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Study of the Choleretic Activity of Ferulla Assa-Foetida in Acute Paracetamol Induced Hepatitis

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Annotation: On white male rats on the model of acute medicinal hepatitis induced by paracetamol, the hepatoprotective property of the gum resin of ferula asafoetid and Legalon was tested. It has been established that the gum of the ferula asafoetida resin is not inferior to Legalon in its pharmacological activity. It is believed that the use of ferula asafoetid resin gum as a hepatoprotector, like Legalon, will increase the effectiveness of therapeutic measures for acute medicinal hepatitis and reduce its complications.

Key words: paracetamol, RGFA, toxic hepatitis, bile secretion, hepatoprotectors.

Actuality. Nonsteroidal anti-inflammatory drugs are often used in practical medicine, since they have not only anti-inflammatory but also antipyretic, analgesic effects. Paracetamol is widely used among them. It has a hepatotoxic effect, as is known [2,6]. In this regard, hepatoprotectors are used to prevent liver damage [1,5]. The above circumstance prompted the conduct of experimental studies on the comparative study of the prophylactic effect of ferula gum asafoetida (RGFA) in a comparative aspect with Legalon in acute paracetamol hepatitis on the bile excretory function of the liver.

The purpose of the study. Comparative study of RGFA and Legalon during prophylactic administration on the bile excretory function of the liver in acute drug-induced hepatitis.

Materials and methods of investigation. All experimental studies were carried out on sexually mature laboratory animals with an initial weight of 180-210 g. Before the start of the experiment, all laboratory animals were carefully examined, weighed, their age, gender, and physical activity were taken into account. During the entire period of preparation for the experiment, during its implementation, laboratory animals were kept in a vivarium at a temperature of 20-25°C, humidity not less than 50%, in a well-ventilated room and light mode day/night, in standard plastic cages of 6 individuals each, with a standard diet, the daily requirement is made in accordance with the age of the animals. All laboratory animals participating in the experiment before the start of the experiment had a healthy appearance and were active. After the completion of the 14-day quarantine, all animals were randomly divided into the following groups: Group 1-control. Rats before the reproduction of acute drug-induced hepatitis (paracetamol per os at a dose of 1500 mg/kg 1 time per day for 2 days) were intragastrically injected with distilled water for 2 days. 2nd and 3rd groups - experienced. Rats with acute hepatitis were intragastrically injected with RGFA at doses of 50-100 mg/kg once a day for 2 days before paracetamol. Group 4 rats with acute hepatitis were intragastrically injected with Legalon (comparator drug) once a day for 2 days and 1 hour before the administration of paracetamol at a dose of 100 mg/kg. 5th group is intact. The rats of this group did not undergo any manipulations. The introduction of the studied substances to the animals was carried out according to the scheme “prophylaxis + paracetamol”. On the 3rd day of the study, acute drug-induced hepatitis was induced in animals of all groups (except intact ones) one hour after the administration of the drugs. For the induction of acute drug-induced hepatitis (DIH), acetaminophen was used at a dose of 1500 mg/kg, once for 2 days. 2T hours after the final administration of the drugs, the biliary function of the liver was examined by inserting a polyethylene catheter into the common bile duct of anesthetized animals (intraperitoneal administration of etaminal sodium at a dose of 50 mg/kg). The choleretic activity of the drug was judged by the total amount of bile excreted over 4 hours of the

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experiment, as well as by the concentration and amount of its components, that is, bilirubin, cholesterol and bile acids. In hourly portions, the concentration (mg%) and the total amount (mg per 100 g of body weight) of bile acids, cholesterol and bilirubin were determined [4,7,8,9]. All experiments were carried out in compliance with the requirements of the European Convention for the Protection of Vertebrate Animals used for Experimental or Other Scientific Purposes (Strasbourg 1986). The obtained results of the study were statistically processed using the Biostat 2009 software package. The data are presented as the mean value (M) and the standard error of the mean (s). A difference at a probability level of 95% or more was taken as a statistically significant change ($p< 0.05$).

Research results. The results of experimental studies have shown that the introduction of paracetamol (two days at 1500 ml / kg) orally leads to a significant violation of the functional state of the liver, which manifests itself in a decrease in the excretory function of the liver and the chemical composition of bile. Thus, in comparison with healthy animals, in animals treated with paracetamol, in the bile secreted during the four hours of the experiment, in terms of 100 g of animal weight, decreased by more than 4.5 times (by 78.1%), which was accompanied by a decrease in the content of bile acids in bile by 69.3%, cholesterol-64.7% and bilirubin" 63.2%. It can be seen that paracetamol when administered enterally leads to the development of significant changes in hepatocytes, which lead to significant changes in the functional state of the liver, which is expressed in a decrease in the excretory function of the organ and the chemical composition of bile. The obtained results directly indicate the presence of hepatotoxicity of paracetamol, which is mainly associated with the depletion of glutathione reserves in the body of mature mammals and the accumulation of intermediate metabolic products with a hepatotoxic effect, namely, the formation of monooxygenases (cytochrome P450) from paracetamol in the enzyme system (cytochrome P450) N-acetyl-p-benzoquinoneimine) [2,3,10]. In contrast, in the group of animals previously treated with ferula gum asafoetida, there is a distinct preservation of the exocrine function of the liver and the chemical composition of bile. However, they did not reach the level of healthy rats. Similar characteristic results were obtained by us in the group of animals previously treated with Legalon. Therefore, if under the influence of paracetamol the biliary function of the liver is significantly inhibited, then under the influence of RGFA and Legalon it is clearly preserved. Preventive administration of RGFA and Legalon in animals with acute paracetamol hepatitis also has a clear positive effect on the studied bile components. Thus, the total content of bile acids in the bile in the group of animals treated with RGFA at a dose of 50 mg/kg was 123.5% higher compared to the control, and at a dose of 100 mg/kg by 117.9%. In this group of animals, the content of cholesterol and bilirubin also exceeds the control level by 95.7% and 113.9%, respectively. Doubling the dose of the drug, as can be seen from the data in Table 1, did not lead to an increase in the marked effect, that is, the amount of cholesterol and bilirubin in the bile for four hours of the experiment was greater by 81.0% and 96.2%, respectively. It should be noted that the effective dose of RGFA in the prevention of violations of the bile-forming function of the liver in acute paracetamol hepatitis is 50 mg/kg. The drug at this dose clearly outperforms the effect of Legalon, under the influence of which the level of bile acids cholesterol and bilirubin increased by 102.2%, 73.3%, 78.7%, respectively, compared with the control.

Thus, the results of the pharmacological and biochemical studies carried out allow us to conclude that CSFA, like Legalon, prevents liver damage when exposed to paracetamol. Such a positive effect of the studied drugs is probably due to the fact that they have an antioxidant effect, since paracetamol initiates lipid peroxidation (LPO) by activating the production of free radicals that destroy liver cell membranes [3].

Table 1

Comparative study of the prophylactic effect of various doses of RGFA and Legalon on the biliary function of the liver in acute paracetamol hepatitis (for 4 hours of experience in terms of 100 g of rat body weight)

Groups	Bile	Bile acids, mg	Cholesterol, mg	Bilirubin, mkg

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Intact	1,46±0,10	7,45±0,49	0,329±0,025	122,52±6,42
H_2O +АН(control) P	0,32±0,05 <0,001	2,29±0,22 <0,001	0,116±0,014 <0,001	45,05±6,45 <0,001
RGFA $_{50}$ мг/кг+ АН P Pi	0,84±0,13 <0,02 <0,02 *	5,12±0,59 <0,05 <0,01	0,227±0,023 <0,05 <0,01	96,35±6,61 <0,05 <0,01
RGFA $_{100}$ мг/кг+АН P Pi	0,77±0,13 <0,01 <0,05	4,99±0,42 <0,02 <0,01	0,210±0,022 <0,02 <0,02	88,39±5,84 <0,02 <0,01
Legalon $_{100}$ + АН P Pi	0,76±0,07 <0,01 <0,01	4,63±0,33 <0,01 <0,002	0,201±0,023 <0,02 <0,05	80,49±7,04 <0,01 <0,02

Note: P - reliability of data on animals of intact groups, Pi - reliability of data of treated animals in relation to control groups.

Conclusion. 1. In rats with acute drug-induced hepatitis induced by paracetamol, there are significant violations of the excretory function of the liver and the chemical composition of bile.

2. Hepatoprotector Legalon with prophylactic administration clearly prevents violations of the functional state of the liver in acute paracetamol hepatitis, which manifests itself in a decrease in the biliary function of the organ.

3. RGFA in acute drug-induced hepatitis has a distinct hepatoprotective property and in terms of its pharmacological activity it is not inferior to Legalon**.**

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