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Evaluation of the Effectiveness of Rutan and Karsil in Correcting Antipyrine Pharmacokinetics Disorders in Rabbits with Acute Toxic Hepatitis During the Growth Period

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Abstract: This study investigates the pharmacokinetic features of antipyrine and the effectiveness of Rutan and Karsil in correcting its alterations in prepubertal rabbits with acute toxic hepatitis. It was established that carbon tetrachloride (CCl_4) administration in young rabbits led to significant disturbances in antipyrine pharmacokinetics, including a marked prolongation of the half-life, a decrease in metabolic clearance and elimination constant, along with an increase in the area under the pharmacokinetic curve (AUC). These changes persisted clearly during the first week after toxin exposure. Administration of Karsil and Rutan successfully reversed these pharmacokinetic impairments. Since antipyrine elimination occurs after hepatic metabolism, it is assumed that Rutan, like Karsil, counteracts the suppression of the monooxygenase system in hepatocytes. Considering the strong antioxidant activity of both agents, their positive effects on antipyrine pharmacokinetics are likely associated with the restoration of structural and functional integrity of the endoplasmic reticulum membranes, where the monooxygenase enzyme system is localized. The authors conclude that Rutan may be considered for use in pediatric clinical practice as a hepatoprotective agent that enhances the liver's detoxification capacity, particularly in pathologies of the hepato-biliary system.

Key words: *prepubertal period, acute toxic hepatitis, monooxygenase system, endoplasmic reticulum, hepatocytes, Rutan, Karsil.*

Introduction

Pharmacokinetics of many drugs (DPs) is significantly altered in patients with liver and kidney diseases, which leads to changes in pharmacodynamics and potentially increases the risk of adverse drug reactions [1,2]. Proper selection and dosing of DPs for these patient populations is a complex task in clinical practice across all medical specialties. A particular challenge is presented by DPs for which the liver is the primary organ of metabolism and excretion. The stages of drug biotransformation in the liver include hepatic

delivery, hepatic cellular uptake, phase I reactions (hydrolysis, reduction, oxidation), and phase II reactions (conjugation with endogenous substances such as glucuronic acid, sulfate, glycine) [1, 3, 4].

Liver dysfunction is a common occurrence in clinical settings. It may present asymptomatically, progress over a long period, or manifest as acute liver failure or fulminant hepatitis. Liver dysfunction is a polyetiological syndrome. According to an epidemiological study conducted in the USA from 1998 to 2008, the main causes of liver dysfunction were: paracetamol overdose (46%); idiopathic liver dysfunction (14%); drugs other than paracetamol (11%); hepatitis B virus (7%); other infectious and non-infectious liver diseases excluding viral hepatitis (7%); autoimmune hepatitis (5%); ischemic hepatitis (also known as hypoxic hepatitis or liver infarction, 4%); hepatitis A virus (3%); and Wilson's disease (2%) [3, 5].

Liver dysfunction can result in reduced activity of drug-metabolizing enzymes, decreased hepatic blood flow, and reduced plasma protein levels due to impaired synthesis [6]. In patients with liver dysfunction, changes in drug pharmacokinetics may result from hepatocyte necrosis, shunting of blood through collateral circulation, hypoproteinemia due to reduced protein synthesis, increased volume of distribution due to edema and ascites, and concomitant kidney damage [7].

In addition, other studies have shown that drug metabolism in children differs with age and is distinct from that in adults in both phase I and phase II reactions [8]. Pediatric drug doses are often derived from adult dosages and adjusted according to body weight or body surface area. These estimations may expose children to subtherapeutic or supratherapeutic doses, leading to treatment failure or toxicity [9]. Advances in our understanding of hepatic metabolism ontogeny have led to the development of physiologically based pharmacokinetic models, which integrate age-related enzymatic trends with adult data, although these cannot completely replace clinical studies [10].

The detoxification function of the liver is most often assessed indirectly, based on clinical symptoms, severity of hepatocellular cytolysis, protein-synthesis impairment, and homeostasis disturbances in combination with virological testing. Ultrasonography and radioisotope scanning also provide insights, where more severe structural changes are presumed to reflect greater hepatic dysfunction [11–13].

Direct indicators of liver detoxification function include challenge tests, the most commonly used being the antipyrine test [14–16]. To date, a large number of studies have assessed hepatic detoxification capacity in various liver pathologies in adulthood and old age. However, data on this function in prepubertal patients remain limited.

Objective of the study:

To investigate the effect of Rutan and Karsil on the pharmacokinetics of antipyrine in young rabbits with acute toxic hepatitis induced by carbon tetrachloride, during the growth period.

Materials and Methods

The study was conducted on 30 rabbits of the Chinchilla breed, of both sexes, aged one month, with an initial body weight ranging from 470 to 535 grams, all born and raised under vivarium conditions. The experiments were carried out in accordance with the regulations of the International Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986). Experimental procedures were approved by the Ethics Committee of the Tashkent Medical Academy under the Ministry of Health of the Republic of Uzbekistan (Protocol No. 9 dated May 26, 2025).

Acute toxic hepatitis was induced in the young rabbits by intragastric administration of a 50% oily solution of carbon tetrachloride (CCl_4) at a dose of 0.25 mL per 100 g of body weight, administered once daily for four consecutive days.

Twenty-four hours after the last dose of the hepatotoxin, animals were divided into four groups:

The first and second groups received Rutan intragastrically via a feeding tube at doses of 25 mg/kg and 50 mg/kg, respectively.

The third group received Karsil at a dose of 40 mg/kg.

The control group was administered an equivalent volume of distilled water. All treatments were given once daily for six days.

The pharmacokinetics of antipyrine were studied 24 hours after the final administration of the drugs. Antipyrine was selected because its metabolism occurs exclusively in the liver via the monooxygenase enzyme system of hepatocytes [17–19].

A freshly prepared solution of antipyrine was administered intraperitoneally at a dose of 25 mg/kg. Blood samples were collected from the jugular vein at 30 minutes, 2 hours, and 4 hours' post-injection, and the serum concentration of antipyrine was determined using a method previously described by our team [15].

Statistical analysis of the obtained data was performed using the Statistica for Windows software package. Descriptive statistics were expressed as mean ± standard error (M ± m). Group comparisons were made using Student's t-test, with statistical significance considered at $p < 0.05$ (95% confidence level).

Results and Discussion

Antipyrine is widely used in studies assessing the detoxification capacity of the liver, since its elimination occurs exclusively through biotransformation in hepatocytes by the monooxygenase enzyme system, with cytochrome P450 as the central component. Inhibition of this system leads to the accumulation of xenobiotics and enhancement of their toxic effects, which can significantly exacerbate pathological conditions, particularly hepatic disorders. Therefore, the use of hepatocyte-protective agents, or hepatoprotectors—such as Karsil, Silibor, Silymarin, LIV-52, etc.—is considered justified. In recent years, Rutan has been shown to have significant anti-inflammatory effects due to its antioxidant activity [20]. However, its hepatoprotective effect in liver pathology during the prepubertal period had not been studied until now.

An analysis of our experimental data in young rabbits with acute toxic hepatitis induced by carbon tetrachloride demonstrated that administration of the hepatotoxin resulted in significant alterations in the pharmacokinetics of antipyrine. Specifically, six days after cessation of CCl_4 administration, the elimination half-life ($t_{1/2}$) of antipyrine increased by 1.85 times compared to healthy animals. Since biotransformation is the main pathway for antipyrine clearance from the bloodstream [16, 18, 19], the prolonged circulation of the unchanged drug in plasma is likely due to a disruption in its metabolic clearance (MCR).

Indeed, MCR values at this time point were 54.5% lower than in healthy rabbits of the same age. Additionally, the elimination rate constant (Kel) decreased by 52.4%. These pharmacokinetic changes ultimately led to a significant increase in the area under the concentration-time curve (AUC)—an integral indicator of antipyrine pharmacokinetics—which was 105.8% higher than that of healthy animals. Notably, the volume of distribution (Vd) showed the least alteration, changing by only 26.5%(Table 1). Given that antipyrine is metabolized in the liver via the monooxygenase enzyme system [18, 19], these observed changes in its pharmacokinetics clearly indicate suppression of hepatic monooxygenase activity in prepubertal animals.

Thus, the results of our study confirm that acute toxic hepatitis, induced by carbon tetrachloride in growing animals, is accompanied by significant disruptions in antipyrine pharmacokinetics. These findings are consistent with other research and are attributed to enhanced lipid peroxidation processes within the endoplasmic reticulum of hepatocytes, leading to cytochrome P450 degradation [18, 19].

In contrast, experimental treatment with Rutan and Karsil significantly ameliorated the observed pharmacokinetic disturbances. For example, animals that received Rutan at doses of 25 and 50 mg/kg for six days showed a reduction in antipyrine half-life by 40.7% and 34.3%, respectively, compared to the control group. These values were not statistically different from those of healthy rabbits.

Moreover, the metabolic clearance and elimination rate constant of antipyrine increased by 97.8% and 94.1% (for 25 mg/kg) and 91.3% and 89.5% (for 50 mg/kg), respectively. Meanwhile, the AUC values decreased by 44.9% and 40.4% compared to the control group and were also not significantly different from those of healthy animals.

Table 1.

Pharmacokinetics parameters of antipyrine in acute tetrachloromethane hepatitis in immature rabbits treated with Rutan and Karsil

Groups Animals	Dose, mg/kg	Antipyrine pharmacokinetics indicators				
		t 1/2, h	avd, vk/ru	MCR, ml/kg.h	k el, h-1	AUC, mcg/ml.h
Healthy	-	2,18 ± 0,16	811,213 ± 62,41	334,96 ± 29,17	0,391 ± 0,032	86,83 ± 5,67
OTG	-	3,93 ± 0,32*	1026,10 ± 74,33	152,33 ± 10,31*	0,186 ± 0,013*	178,71 ± 16,68*
Rutan	25	2,33 ± 0,21#	852,03 ± 82,09	301,31 ± 25,07#	0,361 ± 0,025#	98,37 ± 9,02#
Rutan	50	2,58 ± 0,20#	870,35 ± 59,43	291,45 ± 26,51#	0,323 ± 0,028#	106,53 ± 9,91#
Karsil	40	2,42 ± 0,25#	864,58 ± 44,63	284,54 ± 29,79#	0,341 ± 0,027#	101,93 ± 6,79#

Note: *— statistically significant differences compared to healthy animals.*

— statistically significant differences compared to the acute toxic hepatitis (ATH) group.

At the same time, the volume of distribution did not undergo significant changes either in comparison with the control or with the healthy rabbits.

Experimental therapy with Karsil, as shown by the data in the tables, did not significantly differ from the values in the healthy animals or those treated with Rutan. Specifically, the elimination half-life of the test drug was shortened by 38.4%, metabolic clearance and elimination rate constant increased by 86.8% and 83.3%, respectively, and the area under the pharmacokinetic curve decreased by 42.9%, compared to untreated animals.

Many studies have indicated that hypoxia may be one of the important factors contributing to impaired function of the mixed-function monooxygenase system. At the same time, hypoxia can develop as a result of impaired blood flow to a given organ [21]. As shown in previous research, rabbits with acute toxic hepatitis exhibit reduced hepatic blood flow [22, 23]. It is likely that experimental therapy with Rutan and Karsil contributed to an increase in hepatic blood flow and the elimination of hypoxia—a key pathogenic factor in the intensification of lipid peroxidation.

Thus, acute toxic hepatitis induced by carbon tetrachloride is accompanied by impaired pharmacokinetics of antipyrine due to decreased biotransformation resulting from inhibition of the hepatocytic monooxygenase enzyme system. The investigated agents effectively restore the impaired activity of monooxygenase enzymes in hepatocytes, correcting the reduced biotransformation intensity and disrupted pharmacokinetic parameters of antipyrine.

Conclusions:

1. Acute toxic hepatitis induced by carbon tetrachloride during the prepubertal period is associated with pronounced impairments in the pharmacokinetics of antipyrine.
2. In prepubertal animals with acute toxic hepatitis, Rutan—similarly to the reference hepatoprotective agent Karsil—eliminates disturbances in the pharmacokinetics of antipyrine, a drug metabolized in the liver.

Rutan may be recommended as a pathogenetically acting agent to restore hepatic detoxification potential in pediatric practice for diseases of the hepatobiliary system.

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