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STUDY OF THE EFFECT OF RUTAN AND KARSIL ON THE ABSORPTIVE-EXCRETORY FUNCTION OF THE LIVER IN ACUTE TOXIC HEPATITIS DURING THE PREPUBERTAL PERIOD

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Abstract

The absorptive-excretory function of the liver plays a crucial role in ensuring the organ's detoxification potential. This study investigated the state of this function in prepubertal (PP) rabbits of both sexes using a carbon tetrachloride-induced model of acute hepatitis. A chromodiagnostic test with cardiogrin was employed to assess liver function. The efficacy of Rutan was compared to that of the hepatoprotector Karsil in correcting the observed impairments. It was found that administration of carbon tetrachloride led to significant alterations in the pharmacokinetic parameters of cardiogrin, indicating a marked suppression of the absorptive-excretory function of hepatocytes. This was accompanied by hepatic hypoxia due to reduced liver blood flow. Experimental pharmacotherapy with Rutan and Karsil almost equally restored hepatic blood flow and corrected the pharmacokinetic disruptions of cardiogrin, reflecting the recovery of hepatocellular absorptive-excretory function. These findings suggest that Rutan may be a viable option for restoring liver detoxification potential and absorptive-excretory function.

Keywords. Prepubertal period, acute hepatitis, pharmacokinetics, absorptive-excretory function, hepatic blood flow, Rutan, Karsil.

Introduction

Hepatobiliary system diseases in both adults and children remain a global medical and social problem. According to the World Health Organization (WHO) Global Hepatitis Report (2024), mortality from these diseases continues to increase. Over the next 10–20 years, the death rate from liver diseases is expected to double. WHO data published in 2020 reported 9,568 deaths in Uzbekistan due to liver diseases, accounting for 5.93% of total mortality. The age-standardized mortality rate was 35.87 per 100,000 population, placing Uzbekistan 42nd worldwide [1,2].

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Structural and functional alterations in hepatocytes, reduced synthetic activity, and metabolic disturbances lead to impaired detoxification, accumulation of endo- and xenobiotics in biological fluids, and the development of endotoxemia, resulting in multiple organ failure and worsening of the primary condition [3–6]. Despite advances in the pharmacological treatment of hepatobiliary diseases, complication rates remain high [7]. Although a wide array of treatment options is available, their limited efficacy necessitates the development of new pharmacological agents to restore liver function in diseases of various etiologies [8–11].

A major factor exacerbating liver disease progression is the development of endotoxemia, which arises from reduced hepatic detoxification potential. The process of biotransformation of endo- and xenobiotics in the endoplasmic reticulum of hepatocytes begins with the absorption of chemical substances [12–14]. Disruption of this initial phase is believed to be one of the key factors in intoxication syndrome development. It has been shown that acute hepatitis and other hepatobiliary pathologies are commonly accompanied by impaired absorptive-excretory liver function [15–17]. In such cases, pharmacological agents that enhance this function are recommended. However, the status and correction methods of impaired absorptive-excretory liver function in pediatric patients remain insufficiently studied. Addressing this issue would provide a basis for improving the treatment of acute and chronic liver diseases in pediatric practice.

Objective

To conduct a comparative study of the efficacy of Rutan and Karsil in correcting impaired absorptive-excretory liver function in a model of acute liver injury during the prepubertal period.

Materials and Methods

The experiments were conducted on 30 one-month-old Chinchilla rabbits of both sexes, bred under vivarium conditions. A model of acute toxic hepatitis (ATH) was induced via enteral administration of a 50% oil solution of carbon tetrachloride (CCl_4) at a dose of 0.25 mL/100 g of body weight once daily for four days. Each experimental group consisted of six rabbits. Twenty-four hours after the final administration of the hepatotoxin, animals in the first and second groups received intragastric Rutan at doses of 25 and 50 mg/kg, respectively; animals in the third group received Karsil at a dose of 40 mg/kg; and the control group was administered an equivalent volume of drinking water for six consecutive days.

Twenty-four hours after the final treatment, the absorptive-excretory liver function was assessed using a chromodiagnostic test with the dye Cardiogreen (CG, USA) [18]. The study was conducted in the morning. A freshly prepared solution of the dye was injected into the jugular vein at a dose of 0.5 mg/kg body weight. Blood samples were collected before and at 1, 3, 5, 15, 30, and 45 minutes after dye administration, and plasma concentrations were measured spectrophotometrically. Dye concentration was determined based on a calibration curve constructed using standard solutions of Cardiogreen.

Pharmacokinetic (PK) parameters of CG were calculated using a two-compartment model for intravenous administration [19]. The following parameters were measured:

- **t½α** – distribution half-life (minutes)
- **t½β** – elimination half-life (minutes)

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- **Vc** – volume of distribution in the central compartment (mL/kg)
- **Vdss** – volume of distribution at steady state (mL/kg)
- **Vp** – volume of distribution at equilibrium (mL/kg)
- **K_{12}** – transfer rate constant from blood to liver (min^{-1})
- **K_{21}** – transfer rate constant from liver to blood (min^{-1})
- **Kel** – transfer rate constant from liver to bile (min^{-1})
- **AUC** – area under the pharmacokinetic curve (μg·min/mL)
- **Clp** – plasma clearance (mL/min)

Additionally, circulating blood volume (CBV) and hepatic blood flow rate (Vn) were determined using the following formula [10]:

Vn = (CBV × 0.693) / (t½ × m) = mL/min/kg

Where:

Vn – hepatic blood flow rate

t½ – distribution half-life

m – body mass (kg)

All experiments were conducted in accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (ETS No. 123, Strasbourg, 18.03.1986). The animal studies were approved by the Ethical Committee of the Tashkent Medical Academy under the Ministry of Health of the Republic of Uzbekistan (Protocol No. 9, dated May 26, 2025).

The obtained data were statistically analyzed using Statistica for Windows software. Conventional methods of variational statistics were applied with evaluation of statistical significance using Student's t-test.

Results and Discussion

The pharmacokinetics of Cardiogreen (CG) primarily depend on its binding to plasma proteins and the absorptive-excretory function of the liver, as it is not metabolized in the body and is excreted unchanged via bile [16,17]. Therefore, the pharmacokinetic parameters of CG provide an indirect measure of hepatic absorptive-excretory function.

The results showed that six days after cessation of CCl_4 administration, there was a 110.5% increase in the distribution half-life (t½α) and a 237.1% increase in the elimination half-life (t½β) of CG compared to healthy controls (Figure 1). The volumes of distribution in both the central (Vc) and peripheral (Vdss) compartments also increased by 72.9% and 68.3%, respectively, over baseline values (Table 1). Consequently, the equilibrium distribution volume (Vp) increased by 83.0% relative to the intact group. These changes were accompanied by a reduction in the transfer rate constants from blood to liver (K_{12}) by 48.3%, from liver to blood (K_{21}) by 54.3%, and from liver to bile (Kel) by 69.4% (Table 2). Overall, these alterations led to more than a twofold increase in the AUC and a 53.7% decrease in plasma clearance (Clp) of CG. Simultaneously, hepatic blood flow (Vn) decreased by 35.1% compared to normal levels (Table 3).

Reduced hepatic perfusion is one of the key causes of hypoxia [20], which in hepatocytes enhances lipid peroxidation processes due to the suppression of antioxidant enzyme systems [4]. The resulting

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loss of hepatocyte membrane integrity promotes the development of cytolytic syndrome and endotoxemia [12,21].

Thus, the findings indicate that in prepubertal (PP) rabbits with ATH, there are pronounced impairments in the absorptive-excretory function of hepatocytes and a significant reduction in hepatic blood flow.

Experimental pharmacotherapy with Rutan and Karsil for six days resulted in statistically significant restoration of CG pharmacokinetic parameters. Rutan at a dose of 25 mg/kg reduced the distribution ($t½\alpha$) and elimination ($t½\beta$) half-lives of CG by 39.5% and 60.9%, respectively, compared to untreated animals. The volumes of distribution in the central (Vc) and peripheral (Vdss) compartments, as well as at equilibrium (Vp), decreased by 36.7%, 24.2%, and 41.2%, respectively. On this background, the transfer rate constants of CG from blood to liver (K_{12}), from liver to blood (K_{21}), and from liver to bile (Kel) increased by 51.6%, 78.4%, and 145.4%, respectively, relative to control values. Concurrently, the AUC decreased by 49.6%, while plasma clearance (Clp) and hepatic blood flow (Vn) increased by 80.2% and 35.9%, respectively. Notably, these parameters did not differ significantly from those observed in healthy animals. Doubling the Rutan dose produced an almost identical corrective effect on the pharmacokinetic parameters.

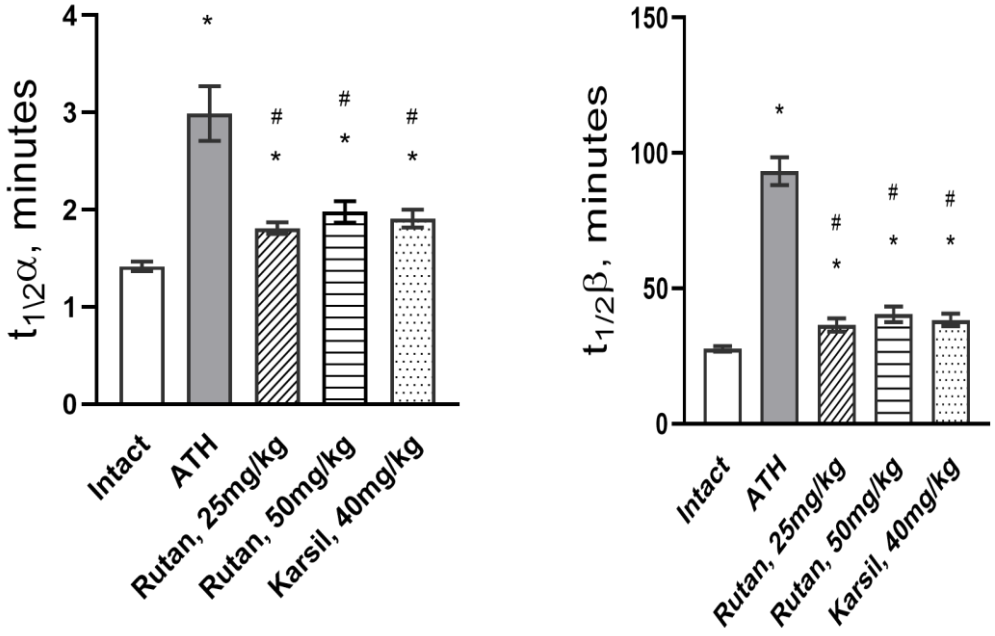

Fig. 1,2. The effect of Rutan and Karsil on the half-life ($t_{1/2\alpha}$) and half-elimination ($t_{1/2\beta}$) period of cardiogreen in rabbits with acute toxic hepatitis in the pre-burst period. * - statistically significant differences in relation to intact, # - statistically significant differences in relation to OTG

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Table 1 Effect of Rutan and Karsil on the volume of distribution of Cardiogreen in the central and peripheral compartments and the equilibrium distribution volume in rabbits with acute toxic hepatitis in the prepubertal period.

Groups	Dose, mg/kg	Vc, ml/kg	Vdss , ml/kg	Vp, ml/kg
intact	-	14,65 ± 0,85	17,50 ± 0,99	2,65 ± 0,17
OTG	-	2,99 ± 0,28*	93,31 ± 5,17*	93,31 ± 5,17*
Rutan	25	1,81 ± 0,06*,#	36,51 ± 2,47*,#	36,51 ± 2,47*,#
Rutan	50	1,98 ± 0,11*,#	40,47 ± 2,89*,#	40,47 ± 2,89*,#
Karsil	40	1,91 ± 0,09*,#	38,35 ± 2,32*,#	38,35 ± 2,32*,#

Note: Here and in other tables * - statistically significant differences in relation to intact, # - statistically significant differences in relation to OTG

Pharmacotherapy with Karsil resulted in statistically significant decreases in the distribution half-life (t½α) and elimination half-life (t½β) of Cardiogreen by 36.1% and 58.9%, respectively, compared to control values. The volumes of distribution of the drug in the central (Vc) and peripheral (Vdss) compartments, as well as the equilibrium distribution volume of the dye (Vp), decreased by 24.2%, 24.0%, and 39.4%, respectively. The transfer rate constants of Cardiogreen from blood to liver (K_{12}), from liver to blood (K_{21}), and from liver to bile (Kel) exceeded the values of untreated animals by 47.0%, 91.9%, and 129.5%, respectively. This was accompanied by a 48.6% reduction in the area under the pharmacokinetic curve (AUC) and an 83.9% increase in plasma clearance (Clp). Hepatic blood flow rate (Vn) increased by 32.8%, which was statistically not significantly different from the values in healthy animals.

Table 2 The effect of Rutan and Karsil on the constants of transfer from blood to liver, constants of drug transfer from liver to blood and constants of transfer from liver to bile in rabbits with acute toxic hepatitis in the preburst period

Groups	Dose, mg/kg	K12, minutes -1	K21, minutes -1	Kel, minutes -1
intact	-	0,292 ± 0,015	0,081 ± 0,005	0,144 ± 0,005
OTG	-	0,151 ± 0,011*	0,037 ± 0,002*	0,044 ± 0,002*
Rutan	25	0,299 ± 0,008*,#	0,066 ± 0,005#	0,108 ± 0,008*,#
Rutan	50	0,213 ± 0,007*,#	0,061 ± 0,006#	0,097 ± 0,009*,#
Karsil	40	0,221 ± 0,016*,#	0,071 ± 0,007#	0,101 ± 0,011*,#

Table 3 Effect of Rutan and Karsil on plasma clearance, area under the pharmacokinetic curve and hepatic blood flow rates in rabbits with acute toxic hepatitis in the preburst period

Groups	Dose, mg/kg	Clp, ml/min	AUC, mcg/ml/minute	Vn, ml/min/kg
intact	-	2,29 ± 0,09	217,49 ± 8,82	10,65 ± 0,62
OTG	-	1,06 ± 0,07*	468,76 ± 32,81*	6,91 ± 0,43*
Rutan	25	2,01 ± 0,14#	236,18 ± 13,67#	9,39 ± 0,54#
Rutan	50	1,91 ± 0,11*,#	252,60 ± 20,76#	8,88 ± 0,70#
Karsil	40	1,95 ± 0,10*,#	241,03 ± 16,89#	9,18 ± 0,89

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Analysis of the results of the conducted studies allows us to conclude that OTG induced by tetrachloromethane (a strong agonist of free radical oxidation) is accompanied by a significant decrease in hepatic blood flow, causing the development of hypoxia and a significant disruption of the absorption and excretion function of hepatocytes, which is one of the pathogenetic factors in the suppression of the detoxifying potency of the liver.

Rutan, similarly to the hepatoprotective agent Karsil, effectively eliminates the identified disturbances in the pharmacokinetics of Cardiogreen, indicating restoration of the absorptive-excretory function of hepatocytes. Notably, the observed effect of these pharmacological agents is accompanied by a distinct enhancement of hepatic blood flow. Rutan may be used as a therapeutic agent for hepatobiliary system pathologies associated with endogenous intoxication syndrome, as its pharmacological activity is comparable to the well-known hepatoprotector Karsil.

Conclusions

1. In prepubertal animals, acute toxic hepatitis induced by carbon tetrachloride causes significant impairment of Cardiogreen pharmacokinetics.
2. Disturbances in the chromo-diagnostic test parameters in immature rabbits with acute toxic hepatitis are accompanied by suppression of hepatic blood flow, a critical factor in the development of hepatocyte hypoxia.
3. Rutan, similarly to Karsil, nearly completely corrects the pharmacokinetic disturbances of Cardiogreen and improves hepatic blood flow.
4. For enhancing the effectiveness of pharmacotherapy of hepatobiliary system pathologies, Rutan, like Karsil, may be used in pediatric practice as a pathogenetic agent.

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