American Journal of Medical Sciences and Medicine, 2025, Vol. 13, No. 4, 60-63
Available online at http://pubs.sciepub.com/ajmsm/13/4/2
Published by Science and Education Publishing
DOI:10.12691/ajmsm-13-4-2

Some Indicators of Carbohydrate Metabolism in Acute Toxic Hepatitis in Prepubertal Animals Treated with Rutan

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Received August 12, 2025; Revised September 14, 2025; Accepted September 22, 2025

Abstract In prepubertal rats, on a model of acute toxic hepatitis induced by carbon tetrachloride, some indicators of carbohydrate metabolism were studied after pharmacotherapy with Rutan and Karsil. It was established that acute toxic hepatitis is accompanied by hyperglycemia and a sharp decrease in glycogen content, along with an increase in lactic acid concentration and a decrease in pyruvic acid, which, according to the authors, indicates the development of hepatic hypoxia and lactic acidosis. Experimental therapy with Karsil and especially Rutan led to the elimination of hyperglycemia and an increase in glycogen levels, a reduction in lactic acid, and a slight increase in pyruvic acid. These changes indicate the restoration of the energy supply of hepatocytes and create favorable conditions for the course of biosynthetic processes. It is concluded that Rutan, similar to Karsil, can be used in the treatment of acute toxic hepatitis in pediatric practice.

Keywords: *acute toxic hepatitis, glucose, glycogen, lactic acid, pyruvic acid, energy potential, Rutan, Karsil, prepubertal age*

Cite This Article: Khakimov Z.Z., Rakhmanov A.Kh., and Khalmuratova F.A., "Some Indicators of Carbohydrate Metabolism in Acute Toxic Hepatitis in Prepubertal Animals Treated with Rutan." *American Journal of Medical Sciences and Medicine*, vol. 13, no. 4 (2025): 60-63. doi: 10.12691/ajmsm-13-4-2.

1. Introduction

One of the global medico-social problems is diseases of the hepatobiliary system. The number of victims of this pathology is constantly increasing [1]. The leading role of the liver in detoxifying toxic substances of both endogenous and exogenous origin, as well as its involvement in various types of metabolism, imposes a significant burden on this organ, which often leads to its damage. In the treatment of hepatobiliary system pathologies, substances with antioxidant properties—hepatoprotectors—are widely used. However, their effectiveness does not fully satisfy clinicians, since they do not always produce the desired results, which is why the search for effective agents for correcting structural and functional disturbances in liver pathologies of various etiologies continues.

This problem is of particular importance in pediatric practice, since the number of acute hepatobiliary system diseases in children tends to increase [2,3,4]. It is well known that the liver plays a key role in carbohydrate metabolism. It should be noted that hepatocytes are the main storage site for carbohydrates necessary for providing the body with energy, especially in children, who have a fairly high demand for carbohydrates. It is believed that in the tissues of newborns and children, anaerobic glycolysis proceeds actively, which is associated with a considerable degree of resistance of children to hypoxia [5].

At the same time, the development of hypoglycemia due to the depletion of carbohydrate stores in the liver (glycogen), immaturity of regulatory mechanisms, especially under hypoxic conditions, leads to an energy deficit state, causing an unsatisfactory energy supply to tissues. It should be taken into account that in young and preschool-aged children, there is a tendency toward hypoglycemia [5]. Such a hypoglycemic reaction of the child's body is often due to the imperfection of regulatory mechanisms, the exhaustion of weak glycogen depots, and the increased utilization of glucose by tissues (twice as high compared to adults).

Previously, we showed that the interferon inducer Rutan possesses distinct antioxidant properties, which contribute to the restoration of absorptive-excretory and detoxifying liver functions in acute toxic hepatitis in prepubertal animals [6,7,8]. Since these functions of hepatocytes can be restored only under satisfactory conditions of energy supply for biosynthetic processes in the organ, it can be assumed that Rutan, in hepatitis, stimulates the functional activity of electron-transport systems localized both in the mitochondria and in the cytoplasmic network of hepatocytes. Addressing this issue

would serve as a basis for understanding the mechanism of Rutan's beneficial action in hepatitis of various etiologies in children.

Aim of investigation was an experimental study of the effect of Rutan on some indicators of carbohydrate metabolism in acute toxic hepatitis in prepubertal animals.

2. Material and Methods

2.1. Experiments

The study was conducted on 30 white growing rats of both sexes, one month of age. The experiments were carried out in compliance with the rules adopted by the International Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986). The experimental studies on laboratory animals were approved at a meeting of the Ethics Committee of the Tashkent Medical Academy under the Ministry of Health of the Republic of Uzbekistan (protocol No. 9, May 26, 2025).

Acute toxic hepatitis (ATH) in the young rats was induced by intragastric administration of a 50% oil solution of carbon tetrachloride (CCl_4) at a dose of 0.2 ml/100 g, once daily for four days [9]. Twenty-four hours after the last administration of CCl_4, the animals were divided into four groups. The animals of the first and second groups received Rutan at doses of 25 and 50 mg/kg, respectively; the third group received Karsil at 40 mg/kg; and the fourth group remained untreated. The fifth group consisted of healthy rats of the same age and served as a control in relation to all other groups. The drugs were administered once daily for six days.

Twenty-four hours after the last manipulation, under light ether anesthesia, the rats were euthanized in a cold room (0–2°C) by instantaneous decapitation, and blood samples were collected. The liver was then excised: a portion was taken for glycogen determination [19], while the remainder was homogenized in a glass homogenizer with a Teflon pestle in an isolation medium consisting of 0.05 M KCl in 0.05 M Tris-HCl buffer solution (pH 7.4). To precipitate nuclei, mitochondria, and fragments of destroyed cells, the homogenates were centrifuged at 9000 g for 20 minutes. In the liver homogenate, to study energy metabolism, the concentrations of pyruvic acid (pyruvate) and lactic acid (lactate) were determined [10,11]. Glucose levels were measured using standard reagent kits and conventional biochemical methods.

2.3. Statistical Analysis

The obtained research results were statistically processed using the Biostat 2009 software package. Data were presented as mean value (M) and standard error of the mean (m). Student's t-test was used to test statistical hypotheses about differences between the studied groups. A change was considered statistically significant at a probability level of 95% or higher ($p < 0.05$). Indicators of the control (untreated) group were evaluated relative to those of intact (healthy) animals; indicators of the groups treated with Rutan and Karsil were compared both with the control and with intact animals.

3. Results and Discussion

In hepatitis of various etiologies, as noted in many studies, a distinct disturbance of blood circulation is observed, leading to organ hypoxia. The intensification of free radical lipid oxidation under these conditions provokes the development of acquired apoptosis. This circumstance is the main factor leading to organ dysfunction, the elimination of which requires a balanced supply of energy for synthetic processes. In critical conditions, this demand is met by stimulation of glycolysis. From this perspective, the restoration of glycogen levels in hepatocytes during damage of various etiologies is of great importance. Based on this, we studied, in a comparative aspect, the effects of Rutan and Karsil on glycogen levels in the liver of prepubertal rats with acute toxic hepatitis. Analysis of the data presented in Figure 1 shows that in prepubertal rats with acute toxic hepatitis there is a significant increase (1.5-fold) in blood glucose levels. In our view, this is likely due to the suppression of the liver's glycogen-forming function. Treatment with hepatoprotectors significantly reduced blood glucose concentration (by 19.0–24.5%), almost to the same extent, which is probably associated with the restoration of the functional activity of enzyme systems localized in the cytoplasmic reticulum of hepatocytes, responsible for the conversion of glucose into glycogen [12,17,18]. To clarify this assumption, we studied liver glycogen content in parallel with glucose levels. Indeed, in rats with acute toxic hepatitis (ATH), glycogen content in the liver was reduced more than twofold. As noted, this circumstance is likely largely due to the suppression of the activity of enzymes responsible for the conversion of glucose into glycogen. According to the literature, this enzyme system is localized in the cytoplasmic network of hepatocytes [12,13], where the monooxygenase enzyme system also functions, providing the biotransformation of endobiotics and xenobiotics [14,15].

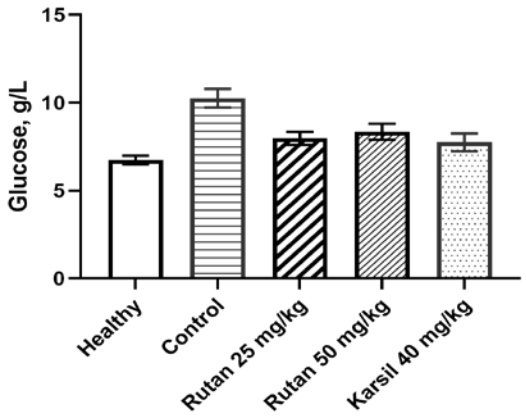

Figure 1. The effect of Rutan and Karsil on blood glucose levels in rats with acute toxic hepatitis

Table 1. Effect of Rutan and Karsil on the Content of Glycogen, Lactic Acid, and Pyruvic Acid in the Liver of Rats with Acute Toxic Hepatitis (M±m, n=6)

Parameters / Groups	Glycogen, mg/g	Lactic acid, mmol/L	Pyruvic acid, mmol/L	Ratio LA/PA
Intact	44,53 ± 2,48	3,113± 0,228	0,285 ± 0,026	11,22 ± 0,91
ATH P	21,98 ± 2,16 <0,001	7,196± 0,521 <0,001	0,201 ± 0,017 <0,05	35,15 ± 4,28 <0,01
ATH+Rutan (25 mg/kg) P P_1	38,88 ± 3,16 >0,05 <0,01	4,887± 0,467 <0,02 <0,05	0,2263 ± 0,015 >0,05 <0,05	19,17 ± 1,98 <0,02 <0,02
ATH+Rutan (50 mg/kg) P P_1	37,78 ± 4,09 >0,05 <0,02	5,041± 0,516 <0,02 <0,05	0,251 ± 0,013 >0,05 >0,05	20,26 ± 1,56 <0,01 <0,05
ATH+Karsil (40 mg/kg) P P_1	34,27 ± 3,02 <0,05 <0,05	5,186± 0,497 <0,02 <0,05	0,245 ± 0,014 >0,05 >0,05	21,48 ± 1,72 <0,01 <0,05

Note: P – statistically significant differences compared to intact animals; P_1 – statistically significant differences compared to controls.

The liver is the main organ responsible for the clearance of lactic acid (LA). Based on this, we also investigated the levels of LA and pyruvic acid (PA) in the liver of rats with acute toxic hepatitis (ATH). The results of biochemical studies showed that ATH in prepubertal animals was accompanied by a 2.3-fold increase in liver LA concentration, while PA concentration decreased by 30.0%.

LA is the end product of glycolysis and is formed as a result of the reduction of PA, where the redox coenzyme NAD acts as the electron carrier, catalyzed by lactate dehydrogenase [12,17,18]. At present, the state of redox processes is expressed by the LA/PA ratio [19,20,21]. It is believed that a sharp increase in this ratio should be considered as evidence of hypoxia, since it is the obvious cause of LA accumulation. Under hypoxic conditions, a sharp release of LA by the liver causes severe acidosis, as the entire liver glycogen store is converted to LA within a matter of hours. Characteristically, almost all of the LA of this origin accumulates without a corresponding increase in PA. These changes led to an increase in the LA/PA ratio by more than 3-fold.

In the normal liver, partial clearance of lactate occurs through gluconeogenesis, and the liver has the highest lactate clearance rate compared to other organs [12,16]. In the cytoplasm, glucose undergoes a series of reactions forming pyruvate, which is subsequently converted to lactate in the presence of lactate dehydrogenase. A secondary source of lactate production is the conversion of alanine into glutamate via alanine aminotransferase [16]. The suppression of these biochemical reactions serves as the basis for the development of lactic acidosis in ATH.

After pharmacotherapy with hepatoprotectors, particularly Rutan and Karsil, a decrease in the concentrations of both LA and PA in the liver was observed, which resulted in a reduction of the LA/PA ratio by 45.5%, 42.4%, and 38.9%, respectively, with Rutan at doses of 25 and 50 mg/kg, and Karsil at 40 mg/kg.

Thus, the studied pharmacological agents eliminate disturbances in glucose metabolism in the liver, thereby contributing to an increase in the energy potential of hepatocytes.

4. Conclusions

1. In immature rats with acute toxic hepatitis, Rutan, similar to Karsil, eliminates hyperglycemia while reducing lactate concentration.

2. Acute toxic hepatitis in young rats is accompanied by more than a twofold decrease in hepatic glycogen content, which, after pharmacotherapy with Rutan, was restored almost to the values observed in healthy animals.

3. Rutan is more effective than Karsil in correcting carbohydrate metabolism disorders in prepubertal animals with acute toxic hepatitis.

4. Considering the hepatoprotective activity of Rutan, its use can be recommended for the treatment of acute and chronic hepatobiliary diseases in pediatric practice.

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