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Histological and Biochemical Evaluation of the Effect of Desloratadine Drug in Hepatic Tissues

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Abstract: The main active element of loratadine (Claritin) is desloratadine (Clarinex), a non-sedating antihistamine used to treat pollen allergies and hives. The liver is responsible for drug metabolism, bioregulation, and immunomodulation. As a result, the impact of different desloratadine doses on hepatic tissues, histological characteristics, and serum liver enzymes is explored in this research. Materials and methods: In this work, thirty rats were utilized. Three organizations were made (each containing ten rats). Controls rat (Group A)./Desloratadine was given to groups B and C for 3 weeks at doses of 0.142 mg per kilogram of body weight and 0.245 mg per kilogram, respectively. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in the blood were measured three weeks later; three groups had their alkaline phosphatase (ALP) levels measured. Animals were then sacrificed, and five μm formalin-fixed paraffin-embedded tissue blocks from the liver were consistently produced for histological assessment under a light microscope. The histological evaluation of hepatic tissues in both treated-groups was revealed a great dilatation, congestion, edema, and necrosis, degeneration, infiltration, and atrophy of liver tissue. The treated groups had significantly increased AST, ALT, and ALP serum levels regarding the biochemical analysis. Desloratadine administration produces noticeable histological changes in a dose-dependent manner associated with increased liver enzymes AST, /ALT, and ALP.

Keywords: desloratadine, histamine, CYP3A4, liver, histology, hepatotoxicity

地氯雷他定药物对肝组织作用的组织学和生化评价

摘要：氯雷他定(克拉丽汀)的主要活性成分是地氯雷他定(克拉丽娜)，这是一种用于治疗花粉过敏和荨麻疹的非镇静抗组胺药。肝脏负责药物代谢、生物调节和免疫调节。因此，本研究探讨了不同地氯雷他定剂量对肝组织、组织学特征和血清肝酶的影响。材料和方法：在这项工作中，使用了 30 只大鼠。制作了三个组织（每个组织包含十只大鼠）。对照组大鼠（A 组）/地氯雷他定给予 B 组和 C 组 3 周，剂量分别为每公斤体重 0.142 毫克和每公斤 0.245 毫克。三周后测量血液中的丙氨酸氨基转移酶和天冬氨酸氨基转移酶水平；测量了三组的碱性磷酸酶水平。然后处死动物，并一致地从肝脏中制备 5/微米福尔马林固定石蜡包埋的组织块，用于在光学显微镜下进行组织学评估。两组肝组织的组织学评价均显示肝组织大量扩张、充血、水肿、坏死、变性、浸润、萎缩。就生化分析而言，治疗组的丙氨酸氨基转移酶、丙氨酸氨基转移酶和碱性磷酸酶血清水平显着增加。地氯雷他定给药以剂量依赖性方式产生显着的组织学变化，与增加的肝酶丙氨酸氨基转移酶、丙氨酸氨基转移酶和碱性磷酸酶相关。

Received: May 1, 2021 / Revised: June 6, 2021 / Accepted: August 24, 2021 / Published: September 30, 2021

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关键词：地氯雷他定，组胺，CYP3A4，肝脏，组织学，肝毒性。

1. Introduction

Desloratadine (Clarinex) is a non-sedating, long-acting second-generation selective peripheral H1-antagonist prescribed to treat seasonal allergies and chronic autoimmune/urticaria. It has a half-life of 21-27 hrs and moderate complement proteins binding (82–87%), allowing for once-daily administration. Histamine is a substance responsible for many of the symptoms associated with allergic reactions, such as tissue swelled. Histamineais produced by histamine-storing cells (mast cells) and binds to cells that have histamine receptors. When histamine binds to the receptors, the cell becomes "activated," releasing additional chemicals that create the symptoms associate with allergies. Desloratadine selectively suppresses peripheral histamine H1-receptors since the chemical does not effectively infiltrate the central nervous system from blood and, hence, does not cause drowsy. Consequently, desloratadine's active component in humans is 3-hydroxy desloratadine (due to pyridine ring hydroxylation), which is then glucuronidated to 3-hydroxy desloratadine O-glucuronide. In urine and feces, both are expelled in nearly equal proportions. CYP3A4 and CYP2D6 are involved in the metabolism of loratadine and its metabolite desloratadine [1], [2].

Because of the critical involvement in the metabolism, transportation, and elimination of alien substances, the liver is one of the vital bodily organs and the initial defense barrier that plays a crucial role in identifying drug toxicity [3]. Liver tissue releases inflammatory cytokines and contains a considerable level of enzyme activity [4]. Because the liver plays such a crucial role in metabolizing xenobiotics and pharmaceuticals, it is constantly damaged. Two primary processes were shown to be responsible for hepatocellular damage. The quick procedure involves fatty-acid cytotoxicity on hepatocytes due to massive intracellular fatty acid buildup, whereas the indirect mechanism involves the cytotoxic activity of fatty-acid induced toxicity [5].

The direct action of a pharmacological substance or its reactive metabolites on liver cells, which results in necrosis or induction of apoptosis, is one of the most common mechanisms for developing these disorders [1], [2].

Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline Phosphate (ALP), overall protein (TP), as well as albumin are indicators for liver function and integrity. It can illustrate the loss of internal structure of the liver to a great extent, due to the distribution of cytoplasmic the exclusive of ALT/and a relatively long half-life in the blood (about 50 hours) than for albumin (about 16 hours) [6], [7].

ALP is noticed in many organs, including the liver, bone, kidney, intestine, and placenta, as well as its exact function varies depending on the tissue. However, the major ascent of serum ALP is associated with the liver or bone, where ALP is rapidly elevated due to bile flow deficits or various types of expanded lesions [8].

2. Materials and Methods

2.1. Experimental Animals

Twenty mature male rats weighing 220-250 g were obtained from Tikrit University's Veterinary Medicine Faculty's animals home in January 2020. The set of criteria utilized in this experiment was accepted by the Animal Ethics Committee of Tikrit University's Veterinary Medicine College (4644/18/7 in 14.03.2019). Animals were housed in plastic cages and subjected to a 12D:12L reverse light cycle at 260°C and relative humidity of 40%. Water and normal diets were readily accessible.

2.2. Experimental Protocol

The rats were split into three groups, each with 10 rats, and they were given the following treatment for three weeks:

Group 1: Normal saline was injected into group one animals.

Group 2: Desloratadinea was given to Group 2 rats at a dose of 0.142 mg/kg in saline every day constantly for three weeks.

Group 3: Desloratadineeat a dose of 0.245 mg/kg in saline was given to rats in group 3 every day for three weeks.

Blood samples were taken from all of the rats in each category at the end of the experiment. Clear serum samples were obtained by centrifugation at 4,500 RPM for 5 minutes, then stored at -20°C until used for biochemical assays.

The commercial kits' instructions for analyzing ALT, AST, and ALP were ordered from Biodiagnostic Co., Giza, Egypt. The rat's livers were collected after sacrifice and immediately fixed in 10% formalin. For histological assessment, the organs were then fixed with paraffin wax, sectioned (4 m), and stained with Eosin and Hematoxylin stains. [9], [10], [11], [12].

The data was examined using the SPSS statistical software, including one-way analysis of variance (ANOVA) and Dunnett's multiple comparison test. P <

0.05 was used to determine if differences in means were significant.

3. Results

When comparing the desloratadine-treated group to the control group, there was a significant rise in serum ALT and AST activity ($P < 0.05$).

Table 4 The ANOVA test was used to compare the mean values of ALT and AST in the various study groups

Treatment	Control	Desloratadine (0.142 mg/kg)	Desloratadine (0.245 mg/kg)
AST (U/L)	33.1 ± 3.13	56.08 * ± 2.04	79 ± 0.2
ALT (U/L)	27.7 ± 0.97	38.1 * ± 0.67	58.2* ± 1.26
ALP (U/L)	91.3± 1.63	120.17 * ± 1.64	135.15 * ± 1.95

3.1. Results of Liver Histopatholog

When comparing the results of group 1 to the control group, the texture of the liver tissue changed somewhat, and the liver sinusoids were slightly clogged, with little disorientation of the hepatic plates (Fig. 1 and 2). Fig. 3-5 demonstrate scattered sinusoid congestion, mainly towards the central vein, with inflammatory cell aggregation and hepatocyte degradation when group 2 results are compared to the control group. A local was found over certain samples. The figure shows a microgranuloma located far from the central vein, with a collection of WBC, most likely lymphocytes, with few macrophages and neutrophils [6].

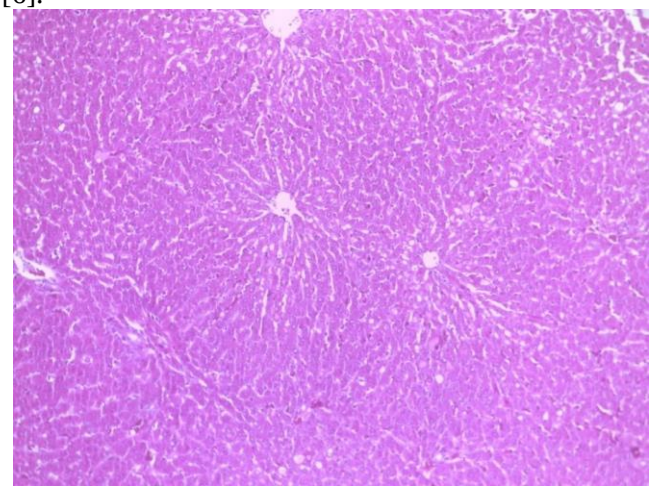

Fig. 1 Control group shows normal hepatocytes with homogenous texture. 10X, H&E

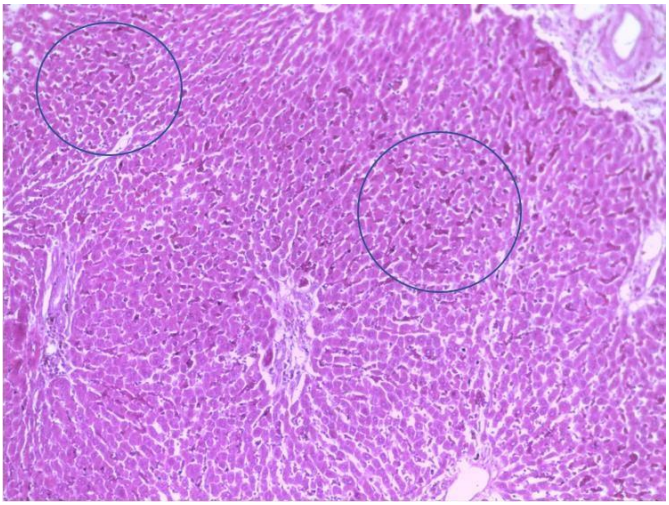

Fig. 2 Experimental group 1 showing slight sinusoid congestion (areas within the circle) 10X, H&E

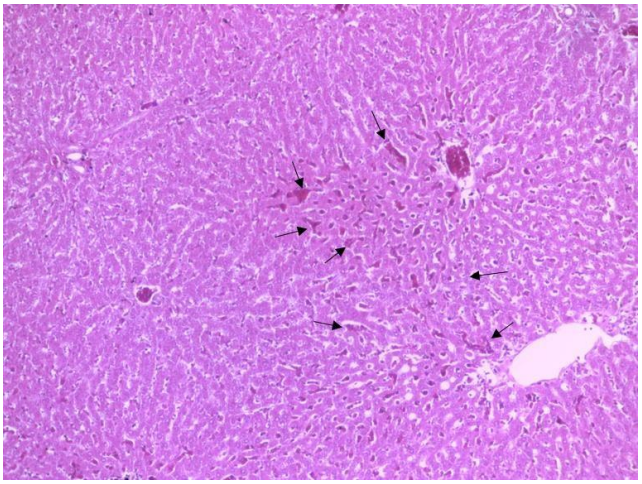

Fig. 3 Liver of experimental group 2 clarify sinusoid congestion (black arrows) with an area of focal lymphocytes infiltration and hepatocytes degeneration adjacent to the central vein (area within the rectangle) 10X, H&E

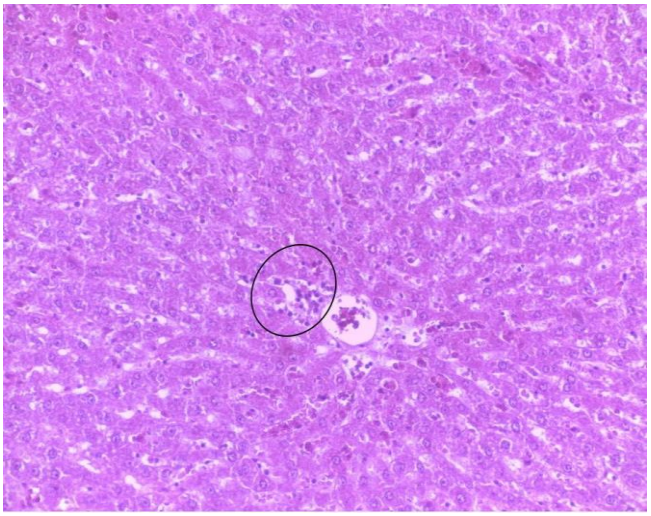

Fig. 4 Experimental group 2 showing inflammatory cells aggregated near the lining of the central vein (area within the circle) 20X, H&E

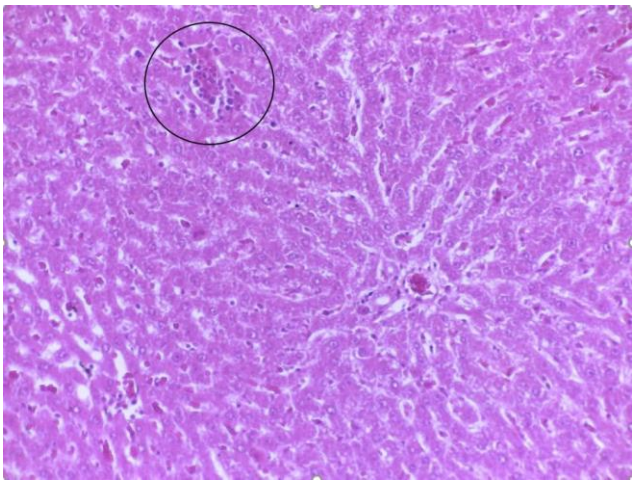

Fig. 5 Liver of experimental group 2 revealed microgranuloma (areas within the circle) 20X, H&E

4. Discussion

The present study was revealed significant histo-morphological alterations within the liver parenchyma in the groups treated with desloratadine in a dose-dependent manner. These alterations were reflected tissue degeneration and atrophy.

Each morphological alteration is a consequent event for molecular changes that affect many reactions. A malfunction in the nucleus is frequently linked to changes in the entire bioactivity of the cell. On the other hand, changes in the cytoplasm occur when the cell's functional activity is interrupted [10].

These findings might be attributed to an increase in these liver parameters, which are clear indicators of cellular leakage and loss of membrane's functional integrity due to liver damage and mitochondrial dysfunction, which is caused by the disruption of lipid - oxidation and oxidative energy production within hepatocytes. A disruption in the mitochondrial membrane can lead to ATP depletion and necrosis, while permeabilization of the mitochondrial membrane may cause cell death [11], [12]. The upregulation of the enzymes AST, ALT, and ALP in this report suggests that desloratadine has caused liver tissue damage, as demonstrated by histological defects such as dilatation, congestion, edema, inflammatory cells, and necrosis.

The present study found that after receiving desloratadine, serum ALP, ALT, and AST levels increased, which could be due to hepatocyte damage, with changes in transport function and membrane permeability, allowing enzymes to escape from the cells. The significant destruction of hepatic tissue membranes is indicated by the marked release of AST and ALT from liver cytosol into circulation accordingly [13], [14], [15], [16], [17].

5. Conclusion

Desloratadine causes hepatic disorders and changes in the histological architecture of the liver if used for three weeks.

5.1. Recommendation

Additional research into immunology, histology, and histochemistry may be required.

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