IMPACT OF DEHYDRATION ON HEMOSTASIS AND RENAL FUNCTION IN EXPERIMENTAL PARACETAMOL-INDUCED TOXIC HEPATITIS

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ABSTRACT

Paracetamol-induced toxic liver injury remains one of the most pressing issues in modern experimental and clinical medicine, being a leading cause of drug-induced hepatotoxicity and acute liver failure [1]. The pathogenesis is primarily associated with the formation of the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI), which induces pronounced oxidative stress, mitochondrial dysfunction, and hepatocyte death [4].

In addition to liver damage, increasing attention has been given to renal involvement, as paracetamol is capable of inducing nephrotoxicity, manifested by elevated levels of creatinine and urea, as well as impaired glomerular filtration [2]. Experimental studies demonstrate that kidney injury is accompanied by activation of lipid peroxidation processes, inflammation, and apoptosis of renal cells [6].

Particular importance is attributed to the study of dehydration as an additional pathogenetic factor. Fluid deficiency enhances hypovolemia, reduces renal blood flow, and contributes to the aggravation of the toxic effects of paracetamol on nephrons, leading to more pronounced impairment of kidney function [5].

In addition, toxic liver injury is accompanied by the development of a systemic inflammatory response and activation of the hemostatic system, which may manifest as alterations in coagulation parameters and an increased risk of thrombotic complications [3]. Oxidative stress and inflammation act as key mechanisms linking damage to the liver, kidneys, and the hemostatic system [7].

Thus, a comprehensive study of the effects of dehydration on the hemostatic system and renal functional status in paracetamol-induced toxic hepatitis is of significant scientific and practical interest, as it allows for a deeper understanding of inter-organ interactions and contributes to the optimization of approaches to the prevention and treatment of these conditions..

Objective: To evaluate the effect of dehydration on coagulation hemostasis parameters and renal functional status in paracetamol-induced toxic hepatitis.

Materials and Methods: The experiment was performed on white laboratory rats weighing 250–290 g, maintained under standard vivarium conditions in accordance with GLP requirements. The animals were randomized into four groups: an intact group, a dehydration group, a paracetamol group, and a combined paracetamol plus dehydration group.

The model of toxic hepatitis was induced by intraperitoneal administration of paracetamol in increasing doses of 200, 300, and 600 mg/kg over three consecutive days. Dehydration was modeled by restriction of water intake throughout the entire experimental period.

After completion of drug administration, the animals were placed in metabolic cages for 24-hour urine collection, followed by urinalysis and blood sampling.

Coagulation hemostasis parameters were assessed, including prothrombin time, thrombin time, international normalized ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen levels. Renal functional status was evaluated based on 24-hour diuresis and parameters of general urinalysis. Statistical analysis was performed using analysis of variance (ANOVA) with a significance level of $p \leq 0.05$.

Results: The obtained data indicate a pronounced dependence of the studied parameters on hydration status and paracetamol exposure.

In the paracetamol group, a shortening of thrombin time was observed compared to the control, indicating activation of the coagulation component of hemostasis. In the dehydration group, a tendency toward prolongation of prothrombin time and activated partial thromboplastin time was noted, reflecting alterations in plasma hemostasis.

The most pronounced changes were identified in the combined paracetamol and dehydration group, where a significant increase in fibrinogen levels was observed up to 632.6±308.26 mg/dL compared to 221.2±43.1 mg/dL in the control group, as well as an increase in aPTT to 36.6±10.73 s.

Analysis of renal function demonstrated that dehydration was associated with a marked decrease in 24-hour diuresis from 6.2±3.4 mL in the control group to 0.7±0.29 mL. In the combined exposure group, diuresis was 1.4±0.55 mL, which was also statistically significantly lower than control values.

In the dehydration group, pronounced proteinuria was detected (up to 1220±1039 mg/dL), along with an increase in urine specific gravity, indicating impairment of renal concentrating function. In the paracetamol group with preserved hydration, no significant changes in urinalysis parameters were observed. In the combined paracetamol and dehydration group, signs of renal functional impairment persisted, including proteinuria and hematuria.

Thus, fluid deficiency represents a key factor determining the development of both hemostatic and renal disturbances, while paracetamol enhances the severity of pathological changes when combined with dehydration.

Conclusions:

1.Paracetamol-induced toxic hepatitis is accompanied by activation of coagulation hemostasis, manifested by shortening of thrombin time and alterations in coagulation parameters.

2.Dehydration exacerbates systemic disturbances, leading to a pronounced decrease in diuresis, development of proteinuria, and increased fibrinogen levels, indicating its key role in the progression of the pathological process.

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