,87 ± 7,07
ADIH + Celagrip	77,01 ± 2,09*#	118,52 ± 7,12*
ADIH + Konvaren	99,84 ± 10,25*#	130,86 ± 8,54
ADIH + Legalon	96,13 ± 8,84*#	133,41 ± 9,05

Note: * - statistically significant differences compared to intact.
- statistically significant differences compared to control.
ADIH- acute drug-induced hepatitis.

Since ALT is an indicator enzyme, its level in the blood indicates damage to the cytoplasmic membranes of liver cells, and its high activity in the blood serum indicates deep cell damage. AST acts as a mitochondrial- cytoplasmic enzyme with a pronounced predominance in mitochondria. Therefore, different ratios of the activity of these enzymes are used to assess the depth of damage to hepatocytes in the pathology of the hepatobiliary system [9].

The minimum amounts of ALT and AST are normally determined in blood plasma due to the fact that they get there during the physiological life cycle of the cells. The active death of many hepatocytes leads to the entry of these intracellular enzymes into the blood and, accordingly, to an increase in their level [10].

The results once again confirm the hepatotoxicity of isoniazid. It is believed that its hepatotoxicity is associated largely with the biotransformation of the drug in the body. The impact of various metabolites resulting from the acetylation of isoniazid can occur in the form of hepatitis

and hepatosis, and requires the administration of hepatoprotectors with the different mechanisms of action [8,10,11].

We have used a number of new medicines with high hepatoprotective activity in the treatment of drug-induced liver damage with isoniazid. Thus, lesbokhol contains a mixture of dry extracts of four medicinal plants: *Hypericum scabrum L., Ziziphora pedicellata, Mediasia macrophylla, Glycyrrhiza glabra L*. [12]. Celagrip is a polymeric complex of gossypol with cellulose. It has a pronounced ability to induce the level of interferons in the body [12].

Konvaren is the sum of extracts of biologically active substances of the aerial part of Convolvulus arvensis L. It has a distinct choleretic effect [14].

The effectiveness of these medicines was compared with the activity of silymarin (trade name Legalon®), a classic hepatoprotector derived from Silybum marianum [6,7].

The results of studies on the effects of these medicines on the cytolytic syndrome showed a clear positive effect of all the studied medicines. Thus, the activity of ALT in comparison with the control group was lower by 33.5% in the group of animals treated with lesbokhol and by 33% in the group of animals treated with legalon. From the data in the table, it can be seen that in terms of their activity, konvaren and lesbokhol have the same activity. Celagrip showed a statistically significant greater activity in comparison with legalon (decrease in enzyme activity by 46.3%). Along with this, in the groups of animals treated with lesbokhol, celagrip, convaren, and legalon, the activity of AST in the blood serum also decreased compared to the control group by 15.5%, 21.7%, 13.5%, and 11.9%, respectively.

Summarizing the obtained results, it can be concluded that there is a pronounced cytolytic syndrome in hepatitis induced by the first line anti-tuberculosis drug isoniazid. Celagrip was the most effective in the elimination of cytolytic syndrome. Celagrip is a gossypol polymer complex that has the ability to stimulate the formation of endogenous interferon and a distinct antioxidant property [13]. So, celagrip significantly reduces the content of initial and intermediate products of lipid peroxidation in animals with acute toxic hepatitis. This effect of the medicine is accompanied by a decrease in the activity of ALT and gamma-glutamyltransferase (GGT) by 2-3 times in the blood, which indicates the restoration of the functional state of the plasma membranes of hepatocytes. At the same time, an increase in the exocrine function of the liver and the content of bile, bile acids, cholesterol, and bilirubin indicates the restoration of the functional activity of hepatocytes. It is noteworthy that such an effect of Celagrip in the treatment of acute toxic hepatitis is accompanied by an increase in biotransformation and glucuronidization of xenobiotics and a restoration of the protein-synthetic function of the liver [13].

Like celagrip, konvaren also has high antioxidant activity. It was shown that in animals with toxic hepatitis, the level of lipid peroxidation products (LPO) in the blood-acetyl hydroperoxide (AcHP), malondialdehyde (MDA)- significantly decreases under the influence of the extract of the aerial part of Convolvulus arvensis L., which indicates a decrease in the intensity of lipid peroxidation, which allows the restoration of the functional activity of biological membranes of liver cells with the restoration of the intensity of biochemical processes occurring in them [17].

4. Conclusions

1. Subchronic administration of isoniazid into rats causes the development of drug-induced hepatitis, which manifests in the development of the cytolytic syndrome.
2. Treatment with celagrip reduces the degree of cytolytic syndrome more than convaren and legalon.
3. With respect to the low toxicity of Celagrip and its higher hepatoprotective activity, we consider the possibility of using it in patients with tuberculosis in the treatment of drug-induced hepatitis.

REFERENCES

[1] Skuratov A.G., Lyzikov A.N., Voropaev E.V., Achinovich S.L., Osipov B.B., 2012, Experimental modeling of toxic damage to the liver. Problems of health and ecology, 4, 27-33.

[2] Antonenko O.M., 2013, Toxic lesions of the liver: ways of pharmacological correction. Medical Council, 6, 45-51.

[3] Zvyagintseva T.D., Chernobay A.I., 2011, Medicinal hepatitis: from pathogenesis to treatment. Newspaper "Medicine and Pharmacy News», Gastroenterology, 375, 23–28.

[4] Loginov A.F., Butorova L.I., Loginov V.A., 2016, Drug-induced liver injury: diagnosis, treatment, 11, 721-727.

[5] Busalaeva E.I., Tarasova L.V., Matveeva T.S., 2015, Hepatoprotectors in clinical practice. Selection algorithm. Zhurn. "Health of Chuvashia", 2, 42-51.

[6] Matveev A.V., 2013, Hepatoprotectors. Analysis of international studies on preparations of a group of drugs for the liver, Simferopol: IT "ARIAL", 384.

[7] Okovity S.V., Sukhanov D.S., Romantsov M.G., 2012, Hepatotropic drugs: current state of the problem. Therapeutic archive, 2, 62-68.

[8] Mozhokina G.N., Elistratova N.A., Mikhailova L.P., Makarova O.V., Sultanov V.S., Trusov V.B., 2014, Experimental rationale for the use of roprene to prevent isoniazid-induced liver damage. Tuberculosis and Lung Diseases, 7, 47-53.

[9] Kishkun A.A., Clinical laboratory diagnostics: textbook. -2nd ed. revised and additional –M.: GEOTAR-Media, 2019, 873.

[10] Higgins K. Deciphering clinical laboratory tests. 7th ed. Knowledge Lab, 2016, 592.

[11] Ayusheeva L.B. Polyphytochol – a new hepatoprotector in the clinic of tuberculosis: Ph.D. dissertation for the degree of candidate of medical sciences, Moscow, 1998, 21.

[12] Khakimov Z.Z., Rakhmanov A.Kh., Mavlanov Sh.R. The effectiveness of a mixture of extracts of medicinal plants in the correction of violations of the functional state of the liver in its lesions of various etiologies. Monography, Tashkent, "O'zkitobsavdonashriyoti", 2020, 153.

[13] Khakimov Z.Z., Faizieva Z.T., Makhmudov S.S. The effect of celagrip, an interferon inducer, on the hepatobiliary system. Monography, Tashkent, 2017, 130.

[14] Khudaiberdiev Kh.I, Khakimov Z.Z., Rakhmanov A.Kh., 2021, Evaluation of the Pharmacological and Therapeutic Effects of Drugs of Natural Origin in the Management of Biliary Insufficiency in Tetracycline Induced Hepatitis. American journal of Medicine and medical sciences, 11, 6, 471-475.

[15] Nikolaev V.P. Liver damage caused by isoniazid and its prevention (clinical and experimental study). // Abstract of the thesis. diss. cand. -M., 1987, 26 p.

[16] Khakimov Z.Z., Mirzokhidov Kh.A., Tsoi I.V., Musaev U.N., 2007, Influence of Convolvulus arvensis extract on the intensity of lipid peroxidation in acute toxic hepatitis. Journal of Theoretical and Clinical Medicine, 2, 13-14.

[17] Akramova Ya.Z., Tsoi I.V., Khakimova D.Z., 2010, Influence of konvaren on metabolic processes intensity of lipid peroxidation in drug-induced liver injury. Pharmaceutical Bulletin of Uzbekistan, 1, 54- 58.