CATACIN AND GERANYL, COMPARATIVE EVALUATION OF THEIR HEPATOPROTECTIVE EFFECT ON THE MODEL OF ACUTE TOXIC DAMAGE OF RAT LIVER

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Abstract: *the article presents data on the pathogenesis of toxic liver damage, the main factors leading to the chronization of the pathological process, in particular, a decrease in oxygen intake, an imbalance of oxidative processes, activation of immuno-mediated and mitochondrial pathways of apoptosis, fibroblast growth factors. Also the results of the evaluation of new domestic preparations, namely, Cavergal, Geranyl and Catacin in the correction of the major hepatic syndromes: cytolysis, cholestasis, mesenchymal inflammation and hepatocellular insufficiency of toxic liver injury of rats.*
Keywords: *Cavergal, Geranyl, Catacin, Karsil, oxidative stress, hypoxia, apoptosis, fibrosis, mesenchymal inflammation, cytolytic syndrome, hepatocytes.*

КАТАЦИН И ГЕРАНИЛ, СРАВНИТЕЛЬНАЯ ОЦЕНКА ИХ ГЕПАТОПРОТЕКТИВНОГО ДЕЙСТВИЯ НА МОДЕЛИ ОСТРОГО ТОКСИЧЕСКОГО ПОРАЖЕНИЯ ПЕЧЕНИ КРЫС

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Аннотация: *в статье приведены данные о патогенезе токсического поражения печени, об основных факторах, приводящих к хронизации патологического процесса, в частности, снижение поступления кислорода, дисбаланс окислительных процессов, активизация иммуноопосредованного и митохондриального путей апоптоза, факторов роста фибробластов. Также рассмотрены результаты оценки эффективности новых отечественных препаратов, а именно, кавергала, геранила и катацина в коррекции основных печеночных синдромов: цитолиза, холестаза, мезенхимального воспаления и печеночно-клеточной недостаточности на модели токсического поражения печени крыс.*
Ключевые слова: *кавергал, геранил, катацин, карсил, окислительный стресс, гипоксия, апоптоз, фиброзирование, мезенхимальное воспаление, цитолитический синдром, гепатоциты.*

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The central element of the pathogenesis of toxic liver damage is oxidative stress, hypoxia, dysfunction of oxidase and oxygenase enzyme systems, a violation of calcium metabolism – a consequence of the direct effects of the toxin or its metabolite formed as a result of biotransformation [6]. The immediate cause of this deficiency in many pathological conditions is a decrease in oxygen intake, imbalance of oxidative processes, activation of immuno-mediated and mitochondrial pathways of apoptosis, fibroblast growth factors, causing irreversible processes of fibrosis, leading to the chronization of the pathological process [6, 8, 9]. Damage and destruction of hepatocytes is a starting point in the activation of other cell populations that initiate an inflammatory response, an adaptive immune response with the development of reactive liver fibrosis (cirrhosis) and hepatocellular cancer [3, 9].

Currently, for the treatment of toxic liver lesions means of plant origin are widely used [10]. In this regard, the problem of remedy correction of liver lesions with herbal preparations (from flavonoids, saponins, coumarins, terpenoids) is extremely important. Widely used drugs such as Cavergal, Essentiale, Silibor, Silymarin, Phosphogliv etc. that have diverse action [5, 9, 10]. The development and study of the mechanism of their hepatoprotective action will not only expand the Arsenal of effective hepatoprotectors, but also introduce them into clinical practice. Despite the presence of different mechanisms of action of hepatoprotectors, their effectiveness remains low, which necessitates the development of new high-performance hepatoprotectors and the study of their mechanism of action.

Purpose of work: to evaluate the effectiveness of new products (Cavergal, Geranyl and Catacin) in the correction of the major hepatic syndromes:

cytolysis, cholestasis, mesenchymal inflammation and hepatocellular failure on the model of toxic liver disease.

Material and methods of research. To achieve this goal, studies were conducted on 60 Mature male rats. The model of acute toxic lesion (ATL) was reproduced by a single injection of heliotrin at a dose of 200 mg/kg of animal body weight in 75 rats, 8 rats were an intact group. The mortality rate for 1-3 days was 13.3%. The development of toxic hepatitis was judged by the activity of ALT and AST, the content of bilirubin and its fractions in the blood. On the 3rd day of toxicant administration the surviving animals were divided into 5 groups: 1) ATL+Saline solution at a dose of 5 ml/kg body weight (control) 15 rats; 2) ATL+Carsil (comparison group) 13 rats; 3) ATL+Catacin 13 rats; 4) ATL+Geranyl 13 rats; 5) ATL+Cavergal 13 rats. The medicines were administered intragastrically at 100 mg/kg for 12 days daily. After 6 and 12 days from the beginning of treatment, animals were slaughtered under Rausch anesthesia in compliance with the rules specified by the European Convention for the protection of vertebrates (Strasbourg, 1986). Biochemical studies of blood serum (content of albumins, prothrombin, bilirubin fractions, cholesterol, activity of enzymes alanine- (ALAT) and aspartate aminotransferase (ASAT), gamma-glutamyltranspeptidase (γ-GT), alkaline phosphatase (aph), thymol sample) were performed on a biochemical analyzer. The obtained data were processed by the method of statistics using computer program Statistica 5. They were considered reliable difference at $P<0.05$.

Results and discussion. The studies have shown the development of cytolysis syndromes, cholestasis, mesenchymal inflammation and hepatocellular insufficiency in rats with acute heliotrine hepatitis, which corresponds to the literature data. It should be said that if the indicators of the cytolytic syndrome were sharply manifested on the 6th day of the study, and then their severity decreased somewhat, although still significantly higher than the standard values. The same dynamics was noted for the indicator of mesenchymal inflammation, while the indicators of cholestasis and hepatic cell insufficiency increased slightly and remained significantly high. In our opinion, this is due to the development of hypoxia of hepatocytes, as according to the literature in acute liver damage by heliotrin, microcirculatory disorders are detected, manifested by the expansion of the diameter of the vessels, a decrease in blood flow in them, the aggregation of shaped elements in the vessels, the phenomena of stasis, hemorrhages and destructive changes in the liver parenchyma [8]. Under these conditions, circulatory and metabolic hypoxia cause increased destructive processes in biomembranes and, as a consequence, the intensification of LPO, the development of an imbalance between prooxidant and antioxidant systems, due to the suppression of the activity of antioxidant enzyme systems due to the decay and inhibition of the synthesis of their protein components, and primarily, SOD, catalase, glutathione peroxidase, glutathione reductase, etc.

Pharmacotherapy with hepatoprotectors contributed to the reduction of high values of cytolysis, mesenchymal inflammation, cholestasis and increase in liver cell failure. However, their severity depended on medicines. Thus, the using of Catacin, Geranyl, Cavergal and the Karsil for 6 days led to a significant decrease of activity of AlAT of 2.76; 2,94; of 1.85 and 2.86 times, activity of AsAT under the action of these medicines did not change significantly. The same dynamics continued in the future. The level of total, bound and free bilirubin 1.97; 2.11 and 1.8 times when using Catacin, 2,98; 4,35 and 2.04 times – when used Geranyl, 1.83; 2 and 1.62 times – Cavergal, 2.31; 2.42 and 2.16 times – Karsil, respectively. The incidences of mesenchymal inflammation statistically significantly decreased in 1,4; 1.56; 1.31 and 1.38 times, respectively. The high activity of alkaline phosphatase and γ-GT under the influence Catacin decreased to 2.07 and 3.06 times, Geranyl 2 and 3.17 times, Cavergal – 1.91 and 1.13 times, and Karsil – 2.47 and 2.88 times respectively. It should be noted that the medications increased the initially low level of albumin 1.29; 1,39; 1.41 and 1.31% in the groups of rats with ATL treated Catacin, Geranyl, Cavergal and Karsil, respectively.

The level of total, bound and free bilirubin with the use of Catacin decreased by 3.11; 3.97 and 2.5 times, with the use of Geranyl – by 3.04; 3.88 and 2.45 times, in those receiving Cavergal this decrease was 1.22; 1.29 and 1.15 times, with the introduction of Karsil – by 1.64; 2.16 and 1.29 times, respectively. The high activity of alkaline phosphatase and γ-GT under the influence Catacin decreased 2.29 and 4.28 times, introduction of Geranyl- 2.49 and 3.85 times, the introduction Cavergal - 1.45 and 1.12 times, and the use of the Karsil - 1.98 and 2.95%, respectively. It should be noted that medications used increased low baseline albumin level of 1.43; 1,47; 1.25 and 1.34 times in groups of rats with OTG treated Catacin, Geranyl, Cavergal and Karsil, respectively. Indicators mesenchymal inflammation statistically significantly decreased 1.87; 2,04; 1.22 and 1.45 times, respectively, when applying Catacin, Geranyl, Cavergal and Karsil. If the continued introduction of Catacin and Geranyl we observed a slight strengthening of action of these drugs in the correction of cytolytic, cholestatic syndromes, mesenchymal inflammation and hepatocellular failure, Cavergal and the Karsil – some reduction in their effectiveness. Despite these positive effects of the above medicines, they did not contribute to the complete restoration of functional and metabolic parameters of the liver, as they were significantly different from the indicators of intact rats.

In our opinion, this is due to the chemical structure of these compounds [4, 11]. Flavonoids can be attributed to a non-enzymatic antioxidant capable of directly or indirectly weakening or preventing cell damage caused by free radicals [5, 11]. This is due to the hydroxyl groups in position 3, which gives additional activity to flavonols and flavan-3-ols. Antioxidant activity is also inherent in the aglikans, but non-glycosylated or conjugated flavonoid derivatives, as the replacement of hydroxyl groups in aromatic rings responsible

for interaction with free radicals, reduces antioxidant activity. The mechanism of protective action of flavonoids is associated with increased activity of antioxidant enzymes, restoration of cell membranes of hepatocytes, their participation in the processes of molecular transport, cell division and differentiation, stimulation of the activity of various enzyme systems, slowing down the synthesis of collagen and increasing the activity of collagenase, which is the basis of their antifibrotic effect [5, 9]. According to the literature, the membrane-stabilizing effect of flavonoids is associated with the interaction with the membranes of hepatocytes, their ability to inhibit the activity of SAMP, reduce the calcium content inside the cell, inhibit the calcium-dependent process of phospholipase activation [9]. Most flavonoids have anti-inflammatory action, inhibiting enzymes responsible for the synthesis of Pro-inflammatory cytokines, prostaglandins, thromboxanes and leukotrienes [2]. According to the authors, the metabolic action of this group of hepatoprotectors is associated with stimulation of protein biosynthesis and acceleration of regeneration of damaged hepatocytes, due to specific stimulation of RNA polymerase 1, activation of transcription and translation, which leads to an increase in the number of ribosomes and activation of biosynthesis of structural and functional proteins [2, 4]. Apparently, we have identified an increase in the content of albumins in blood serum due to these properties. However, they do not affect the speed of replication and translation in the modified cells with the maximum level of DNA synthesis, which excludes the possibility of proliferative action [10]. In studies of G. R. Abdullayev (2016) in rats with emotional pain stress was found to reduce the processes of lipid peroxidation using Catacin, the drug increased the energy potential of cells [1, 3]. This remedy has an antihypoxic effect in various forms of hypoxia and its activity is superior to known antihypoxants [4]. The study of chronic toxicity of Catacin showed the absence of cumulative properties [7]. Proanthocyanidin Geranyl showed antihypoxic properties on the model of occlusion of the carotid artery [8]. Apparently, the more pronounced hepatoprotective properties of Catacin and Geranyl obtained by us are associated with their antihypoxic and antioxidant action, they are not inferior in their hepatrotective properties to the well-known remedy Karsil.

Conclusion

1. The experimental pharmacotherapy of acute toxic liver damage new drugs Catacin and Geranyl significantly reduced the indicators of cytolysis, cholestasis, mesenchymal inflammation and liver cell failure.

2. Catacin and Geranyl for hepatoprotective property not abrogate the hepatoprotective Karsil and significantly surpassed antihypoxant was Cavergal.

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