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Histopathological effects of Imipramine on liver, and brain tissue in mice

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بسم الله الرحمن الرحيم

﴿إِنَّ هَٰذَا كَانَ لَكُمْ جَزَاءً وَكَانَ سَعْيُكُم مَّشْكُورًا﴾

(الإنسان – 22)

صدق الله العلي العظيم

الأهداء

إلى من وهبنا الحياة والأمل، والنشأة على شغف

الاطلاع والمعرفة، ومن علمنا أن نرتقي سلم الحياة بحكمة وصبر؛

برا، وإحسانا، ووفاء لهما ابائنا الاعزاء، وامهاتنا العزيزات

إلى من وهبنا الله نعمة وجودهم في حياتنا إلى العقد المتين

من كانوا عونا لنا في رحلة بحثنا: إخواننا وأخواتنا

وأخيرًا إلى كل من ساعدونا، وكان له دور من قريب أو بعيد في إتمام هذا البحث،

سائلين المولى أن يجزي الجميع خير الجزاء في الدنيا والآخرة.

ثم إلى كل طالب علم سعى بعلمه، ليفيد الإسلام والمسلمين

بكل ما أعطاه الله من علم ومعرفة.

شكر وتقدير

قال تعالى (وَمَن يَشْكُرْ فَإِنَّمَا يَشْكُرُ لِنَفْسِهِ) (لقمان:12)

من جعل الشكرُ خاتمة النعمة

جعلها الله له فاتحة المزيد..

نتقدم بجزيل الشكر والامتنان الى الاستاذة الدكتورة رفاه المطيري على كل ما قدمته لنا من معلومات قيمة ساهمت في إثراء موضوع دراستنا في جوانبها المختلفة..

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Histopathological effects of Imipramine on liver, and brain tissue in mice

1.0 Introduction:

In medication research and development, determining human drug toxicity accurately continues to be an important challenge.[1][2]. Psychiatric medications approved to treat depression are known as antidepressants. Some have additional licenses to treat physical conditions, including as chronic pain management, anxiety disorders, and other illnesses.[3]. However, they don't always treat the primary reasons. For the purpose of treating the underlying causes of mental health issues, doctors frequently prescribe them in addition to talking therapy.While adverse medication responses play a significant role in the non-adherence to antidepressant treatment, it is challenging to assess them due to their overlap with depression symptoms and the absence of appropriate self-report applications.[4]. The largest organ in the human body is the liver. It carries out several vital functions that have the potential to greatly affect the effectiveness and efficiency of every bodily system.The abundance of medications and their metabolites in portal blood makes the liver particularly vulnerable to medication-related toxicity, which is why it plays such an important role in drug metabolism and detoxification[2][7][8].According to estimates, the fourth most common cause of liver dysfunction in Western nations is drug-induced liver disease[2]. Approximately one thousand drugs that are utilized in clinical settings have been linked to liver damage of some kind.[2][9]. Because the human brain enables thoughts, memory, movement, and emotions by a complex function that is the highest product of biological evolution ,The brain represents the controlling centre for the nervous system and.Maintaining a healthy brain during one’s life is the aim to in pursuing health and longevity.[10]

Imipramine is a classic tricyclic antidepressant (TCA), derived from dibenzazepine. Tricyclic ring systems which resemble phenothiazine structures .There is an alkylamine substituent in the middle ring.[5]. It is available in doses of 10mg,25mg,50mg and 75mg .[6]

Imipramine is typically used as a second-line treatment for severe depression with unusual symptoms . Also , imipramine has been proposed as a useful adjuvant treatment for nocturnal enuresis in children over the age of six , and treat chronic neuropathic pain . Tricyclic antidepressants, of which imipramine is the first component, are still often prescribed despite the ongoing development of newer, less toxic antidepressants since they are economical and remain regarded as the most effective class of antidepressants.[2]. Imipramine quickly and effectively absorbed when taken orally The small intestine is the main site of absorption .Because of the significant inter-individual variability, bioavailability varies from 29 to 77%. After oral administration, peak plasma concentration is typically reached two to six hours later.[11]

Imipramine is a lipophilic compound, which explains its high volume of distribution of 10–20L/kg 3 ν. Imipramine is known to bind albumin, α1-acid glycoprotein, and lipoproteins. In circulation, it is 60–96% bound to plasma proteins.[11]

The drug is known to build up in the brain at levels 30–40 times higher than in the bloodstream.[11]

Imipramine subjected to extensive hepatic metabolism by P450 isoenzymes and less than 5% of a its dose is eliminated unchanged. Imipramine acts by preventing the neuronal reuptake of the neurotransmitters norepinephrine and serotonin.[11][12].

The common side effects :dry mouth ,blurred vision, constipation, weight gain. and uncommon side effects headache , nausea, palpitations, postural hypotension, sexual dysfunction, sweating.[13]

Possibly drug interactions monoamine oxidase inhibitors (MAOIs), a class of antidepressants, and tofranil should not be taken combined since this may result in a hazardous reaction that includes rising body temperature, elevated blood pressure, and excessive excitement and agitation. Before using any new medications with Tofranil, including over-the-counter drugs and herbal supplements, patients should speak with their doctor or pharmacist.

Alcohol should be avoided or consumed in moderation by patients on tofranil as the combination may make depression worse.[14]

2.0 Materials and Methods:

The experimental study was carried out on 20 rats (8-10 weeks old) weighing between 170-200 g during the period from December 2022 to March 2023. It has been achieved in the Animal House of Faculty of Pharmacy, University of Babylon. The animals were maintained under controlled environmental conditions and were provided with high fat diet and tap water. The experiments were conducted according to Institutional Animal Ethics Committee guidelines for the care and use of laboratory animals. After one week adaptation period, the rats were divided into 2 groups: (GI): five Healthy control rats . Group 2 (GII): 7 Rats of this group were received of Imipramine10 mg/kg of orally through daily gavage tube for 3 weeks.

3.0 Histological study:

The animals were anesthetized by ether, the liver and brain specimens was dissected out were removed and rinsed thoroughly in physiological saline 0.9 percent NaCl. Brain and liver samples were taken from each animal and were collected and fixed for 48 hours in a 10% neutral buffed formalin solution. According to the approach, histological slides for each section were conducted as outlined by Suvarna et al. 2019. A light microscope was used to view and photograph the tissue sections. [15]

4.0 Results and Discussion:

As demonstrated in the Figure (1) the liver of controlled rats showed normal histology, while in Figure(2) the liver in male albino rats received imipramine10 mg/kg, showed dilatation, congestion of blood vessels and lymphocyte infiltration in (Fig.3).

In brain tissue, The cerebral cortex of the control rat group had normal histological architecture represented by neurons, glial cells (Fig.4. a) , While in (Fig.4. b) brain tissue of Group II of mice administered with Imipramine10 mg/kg, the pathological changes represented by neutrophils or mononuclear leukocytes infiltration.

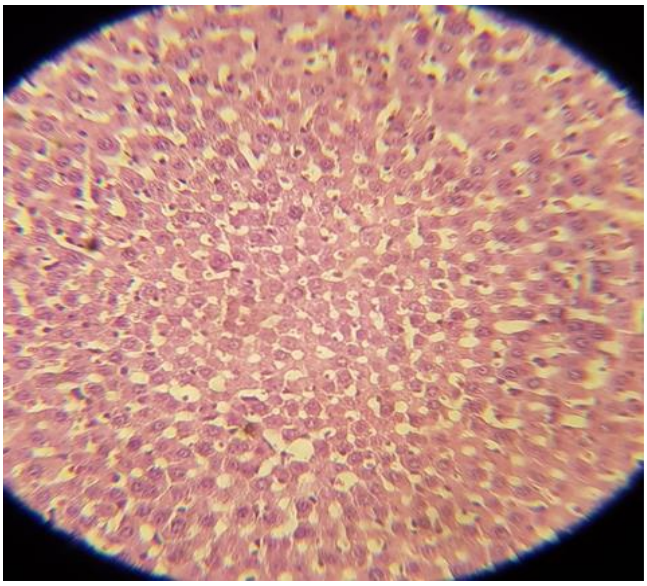

Figure1:cross-section of the liver of a rat of group I showing the normal architecture of liver tissue, stain with(H&E) 400X.

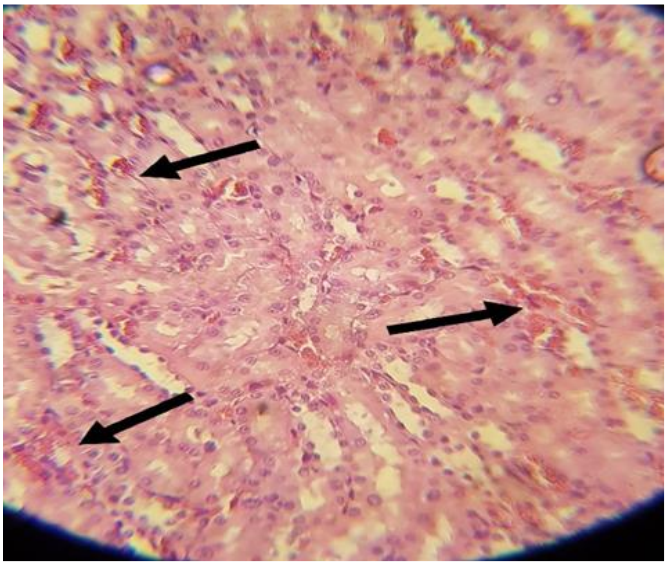

Figure 2: section of the liver tissue of a rat of the imipramine treated group group II showing dilated , congested of vessels (black arrow), stain with(H&E) 400X.

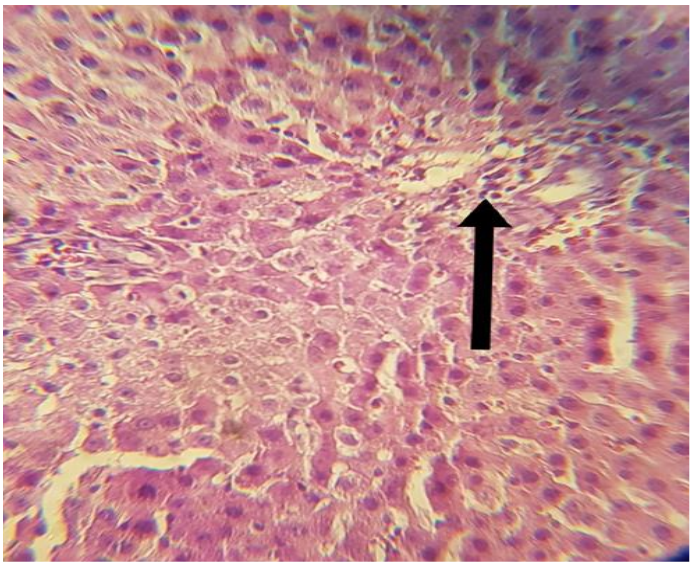

Figure 3 : Cross histological section of the liver of the imipramine treated group (group II) also showed lymphocyte infiltration(black arrow), stain with(H&E) 400X.

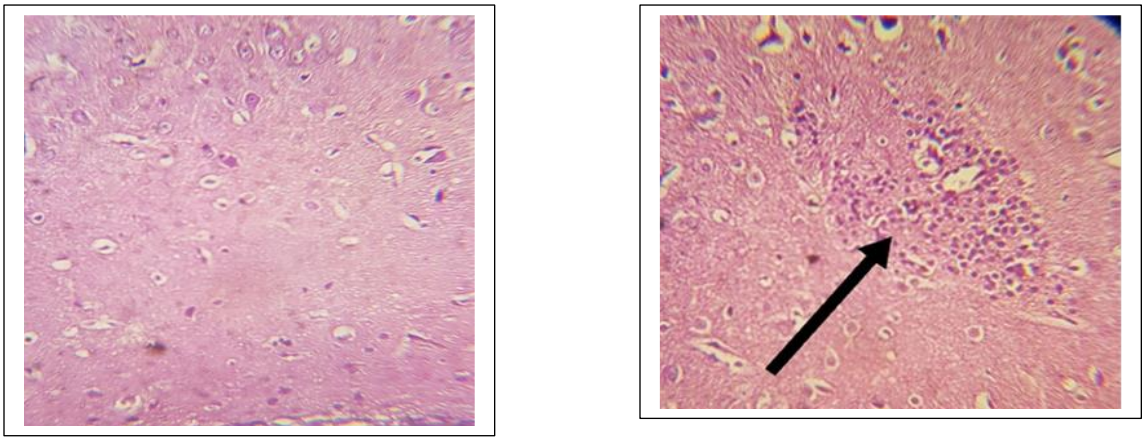

Figure 4: Cross section of the brain tissue of(a) the control rat group showing normal brain tissue (b), brain tissue of Group II dominated by neutrophils or mononuclear leukocytes(black arrow), stain with(H&E) 400X.

5.0 Discussion:

A mouse model of imipramine-induced liver damage has been effectively created in this study, using medication dosages that are comparable to human therapeutic dosages and regimens. One known factor contributing to liver damage is adverse medication responses.[16]The study's findings indicate that the hepatotoxic effect of imipramine is dose-dependent, as demonstrated by the significant rise in liver function indicators and histological alterations in animals given a high dose (10 mg/kg) as opposed to those given a low dose (5 mg/kg). hepatic cross-section from a group I rat, displaying the typical liver tissue architecture. A section of a rat's liver tissue from group II that received imipramine treatment demonstrates dilated, congested vessels, and lymphocyte infiltration.

These results are in agreement with the study that conducted by Ayad *et al.* [2], which investigated the effects of giving mice imipramine 10 mg/kg daily for three weeks.[2] When comparing the treated mice to the control group, there were noticeable alterations in the hepatocellular morphology (hepatocyte enlargement, degeneration, and necrosis).Chang *et al*. recently conducted an experiment in which they fed a high-fat diet to C57BL6/J mice in order to assess the impact of imipramine on liver, kidney, and obesity indicators. Chang *et al.* found that during an eight-week course of imipramine (10 mg/kg), the mice receiving treatment had increased liver and body weights, as well as elevated levels of serum triglycerides, ALT, AST, creatinine, and blood urea nitrogen.[17]

Apart from these modifications in hepatic function, imipramine was also demonstrated to cause significant pathological alterations in the liver architecture of the treated mice, which included prominent hepatocyte swelling in the centrilobulus, portal inflammation, and a large infiltration of inflammatory cells. Imipramine’s fundamental mechanism of liver damage induction is still unclear and needs further explanation. The previously mentioned results suggest that imipramine or its intermediate metabolites may interact with hepatocellular biomolecules to produce highly reactive agents. These agents are likely capable of inducing extensive damage and oxidation destruction to multiple biomolecules, such as proteins and lipids, and consequent loss of hepatocyte membrane integrity. Ultimately, this may lead to histopathological changes in the liver tissues and the release of the liver's enzymes into the bloodstream.[2]

Cross section of the brain tissue of G1 the control rat group showing normal brain tissue , while brain tissue of Group II dominated by neutrophils or mononuclear leukocytes ,These outcomes are identical as those of the study by Shaimaa Wadi which showed :Brain samples from group 2 displayed medulla and cortical blood vessel congestion as well as degeneration of pyramidal cells. a specific pyramidal cell in the cortex that is somewhat enlarged. Reduced brain nitric oxide concentration and nitric oxide synthase activity, as well as inhibited microglial NADPH oxidase activation, reduced reactive oxygen species formation, and reduced oxidative stress are all factors in imipramine-induced neurotoxicity.[19]

6.0 CONCLUSION:

We conclude that administration of antidepressants drug imipramine that had diverse effects on the liver and brain tissues by induce many structural changes, and hence it must be used under medical observation.

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