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Research Article

Histopathological and Biochemical Changes of Cyproheptadine hydrochloride effect on liver and kidney in albino mice

Tara Taher [1], Sama s. Salih [1], Rawa Faris Hussein Al-Saeedi [2*], Zainab Anwar Ali[1], Nawras A. Mzahem[1], Tamara Rafi Khajeek[1]

[1]Collage of Science for women/ University of Baghdad, Baghdad, Iraq.
[2] Collage of Science/ AL Karakh University of Sciences, Baghdad, Iraq.

***Corresponding author:** Dr. Rawa Faris Hussein Al-Saeedi
* Collage of Science/ AL Karakh University of Sciences, Baghdad, Iraq.
E-mails: ruaa.faris@kus.edu.iq

Abstract
The current study aimed to identify some of the effects resulting from the administration of Cyproheptadine hydrochloride to mice by subcutaneous injection at concentrations of 25 and 50 µg/kg for 21 days. Three groups of six mice each were formed out of the animals. The medicine was administered to the second and third groups at concentrations of 25 and 50 µg/kg, respectively, with the first group acting as the control group. Their weights were regularly recorded to measure the drug's impact on their weights, the results showed a substantial difference between the groups ($P<0.05$). Moreover, the concentrations of liver function tests (ALT and AST) were measured and compared to the control group. While changes in the renal function tests (urea and creatinine) revealed a substantial increase in creatinine and a non-significant increase in urea, the observed data showed a significant increase in ALT and AST.

Key words: Cyproheptadine hydrochloride, mice, ALT, AST, Kidney functions.

***Author for correspondence: Email**: ruaa.faris@kus.edu.iq*

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Introduction

Cyproheptadine hydrochloride (CPH) is a fat-soluble molecule that has been used as an antagonist for serotonin and H1 histamine receptors. It can be used as an appetite stimulant for adults, children, and pregnant women, as well as for treating allergies (1, 2). It is used to treat appetite loss, weight loss, growth failure, and muscle weakness (9). Cyproheptadine has also been prescribed to treat post-gastrectomy syndrome and certain skin diseases (3). Cyproheptadine hydrochloride is widely used in adults, children, and pregnant women as an appetite stimulant. It is also used to treat allergy symptoms (e.g., seasonal, food, blood, or plasma allergies) and mild, uncomplicated hives (4). This fat-soluble chemical has been employed as an antagonist against the H-1 histamine and serotonin receptors(5). Sleepiness, dizziness, low blood pressure, diarrhea, constipation, nausea, irregular heartbeat, palpitations, chest tightness, blurred vision, urine retention, and overdosing on antihistamines are among the drug's side

effects. The latter is particularly dangerous in infants and young children, as it can result in hallucinations, depression of the central nervous system, seizures, hemolytic anemia, blood cancer, heart attacks, and death (6). It's possible that CPH affects the central nervous system (CNS). Nevertheless, not much research has been done on the cellular or molecular pathways that CPH uses to operate on primary nerve cells or the central nervous system. Because of its relatively high binding affinity, CPH exhibits a variety of pharmacological actions and functions as an antagonist of muscarinic, adrenaline, histamine, serotonin, and dopamine receptors (7). It has been found that cyproheptadine hydrochloride can improve sleep and calmness (8). It's also used to treat allergy symptoms, such as those caused by seasonal (9).

The chemical composition is {4-(5 H-dibenzo [a ،d] -cyclohepten-5 ylidene) -1 methylpiperidine hydrochloride}. The tricyclic nucleus of cyprohejsonide hydrochloride (Figure 1) has a 1-methyl-4-piperidyl moiety connected to the center.

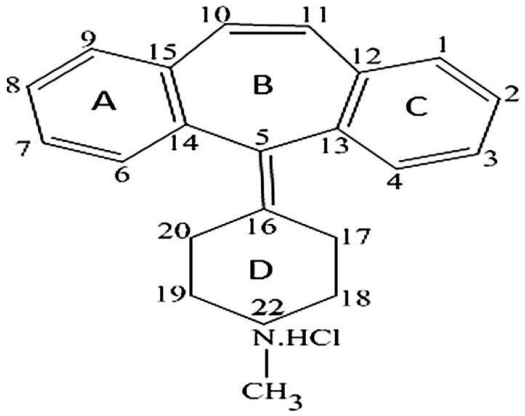

Figure 1. Chemical structure of Cyproheptadine hydrochloride(10).

The liver, which has both left and right lobes, is the biggest organ in the body. These lobes are divided into lobules consisting of masses of parenchymal tissue. The hepatocytes are arranged in cohesive and branching plates, with pseudo-lobular sinusoids between them, and a central vein at the center of each lobule (11). It has several functions including detoxification, as well as abundant cholesterol and bilirubin metabolism, production of plasma proteins such as albumin, alpha and beta globulins, amino acids, carbohydrates, and fats., the liver stores blood, vitamins, and iron Additionally its produce many hormones that's responsible for many functions (12).

Liver enzymes are an indicator of liver function and a guide to the overall safety of the body; they indicate acute and moderate liver inflammations and a decrease in cases of liver cell damage (13). The liver enzyme alanine aminotransferase (ALT) is considered one of the liver enzymes, and a small amount of this enzyme is naturally present in the blood. It is worth noting that doctors monitor the level of this enzyme in the blood to detect any liver diseases and to monitor the progression of liver diseases alongside the levels of other enzymes secreted by the liver (14).

On the other hand, the enzyme Aspartate Transaminase (AST) is primarily produced from the liver, while the kidneys, heart, muscles, and brain also release small amounts of it. Actually, the blood contains a tiny amount of this enzyme. When there is a liver issue, the blood's concentration of this enzyme increases. However, an increase in this enzyme alone does not confirm a liver problem, as the issue could be with another organ that secretes this enzyme. Therefore, liver function tests depend on monitoring the levels of several enzymes secreted by the liver to ensure accurate and precise test results (15).

The main sources of urea are protein consumption in food and tissue protein turnover. The small intestine in the gut is responsible for absorbing proteins. From creatinine phosphate, which is eliminated by the kidney, creatinine is produced as an end product of muscle metabolism. The most recent measure of kidney function is creatinine. The creatinine clearance test is an additional examination that gauges how well the kidneys filter creatinine from the blood. The test compares the amount of creatinine voided and serum creatinine at a predetermined time, often 24 hours (16). Creatinine naturally exists in the body through the breakdown of muscle tissue and can also be obtained through dietary protein. It is considered a waste product in the body. Elevated creatinine levels may result from various health conditions and other factors. When creatinine levels are high, efforts should be made to control the factors that may cause kidney damage. From creatinine phosphate, which is eliminated by the kidney, creatinine is produced as an end product of muscle metabolism. The most recent measure of kidney function is creatinine. The creatinine clearance test is an additional examination that gauges how well the kidneys filter creatinine from the blood. The test compares the amount of creatinine voided and serum creatinine at a predetermined time, often 24 hours (17).

Materials and Method

Chemicals

Cyproheptadine hydrochloride was the drug used to inject the animals in the form of tablets containing 4 mg. To prepare a 50 µg/kg dosage, each tablet was dissolved in 4 cc of distilled water , Another way to

prepare a dose of 25 µg/kg was to dissolve the medication in 8 cc of distilled water.

Animals

In this study, 18 animals were used by (6) Swiss egg mice Mus musculus for each group, where the control group and the treated group included a concentration of 25 µg/kg and the treated group at a concentration of 50 µg/kg, with ages ranging from 10 to 8 weeks and weights ranging from 36 to 21 grams, obtained from a research center at Al-Nahrain University Biotechnology. Twelve hours of light and twelve hours of darkness were provided for the animals' cages, which were kept in rooms between 22 and 27 degrees Celsius, and the plastic cages were dimensioned at 24*50*17 cm, covered with metal mesh lids, containerized on sawdust, and supplied to the animals with water and feed for the duration of the research.

Experimental groups

The animals in group 1 and group 2 received injections of 25 µg/kg and 50 µg/kg of Cyproheptadine hydrochloride (0.1 ml) once a day, respectively. The control group received an injection of distilled water (0.1 ml).

Blood and Serum Samples

rats After starving each group for ten to twelve hours, the rats were put to sleep with sodium pentobarbital so that they could be thoroughly dissected. The serum from the inferior vena cava was extracted and separated using centrifugation for 15 minutes at 3000 rpm. The obtained serum was maintained at -18° C to facilitate analysis and estimation of blood parameters.

Histopathological examination

Fix testicular tissue in 10% neutral buffer formalin, processed for sectioning of paraffin and some sections were used for staining with H&E after Tousson (2016) and the rest were utilized for PCNA expressions after (El-Masry et al. 2020).

Biochemical examination

The Alanine Aminotransferase (ALT; EC 2.6.1.2) and AST , alkaline phosphatase ,urea,creatinine , lactate dehydrogenase and protein concentration Activity in the liver and kidney serum was measured using the technique of (Reitman et al.,1957).

Statistical Analysis

In the data analysis of The Statistical Analysis System-SAS (2012)The statistical analysis program examined the effect of various factors on the studied traits, and the differences were compared morally between the averages by testing the least significant difference (LSD).

Results

Changes in the weights of mice

The average weight of the mice changed significantly ($P<0.05$) between the groups treated with Cyproheptadine Hydrochloride at concentrations of 50 and 25 µg/kg, as compared to the control group, after 21 days from the start of posing, as indicated in Table 1.

Table 1: Shows the effect of different concentrations of the drug Cyproheptadine hydrochloride on the rate of Mice weights.

Groups	Mean ± SE of weight (g)
Control	23.140 ± 0.42
G1: 25	28.127 ± 0.663
G1: 50	28.620 ± 0.087
P value	0.001 *
* A statistically significant difference is seen at a significant level of $P<0.05$, according to analysis of variance (ANOVA).	

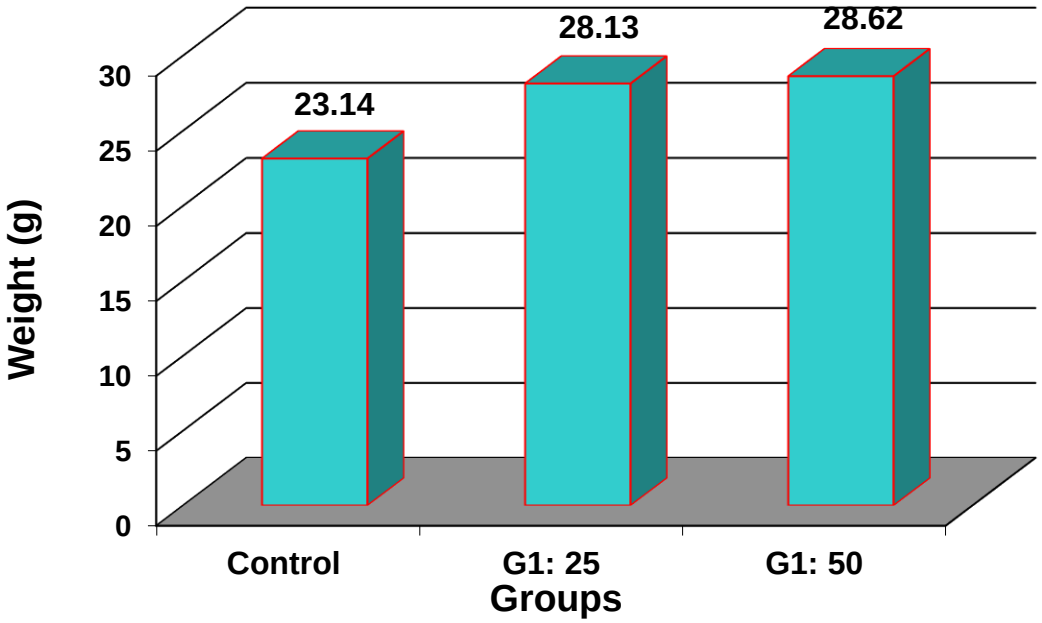

Figure 2. displays the impact of varying dosages of the medication cyproheptadine hydrochloride on the mice weight rate.

After mice were dosed with Cyproheptadine hydrochloride (CH) for 21 days, the research results indicated significant changes in the rate of mice's weights at the level of ($P < 0.05$). The statistical analysis also revealed a significant increase in the weights of the treated mice compared to the control group. It is quite probable that cyproheptadine hydrochloride causes weight gain via stimulating appetite, which raises calorie intake. Two distinct theories were put out to account for this phenomena. According to the first theory, CH acts on 5-HT2 and H1 receptors to directly increase hunger by activating the hypothalamus appetite center. The alternative theory also states that CH encourages eating more frequently, indicating that its effects may be more closely linked to postprandial satiety/hunger signaling than to a route involving food rewards (18, 19).

Cyproheptadine's capacity to enhance appetite may be explained by its antagonistic action on serotonin receptors in the hypothalamic appetite region. Cyproheptadine directly stimulates hunger by stimulating the hypothalamic appetite center. This leads to a rise in weight, which in turn increases energy intake and stimulates the release of growth hormone by inducing deep sleep (20).

Changes in liver function:

The results showed an increase in the studied liver function Alanine transaminase and Aspartate transaminase enzymes (AST, ALT) for serum after 21 days of initiating dosing between treated groups with Cyproheptadine hydrochloride and in concentrations of 50 and 25 µg/kg in contrast to the group under control, according to Table 2.

Table 2: Shows the effect of different concentrations of the drug Cyproheptadine hydrochloride on functions Liver.

Groups	Mean ± SD	
	ALT (IU/L)	AST (IU/L)
Control	24.430 ±0.480	24.17 ±0.352
G1: 25	30.81 ±0.980	26.51 ±1.005
G1: 50	31.2 ±0.595	27.02 ±0.949
P-value	0.004 *	0.012*
* A statistically significant difference is seen at a significant level of P<0.05, according to analysis of variance (ANOVA).		

According to the study's findings, mice given the medication Cyproheptadine hydrochloride at doses of 50 and 25 µg/kg had significantly increase in liver enzyme levels than the control group. This is predicting inflammation in the liver as well as the accumulation of chemicals and drugs in the liver as a result of blood purification (21).

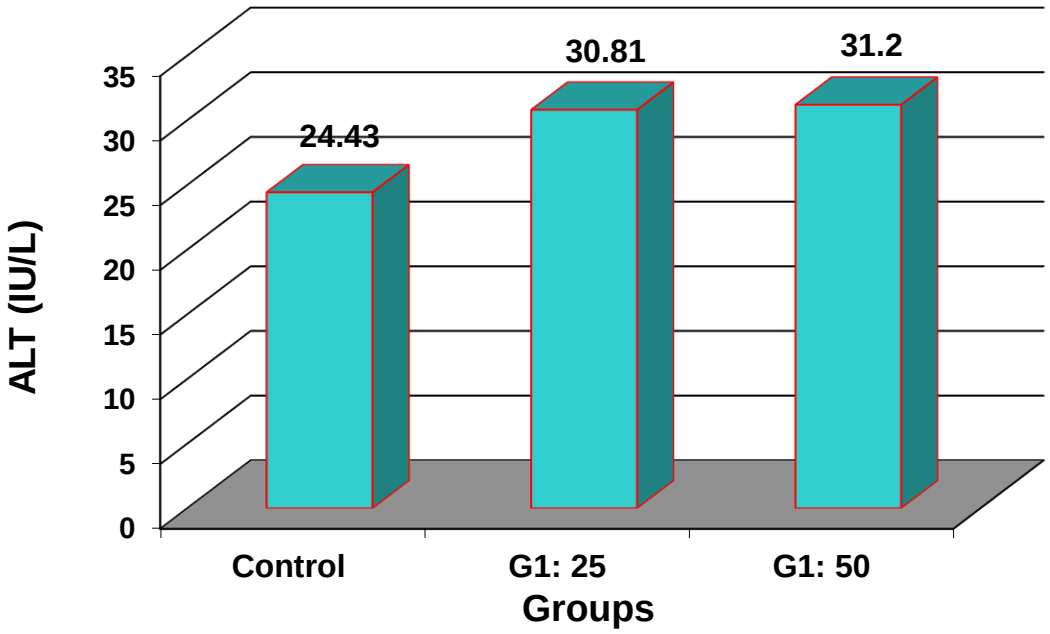

Figure 3. Shows the levels of ALT in different groups

In the groups treated with concentrations of 25 and 50 g/kg, the level of this enzyme increased compared to the control group. Physicians are interested in knowing the level of this enzyme in the blood to detect any liver or other organ diseases. (22). The intake of certain medications may cause an increase in liver enzymes. The percentage of this enzyme increases when there is a problem in the liver or another organ (23).

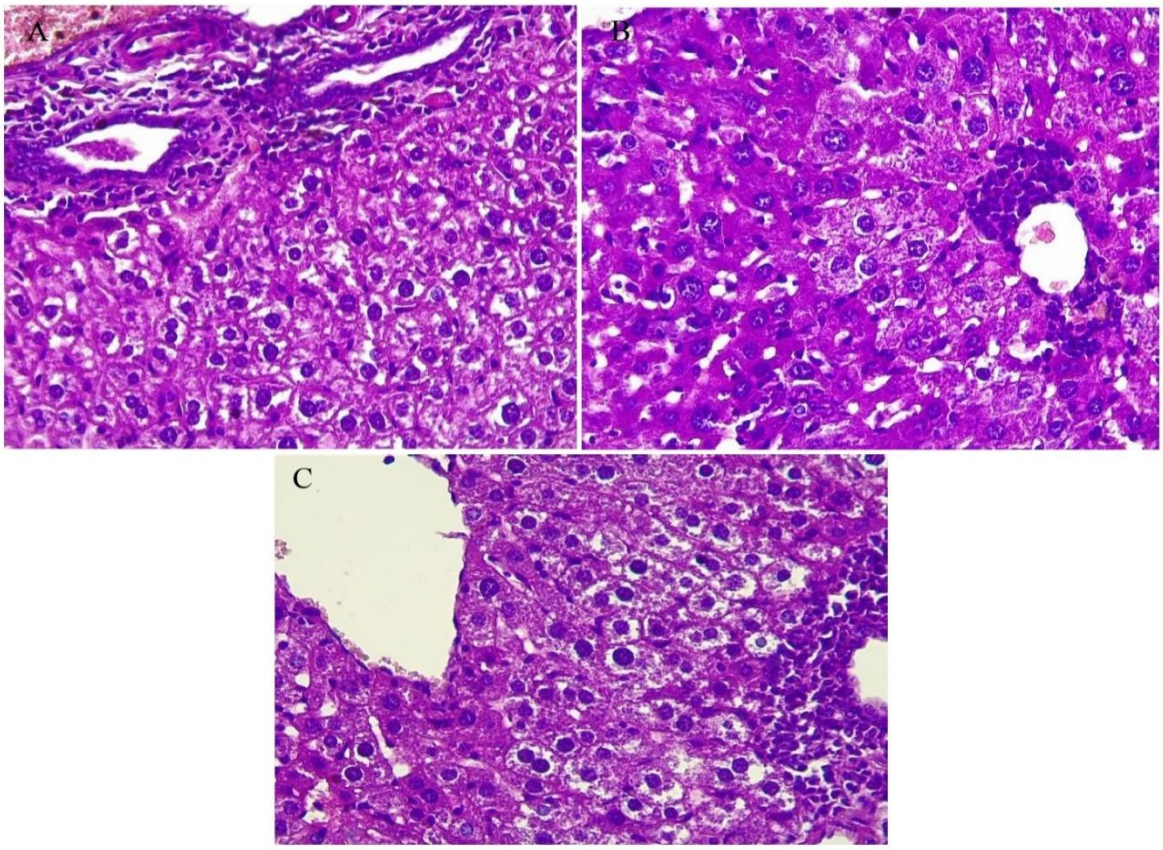

Figure 5. histopathological sections of mice liver :**A;**Normal liver lobules of hepatic tract no congestion of central nerve(control).**B:**Chronic inflammatory cell infiltration around the central nervous system and in the portal, tract is associated with some vascular congestion(treated with 25%).**C:**Vacuolation of hepatocytes with sinisoida dilatation of the central vein, dilatation, and chronic inflammatory cell infiltration(treated with 50%).

Consuming cyproheptadine may result in cholestatic hepatitis and mild cytolysis. With acute liver failure, Cyproheptadine should most likely not be administered to individuals who have had liver illness in the past because of the drug's tricyclic ring structure, which is comparable to that of phenothiazine medications. This structure contains a tertiary amine, which may cause oxidative phosphorylation's separation features (24).
Cyproheptadine causes cholestasis or mixed-pattern acute hepatitis because of its tricyclic ring, which shares structural similarities with other phenothiazine hepatotoxic medications such as imipramine, ajmaline, and chlorpromazine (25). Cyproheptadine treatment in rats results in liver damage and changes to the ultrastructure of liver cells, indicating a potential hepatotoxicity of the drug (26). After stopping Cyproheptadine, elevated liver enzyme levels usually go away after a few weeks. Although cyproheptadine has not been known to cause an autoimmune response, it has been connected to hepatitis, yet there are few reports of acute liver failure (27).

Changes in kidney function

The results showed an effect on kidney function (blood urea, creatinine) for serum after 21 days of initiation of dosing between treated groups with Cyproheptadine hydrochloride and in concentrations (25 and 50 µg/kg) in contrast to the control group, as seen by Table 3.

Table 3: Shows the effect of different concentrations of the drug Cyproheptadine hydrochloride on Kidney functions

Groups	Mean ± Sd(mg/dl)	
	Blood Urea	Creatinine
Control	25.817 ±0.940	0.660 ±0.020
G1: 25	27.500 ±0.849	0.850 ±0.025
G1: 50	25.023 ±0.405	0.826 ±0.009
P- value	0.085 NS	0.005*
* A statistically significant difference is seen at a significant level of P<0.05, according to analysis of variance (ANOVA).		

Blood Urea

After comparing the results of serum tests of the groups that were treated and the control group to detect the level of urea, it was found that the level of urea had increased non-significantly in the totals of treated groups compared to the control group, and group 50 µg/kg had the lowest level of urea compared with group 25 µg/kg.

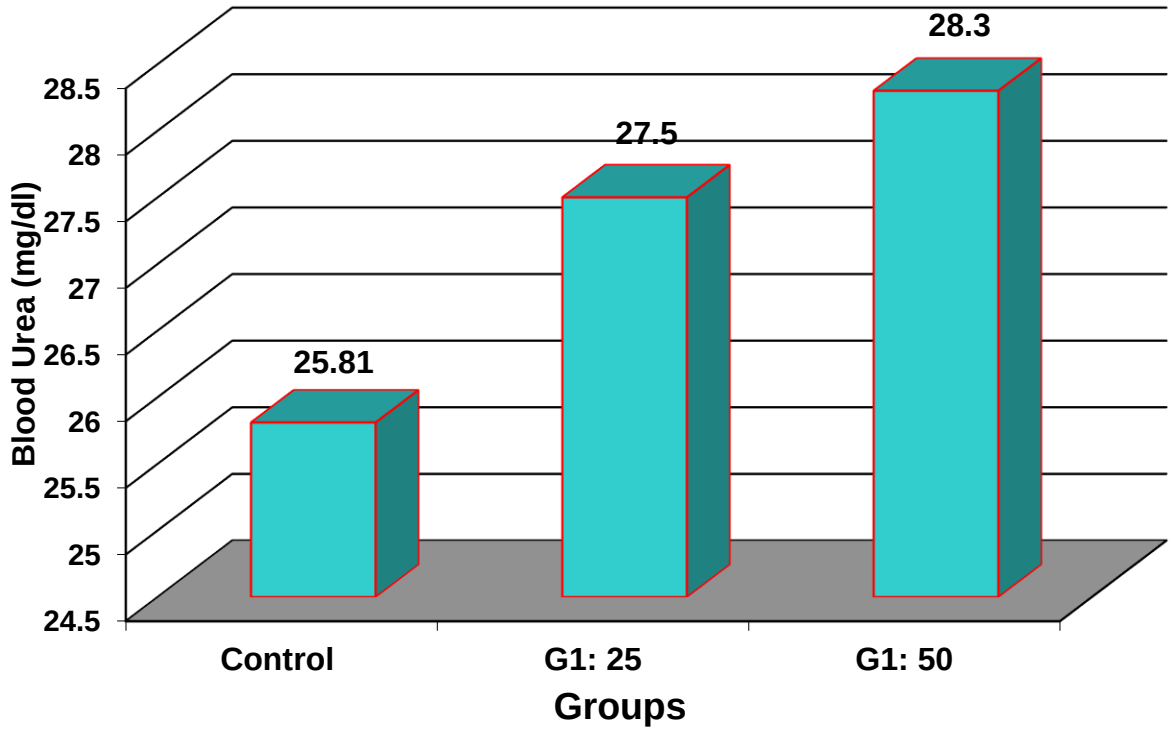

Figure 6. Shows the levels of urea in the blood in different groups

Blood Creatinine

After comparing the serum creatinine levels of the treated groups and the control group, it was found that the level of creatinine had increased significantly in the treated groups compared to the control group.

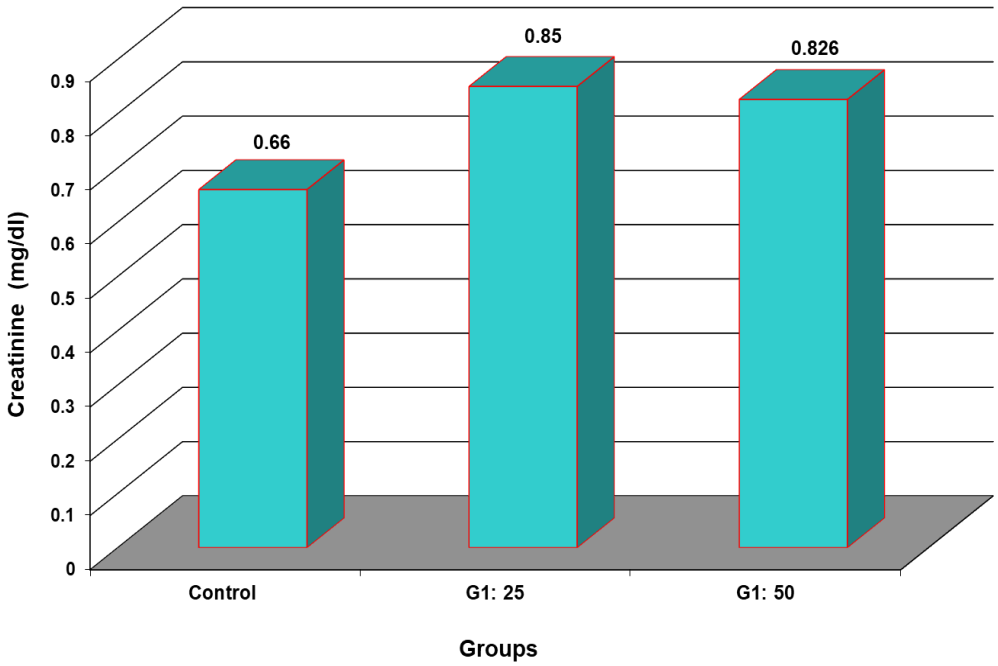

Figure 7. Shows creatinine levels in different groups

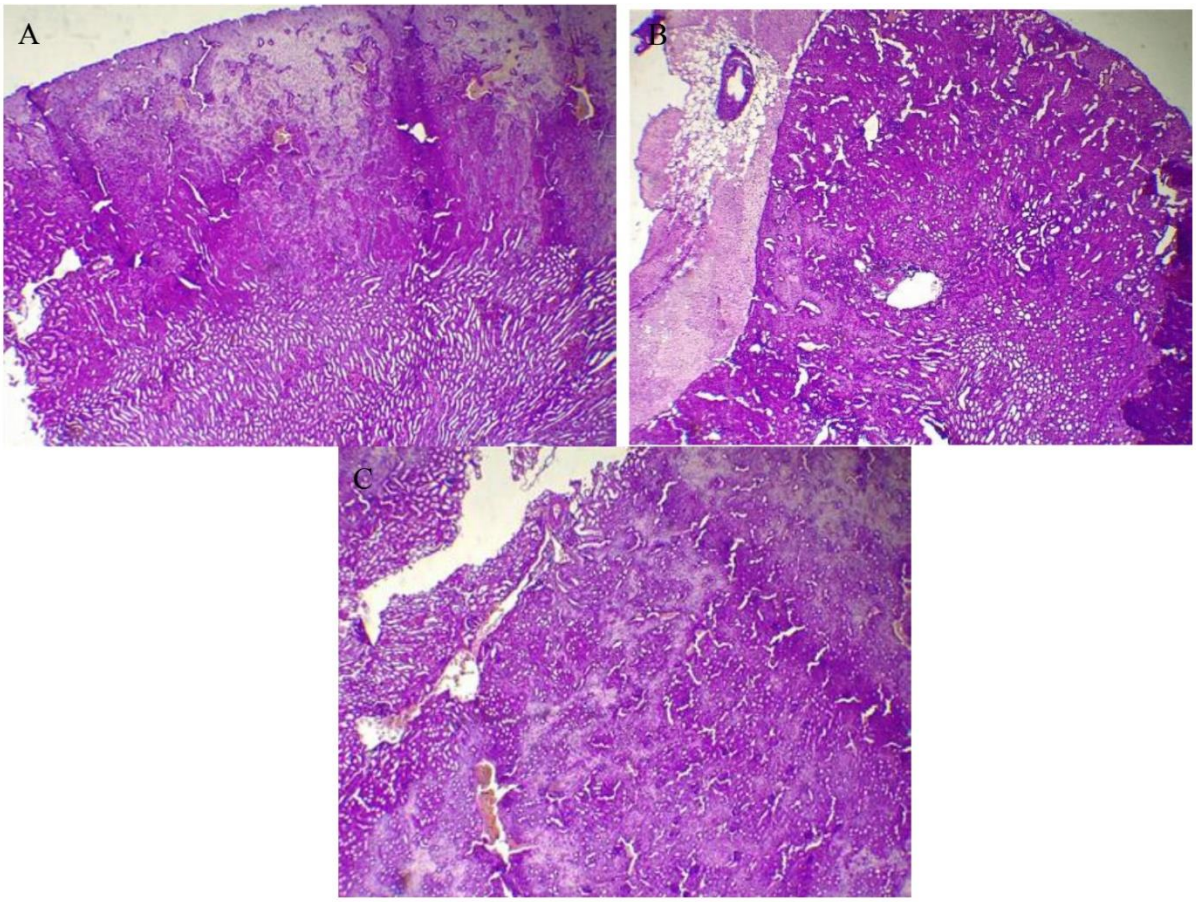

Figure8. histopathological sections if mice kidney:**A:**normal glomerulin and collection tubules (control).**B:** Normal glomeruli and collection tubules with very mild chronic inflammatory cells infiltration (treated with 25%).**C:** Hydropic changes of cuboidal epithelial cells with more inflammatory cell changes (treated with 50%).

Muscle spasms cause creatinine to be released from the body, which is why the treatment group's levels of creatinine were higher than the control group's after receiving cyproheptadine hydrochloride. Additionally, kidney diseases contribute to its excretion from the kidneys. Ultrasonography findings are suggestive of acute kidney injury. Other routine investigations were within the normal limits. Hence, a provisional diagnosis of serotonin syndrome (28).

The studies revealed an increase in kidney function tests (urea and creatinine) levels in treated groups with Cyproheptadine hydrochloride at a concentration of 25 and 50 µg/kg compared to the control group. This elevation is represented by high creatinine levels due to the kidneys' inability to eliminate it. Another study approved our results because creatinine is excreted from the muscles, which causes the kidneys to elevate. Additionally, kidney diseases contribute to its excretion from the kidneys (29). Compared to other tissues, the kidney and lung had greater drug concentrations (30). Other studies don't approve of this elevation in urea and creatinine (31).

Conclusions and Recommendation

Conclusions

The research revealed that cyproheptadine hydrochloride had a notable impact on the treated mice's increased body weight over a period of 21 days. There was a marked rise in liver enzymes and marked changes in liver tissue, indicating liver toxicity. In addition, cyproheptadine hydrochloride increased significantly from the levels of creatinine, indicating the probability of kidney failure, although the increase in urea levels was non- significant. These findings highlight the need to take account of these physiological changes when giving cyproheptadine hydrochloride.

Recommendation

1. Histological study of different organs of the treated mice (uterus, ovaries).
2. Histological study of the liver and kidneys of the treated mice.
3. Future trials should start monitoring hepatic blood tests to check for this possible consequence.

Declaration of Conflicting Interests:

the authors declare that they have no possible conflicts of interest

funding

no funding

Ethics

The study design was approved by the Institutional Ethical Committee for Animal Care and Use (code: IACUC-SCI-TU-0241).

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