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Functional State of the Kidneys in Paracetamol-Induced Hepatitis Under Conditions of Water Deficit

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Abstract In an experimental study, the effects of dehydration and paracetamol on the functional state of the kidneys in laboratory rats were investigated. It was established that water restriction was accompanied by a marked decrease in diuresis, an increase in urine specific gravity, and the development of proteinuria. Administration of paracetamol under conditions of preserved hydration did not cause significant changes in the parameters of the general urinalysis. However, when paracetamol administration was combined with dehydration, signs of renal dysfunction were observed, including proteinuria and hematuria. The obtained results indicate the leading role of water deficit in the development of renal functional disorders.

Keywords Paracetamol, Dehydration, Diuresis, Proteinuria, Hematuria, Renal functional status, Toxic hepatitis, Experimental study

1. Introduction

Drug-induced liver injury remains one of the most significant problems in modern hepatology and toxicology. One of the most commonly used drugs capable of causing toxic liver damage when therapeutic doses are exceeded is paracetamol. It is well known that its metabolism is accompanied by the formation of a highly reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI), which, under conditions of glutathione depletion, initiates oxidative stress, mitochondrial dysfunction, and necrotic damage to hepatocytes [6].

Along with the hepatotoxic effects of paracetamol, increasing attention has recently been paid to its influence on renal functional status. Experimental and clinical studies indicate that paracetamol intoxication may lead to the development of acute kidney injury accompanied by increased serum creatinine and urea levels, impaired glomerular filtration, and damage to the proximal tubular epithelium [7]. It has been established that the nephrotoxic effect of the drug is associated both with the formation of reactive metabolites and with the activation of lipid peroxidation processes and inflammatory reactions in renal tissue [5].

An additional factor capable of enhancing the toxic effects of paracetamol on detoxification organs is dehydration. Water deficit leads to hemoconcentration, decreased renal blood flow, and impaired microcirculation, which in turn contributes to deterioration of the renal filtration function and increases tissue sensitivity to toxic agents. Experimental models have demonstrated that toxic exposure to paracetamol is accompanied by pronounced morphofunctional changes in the kidneys, including damage to the tubular apparatus and impairment of antioxidant defense mechanisms [9].

Despite the considerable number of studies devoted to toxic liver injury associated with paracetamol use, the influence of dehydration on renal functional parameters under conditions of paracetamol-induced toxic hepatitis remains insufficiently investigated. In this regard, studying changes in renal function under the combined effects of dehydration and paracetamol is of important scientific and practical interest, as it will deepen the understanding of the mechanisms of systemic toxic injury and contribute to improving strategies for the prevention and correction of these disorders [3].

Purpose of the research

Aim of the study is to investigate changes in diuresis and urinalysis parameters in toxic liver injury under conditions of dehydration.

2. Materials and Methods

The study was conducted on laboratory white rats weighing 250–290 g, maintained under standard vivarium conditions: in metal cages at a temperature of 23 ± 1 ℃, relative humidity of 30–70%, and a 12/12 h light–dark cycle, with free access to standard laboratory feed in accordance with GLP requirements [1,2]. The animals were randomized into experimental groups consisting of six rats each.

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A model of paracetamol-induced toxic hepatitis was reproduced by intraperitoneal administration of paracetamol in increasing doses of 200, 300, and 600 mg/kg body weight for three consecutive days [4]. The control group received an equivalent volume of solvent according to the same protocol. Dehydration in the corresponding groups was initiated on the first day of the experiment and continued for three days, allowing the evaluation of the effect of water deficit on the severity of toxic liver injury. The experimental animals were divided into the following groups:

1. Intact group — animals were maintained under standard conditions without paracetamol administration or dehydration modeling.
2. Dehydration group (control-1) — animals were subjected to dehydration without paracetamol administration.
3. Paracetamol group (PCM, control-2) — animals received paracetamol at the indicated doses without restriction of the water regimen.
4. Paracetamol + dehydration group (experimental group) — animals received paracetamol in combination with experimentally induced dehydration.

Immediately after the final administration of paracetamol, animals from all experimental groups were placed in metabolic cages for 24 hours to collect daily urine samples. At the end of this period, on the fourth day of the experiment, urinalysis was performed, after which blood samples were collected for subsequent laboratory analysis.

The functional state of the kidneys in experimental animals was assessed based on daily diuresis and urinalysis parameters. For this purpose, animals from all groups were placed in metabolic cages for 24 hours after the final administration of the drug, which ensured separate and quantitative urine collection. The total volume of urine excreted within 24 hours was measured using graduated cylinders and expressed in milliliters, after which the mean values were calculated for each experimental group.

The collected daily urine samples were used to perform general urinalysis. The analysis was carried out using multiparameter diagnostic test strips U-11 Urinalysis Reagent Strips (Mindray). The method is based on the colorimetric assessment of changes in the color of the reaction zones of the test strip after immersion in the urine sample. The results were interpreted in accordance with the manufacturer's instructions by visually comparing the color changes with the provided reference color scale.

Using the test strips, the following parameters were determined: leukocytes, nitrites, urobilinogen, protein, pH, blood (erythrocytes/hemoglobin), specific gravity, ketone bodies, bilirubin, glucose, and ascorbic acid. All parameters were recorded semi-quantitatively with subsequent comparative analysis between the experimental groups.

A comprehensive evaluation of daily diuresis and urinalysis parameters made it possible to characterize renal functional status, the degree of impairment of the concentrating function and water–electrolyte balance, as well as to identify possible signs of paracetamol-induced nephrotoxic effects under dehydration conditions. Statistical analysis of the obtained results was performed using analysis of variance (ANOVA) with a significance level of $p = 0.05$ using GraphPad Prism software version 8.0.0 for Windows (GraphPad Software, San Diego, CA, USA; www.graphpad.com) [8].

3. Results and Discussion

The results of the analysis of the total urine volume (Table 1) demonstrated a pronounced dependence of diuresis on the water intake conditions of the animals. In the control group, the daily urine volume was 6.2 ± 3.4 ml. In the dehydration group, a sharp and statistically significant decrease in diuresis was observed, reaching 0.7 ± 0.29 ml ($p \leq 0.001$ compared with the control).

In the paracetamol group under preserved hydration conditions, the urine volume amounted to 7.24 ± 2.31 ml, which was comparable to the control values. In the PCM + dehydration group, a marked decrease in diuresis was also observed, reaching 1.4 ± 0.55 ml ($p \leq 0.001$ compared with the control); however, this value remained slightly higher than that observed under isolated dehydration.

The obtained data indicate that restriction of water intake is the main factor responsible for the sharp reduction in diuresis, whereas paracetamol administration under conditions of preserved hydration does not exert a significant effect on urine volume.

Table 1. Results of the Study of Total Urine Volume (M ±SD; p=0,05; n=5)

Groups	Urine Volume (ml)
Control	6.2 ±3.4
Dehydration	0.7*** ±0.29
PCM	7.24 ±2.31
PCM + Dehydration	1.4*** ±0.55

*** — *differences are statistically significant compared with the control group* ($p \leq 0.001$).

Table 2. Results of Quantitative Indicators of Urinalysis (M ±SD; p=0,05; n=5)

Groups	Urobilinogen (URO), mg/dL	Protein (PRO), mg/dL	pH	Specific Gravity (SG), g/mL	Ascorbic Acid (ASC), mg/dL
Control	0.2 ±0.0	21 ±8	5.4 ±0.55	1.028 ±0.003	2 ±4
Dehydration	0.2 ±0.0	1220* ±1039	5.4 ±0.55	1.030 ±0.000	34* ±13
PCM	0.2 ±0.0	30 ±0	6.0 ±0.0	1.028 ±0.004	6 ±5
PCM + Dehydration	0.2 ±0.0	220* ±110	5.0 ±0.0	1.030 ±0.000	40* ±0

* — *differences are statistically significant compared with the control group (p≤0,05).*

Table 3. Results of Semi-Quantitative Urinalysis Parameters (M ±SD; p=0,05; n=5), Erythrocytes in Urine (BLO)

Groups	Negative (–), %	Weakly Positive (+), %	Strongly Positive (+++), %	5–10 per Field of View, %
Control	0%	20%	80%	0%
Dehydration	0%	0%	40%	60%
PCM	0%	0%	80%	20%
PCM + Dehydration	0%	0%	20%	80%

Table 4. Results of the Analysis of Other Urinalysis Parameters (M ±SD; p=0,05; n=5)

Groups	Leukocytes (LEU)	Ketone Bodies (KET)	Bilirubin (BIL)	Glucose (GLU)
Control	–	–	–	–
Dehydration	–	–	–	–
PCM	–	–	–	–
PCM + Dehydration	–	–	–	–

Analysis of the quantitative parameters of urinalysis (Table 2) revealed changes primarily in protein and ascorbic acid levels. In the control group, the urinary protein level was 21 ± 8 mg/dL, with a urine pH of 5.4 ± 0.55 and a specific gravity of 1.028 ± 0.003 g/mL.

In the dehydration group, a sharp and statistically significant increase in urinary protein was observed, reaching 1220 ± 1039 mg/dL ($p \leq 0.05$ compared with the control), while the acidic urine reaction was maintained (pH 5.4 ± 0.55). This finding reflects a pronounced concentration of urine under conditions of water deficit.

In the PCM group under preserved hydration conditions, the protein level was 30 ± 0 mg/dL, only slightly exceeding the control values. At the same time, urine pH shifted toward a more neutral reaction (6.0 ± 0.0), while the specific gravity remained comparable to the control (1.028 ± 0.004 g/mL).

In the PCM + dehydration group, urinary protein increased to 220 ± 110 mg/dL ($p \leq 0.05$), which was considerably lower than in isolated dehydration but still higher than the control values. The urine pH in this group was 5.0 ± 0.0, and the specific gravity reached 1.030 ± 0.000 g/mL.

The level of urobilinogen remained unchanged across all groups (0.2 ± 0.0 mg/dL). In contrast, ascorbic acid levels increased under dehydration (34 ± 13 mg/dL) and under combined PCM + dehydration conditions (40 ± 0 mg/dL) compared with the control (2 ± 4 mg/dL), whereas in the PCM-only group it was 6 ± 5 mg/dL.

Thus, the most pronounced alterations in urinary parameters were observed under dehydration, manifested by marked proteinuria and increased urine specific gravity, whereas paracetamol administration under adequate hydration conditions exerted only minimal effects on urinalysis parameters.

Semi-quantitative analysis of erythrocytes in urine (Table 3) demonstrated the presence of hematuria in all experimental groups; however, its severity varied. In the control group, a strongly positive reaction (+++) was observed in 80% of animals, while 20% showed a weakly positive reaction (+), with no cases of 5–10 erythrocytes per field of view detected.

In the dehydration group, 40% of animals exhibited a strongly positive reaction (+++), whereas 60% demonstrated 5–10 erythrocytes per field of view, indicating a pronounced effect of water deficit on the integrity of the renal filtration barrier.

In the PCM group, 80% of animals showed a strongly positive reaction (+++), and 20% had 5–10 erythrocytes per field of view, suggesting a nephrotoxic effect of the drug.

In the PCM + dehydration group, the most pronounced changes were observed in 80% of animals in the form of 5–10 erythrocytes per field of view, while 20% showed a strongly positive reaction (+++), reflecting the combined influence of toxic and dehydration-related factors. In all groups, no negative reactions were recorded.

Other urinalysis parameters, including leukocytes, ketone bodies, bilirubin, and glucose, remained negative in all experimental groups, indicating the absence of a pronounced inflammatory process, ketosis, or disturbances of carbohydrate metabolism at the time of the study.

Restriction of the water regimen led to a marked decrease in diuresis and the development of proteinuria and hematuria, whereas paracetamol administration under dehydration conditions enhanced the manifestations of nephrotoxicity.

The results of the study of renal functional parameters demonstrated that restriction of water intake was accompanied by a marked decrease in diuresis, a significant increase in urinary protein levels, elevated urine specific gravity, and the development of hematuria. When paracetamol administration was combined with dehydration, signs of renal dysfunction persisted, including proteinuria and hematuria, along with reduced urine volume. In contrast, paracetamol administration under conditions of preserved hydration was not associated with significant changes in diuresis or in the main parameters of urinalysis. The obtained data indicate the leading role of water deficit in the development of renal functional disturbances and the enhancement of nephrotoxic manifestations when combined with the toxic effects of paracetamol.

4. Conclusions

1. Dehydration leads to a pronounced decrease in daily diuresis and the development of proteinuria, indicating impairment of the renal concentrating function.
2. Administration of paracetamol under preserved hydration conditions does not cause significant changes in diuresis or in the main parameters of urinalysis.
3. The combination of paracetamol with dehydration is accompanied by reduced diuresis and the development of proteinuria and hematuria, indicating an enhancement of nephrotoxic manifestations under conditions of water deficit.

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