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DEVELOPMENT OF A NEW METHOD FOR THE TREATMENT OF DISEASES OF THE HEPATO-PANCREATOBIARY SYSTEM ON THE BASIS OF THE CHOLERETIC ACTIVITY OF RUTAN

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ABSTRACT

The article deals with hepatitis, one of the most common diseases of today. It analyzes the pharmacological effects of Rutane on the functional state of the liver in experimental acute hepatitis. The results are based on animal studies.

Keywords: *Treatment, hepato-pancreatobiary system, medicine, disease, hepatitis.*

АННОТАЦИЯ

Статья посвящена гепатиту, одному из самых распространенных заболеваний современности. Анализируются фармакологические эффекты рутана на функциональное состояние печени при экспериментальном остром гепатите. Результаты основаны на исследованиях на животных.

Ключевые слова: *Лечение, гепато-панкреатобиарная система, медицина, заболевание, гепатит.*

INTRODUCTION

Diseases of the hepatobiliary system throughout the world is one of the global medical and social problems. According to WHO statistics, about 2 billion people in the world have various liver pathologies [1, 3]. At the same time, such liver diseases as cirrhosis, chronic hepatitis, liver failure, hepatocellular cancer, etc. occupy a significant place among the causes of disability and death [2, 4]. In 2015, viral hepatitis was responsible for 1.34 million deaths worldwide. The number of deaths caused by viral hepatitis is increasing year by year. Despite the successes achieved in the treatment of diseases of the hepatobiliary system with pharmacological agents, the rates of development of complications from pathology remain high [3, 5]. Although there is a large arsenal of means and methods of treatment, the search for effective ways to correct structural and functional disorders of the liver in diseases of chemical etiology does not stop. At the same time, along with synthetic compounds,

natural compounds with antioxidant properties occupy an important place [4]. Among the drugs intensively developed in the last decade, antiviral drugs have moved to one of the first places. An important achievement was the development and widespread use of interferon inducers (IFN) in the treatment of a number of pathologies such as respiratory viral infections, herpes virus infections, viral hepatitis, neuroinfections, chlamydia, etc. [6, 9]. IFN inducers have a universally wide range of antiviral activity and a pronounced immunomodulatory effect. At the same time, their activity coincides with the activity of exogenous IFNs. It is important to emphasize that their combined use with other drugs often leads to a synergistic effect [7, 8]. It has been established that one of the properties of IFN inducers is the formation of persistent long-term antiviral resistance in the body after their administration, since even a single administration of IFN inducers in therapeutic doses leads to long-term production of IFN. It is noteworthy that domestic scientists have created and implemented effective IFN inducers based on polyphenolic compounds of plant origin: Megosin, Celagripp, Rutan [1, 3]. The use of IFN inducers in the treatment of viral hepatitis requires a deep and comprehensive study of their effect on the functional state of hepatocytes. The results of experimental studies conducted in recent years indicate that the IFN inductor Celagripp has a distinct choleretic effect. At the same time, it is effective in restoring the functional state of the liver in its acute toxic lesions of various etiologies. In terms of searching for and introducing into clinical practice effective means of treating hepatitis, our attention was attracted by the drug Rutan, an IFN inducer created by the staff of the Institute of Bioorganic Chemistry of the Academy of Sciences of the Republic of Uzbekistan on the basis of biologically active compounds isolated from the tannin-bearing plant Rhuscoriaria L [2]. This drug is recommended in the treatment of acute viral infections. However, being an IFN inducer, like Celagripple, it can be effective in correcting violations of the functional state of the liver in its pathologies [1, 4].

Purpose of the study. Evaluation of the pharmacological action of Rutan on the functional state of the liver in experimental acute hepatitis.

MATERIAL AND RESEARCH METHODS

Experimental studies were carried out on sexually mature male rats with an initial weight of 185-210g kept under standard conditions in biological clinics. Animals were fed with natural and briquetted feed, in accordance with approved standards. Experimental groups of animals were formed by 6 pieces each, taking into account body weight. The experiments were carried out in accordance with the rules

of the qualitative laboratory (GLP) for preclinical studies, as well as the rules and International recommendations of the European Convention for the Protection of Vertebrate Animals used in experimental studies (1986). Acute toxic hepatitis (ATH) was reproduced by subcutaneous injection of a 50% oily solution of carbon tetrachloride. A 50% oily solution of carbon tetrachloride was prepared in olive oil and injected subcutaneously at a rate of 0.5 ml/100 g. body weight for 4 days. 24 hours after the last injection of hepatotoxin, the animals of one group were intragastrically injected with a freshly prepared aqueous suspension of Rutan at a dose of 25 mg/kg, the other group of animals received Legalon at a dose of 100 mg/kg also intragastrically. The control group of rats received an aliquot of water orally during this period of the experiment. The next after the last injection of drugs under general anesthesia induced sodium etaminal (intraperitoneally, at a dose of 50 mg/kg), the intensity of bile secretion and the chemical composition of bile were studied. The choleretic activity of the drug was judged by the total amount of excreted bile for 4 hours of the experiment, as well as by the concentration and amount of its components (bilirubin, cholesterol and bile acids). In hourly portions of bile, the concentration (mg%) and total amount (mg per 100 g of body weight) of bile acids, cholesterol, and bilirubin were determined [5].

In the second series of experiments in analogous groups of animals, the effect of Legalon and Rutan on the duration of etaminal sleep was studied. For these purposes, a freshly prepared solution of sodium etaminal was administered intraperitoneally at a dose of 50 mg/kg, and the time spent by the animals in the lateral position and the absence of the turning reflex was taken into account. The resulting digital material was statistically processed using the standard Biostat 2009 software package using well-known methods of variation statistics with an assessment of the significance of indicators (M ± m) and differences in the samples under consideration by Student's t-test. Differences in the compared groups were considered significant at a significance level of 95% ($p<0.05$).

RESEARCH RESULTS

Hepatoprotectors are complex preparations, mainly of plant origin, designed to increase the resistance of the liver to toxic effects, help restore its functions, normalize or enhance the activity of enzymes of the antioxidant system of hepatocytes [2, 3]. Carbon tetrachloride is used in experimental work as a model of acute toxic liver injury [1, 5, 6, 9]. Developing liver failure associated with intensification of peroxidation processes, production and accumulation of highly

toxic metabolites leads to hepatocyte necrosis and liver fibrosis [2]. According to modern concepts, free radical reactions play a significant role in the development of pathology in toxic liver damage. Reactive oxygen species cause an increase in the intensity of lipid peroxidation of cell membranes and, as a result, a violation of its function.

It was noted that carbon tetrachloride causes significant structural changes in hepatocytes, which ultimately leads to metabolic disorders, and especially those that occur exclusively in the liver [5, 9].

1-table

Influence of Legalon and Rutan on the biliary function of the liver in rats with acute hepatitis induced by carbon tetrachloride (for 4 hours of experience per 100 g of body weight)

Groups	Bile ml	Bile acids, mg	Cholesterol, mg	Bilirubin, mcg
Intact	1,118 + 0,0332	7,19 + 0,39	0,201 + 0,011	138,6 + 7,17
Hepatitis	0,742 + 0,0298 *	4,35 + 0,13 *	0,148 + 0,007 *	67,45 + 5,74*
Hepatitis + Rutan	1,038 + 0,0102 #	6,85 + 0,40#	0,193 + 0,006 #	130,2 + 3,85 #
Hepatitis + Legalon	0,909 + 0,0285* #	5,88 + 0,18 * #	0,175 + 0,005* #	96,4 + 3,82* #

Note: *statistically significant differences compared to infarcted animals,
- statistically significant differences compared with hepatitis

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As can be seen from the data in Table 1, rats with acute toxic hepatitis have a statistically significant decrease in bile secretion by 33.6% compared with healthy animals. Taking into account the fact that bile is a product synthesized exclusively by hepatocytes [5], it can be assumed that the functional state of the liver is suppressed. Such an effect in acute toxic hepatitis induced by carbon tetrachloride is also reflected in the results of the study of the content of the main components of bile. In animals with hepatitis, the total content of bile acids in bile is reduced by 39.5%, cholesterol - by 26.4% and bilirubin - by 51.3%. Consequently, in acute toxic hepatitis caused by carbon tetrachloride, there is a significant inhibition of the functional state of the liver, which manifests itself not only in inhibition of the amount of secreted bile, but also in a decrease in the content of its main components

in it. Since the synthesis of bile acids from cholesterol is carried out in the endoplasmic reticulum of hepatocytes, where the monooxygenase enzyme system is located, which also performs the biotransformation of xenobiotics [1, 5, 12, 13.], it can be assumed that carbon tetrachloride causes significant damage to the membranes of this organoid. This assumption is based on the fact that the formation of toxic free radicals during the metabolism of carbon tetrachloride leads to degradation of the membranes of the endoplasmic reticulum of hepatocytes, causing suppression of the activity of membrane-bound enzyme complexes that carry out the biosynthesis of the main components of bile [5,12, 13]. Bilirubin is known to be excreted in the bile exclusively in the form of glucuronides, and therefore a decrease in its level in the bile of rats with acute toxic hepatitis indicates inhibition of the activity of UDP-glucuronyltransferase, which is also localized in the endoplasmic reticulum [5, 12, 13]. Animals with acute toxic hepatitis after treatment with Legalon and Rutan show a clear restoration of the functional state of the liver. Thus, the volume of excreted bile for 4 hours of the experiment in rats treated with Legalon increased by 22.5%, and by Rutan - by 40%. At the same time, the value of the studied indicator does not statistically significantly differ from the level of healthy animals. Along with this, in animals treated with Legalon in bile, compared with the untreated group, the content of bile acids increased by 35.2%, cholesterol - by 18.2% and bilirubin - by 42.9%, and in those treated with Rutan, the increase in these substances was, respectively, 57 .5%, 30.4% and 93%

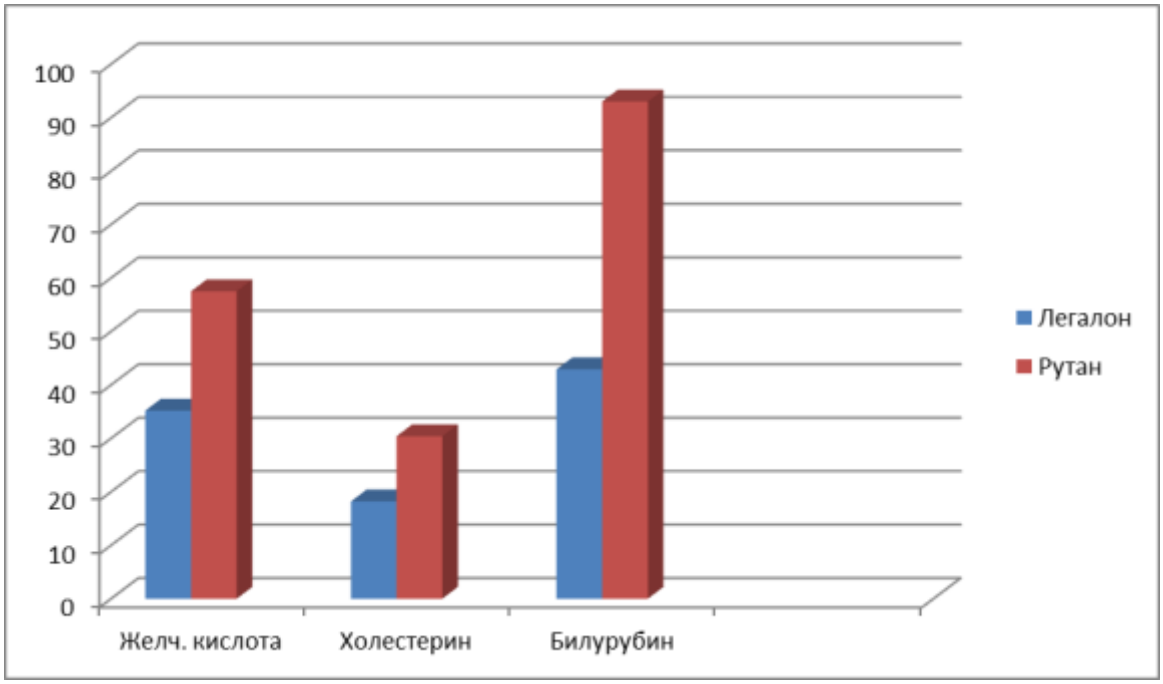

Diagram 1. Effect of Legalon and Rutan on hepatitis caused by carbontetrachloromethane.

It can be seen that the effectiveness of Rutan in the correction of disorders of the biliary function of the liver in acute toxic hepatitis induced by carbon tetrachloride was somewhat high compared to Legalon. Thus, the presented results indicate the high pharmacological activity of Rutan as a choleretic agent. As noted above, violations of the bile-forming function of the liver are based on a violation of the functional activity of the monooxygenase enzyme system localized in the endoplasmic reticulum of hepatocytes. Based on this, it can be assumed that the studied pharmacological agents have a restorative effect on this enzymatic system of hepatocytes. To assess the intensity of xenobiotic biotransformation processes in the liver by the monooxygenase system carried out in vivo, experimental studies using test drugs such as sodium etaminal are widely used; the duration of sleep caused by it fully depends on the intensity of its metabolism [1, 14, 15]. Considering this circumstance, in a separate series of experiments, in a comparative aspect, we studied the effect of Legalon and Rutan in their therapeutic use on the duration of sleep caused by sodium etaminal. The results of this series of experiments showed that in the group of rats with acute toxic hepatitis, the duration of barbituric sleep is 178.2 ± 15.23 minutes versus 82.4 ± 3.74 minutes in healthy ones, that is, compared with the latter in acute hepatitis, the duration of the hypnotic effect sodium etaminal is extended by 116.3% (more than twice) Therefore, it can be assumed that in acute toxic hepatitis, the intensity of the biotransformation of this barbiturate is significantly slowed down. This fact is consistent with the results of other researchers [1, 14, 15]. In contrast, after experimental therapy, the duration of sleep is shortened: in the group of rats treated with Legalon by 33.2%, and in the group treated with Rutan - by 45.8%. At the same time, in the latter, the duration of the hypnotic effect of sodium etaminal did not statistically significantly differ from the values of healthy rats. These data allow us to conclude that the hepatoprotector Legalon, and especially Rutan, in rats with acute toxic hepatitis clearly restore the functional activity of the monooxygenase system, which manifests itself in a shortening of barbituric sleep due to the acceleration of the biotransformation of the drug. These results quite fully confirm the assumption that it is the restoration of the functional activity of the mono-oxygenase enzyme systems of hepatocytes that underlies the favorable effect of Legalon and Rutan on the bile-forming function of the liver in acute toxic gnepatitis induced by carbon tetrachloride. Since the pathogenetic link of the

damaging effect of carbon tetrachloride is associated with the formation of free radicals, the results of this work allow us to assume that Rutan has antioxidant activity, because flavonoids are distinguished by the greatest ability to quench free radical activity [7, 8, 9] and have important pathogenetic significance in restoration of damaged extracellular structures of hepatocytes, ensuring the full functioning of membrane-bound enzymes involved in various metabolic processes.

Given the above data, we can state the presence of a high antioxidant activity of Rutan, which does not differ in the strength of its action from Legalon.

The results of this work can be put as the basis for further research on the creation of drugs with a selective effect on the liver. Relevant is not only the search for new effective and safe hepatoprotective drugs, but also further experimental and clinical study in a comparative aspect of the features of pharmacodynamics and intimate mechanisms of action of already known hepatoprotectors.

CONCLUSION

1. The increase in bile secretion and the restoration of the content of its main components in it after the experimental pharmacotherapy with Rutan in rats with acute toxic hepatitis suggests that the drug has a pronounced choleretic activity.

2. Rutan in its choleretic activity is not inferior to the well-known hepatoprotector Legalon

3. The basis of the favorable effect of Rutan on the biliary function of the liver in its acute toxic damage is the restoration of the functional activity of the monooxygenase enzyme system of hepatocytes.

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