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Histological liver, kidney, and brain changes induced by pregabalin drug in albino rats

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Abstract

Pregabalin is a commonly used medication for the treatment of pain associated with neuropathic conditions, but there has been little research on its harmful consequences. This study divided 20 adult male rats into two sets (I and II). I set was given distilled water (5 ml/kg, orally), while II set was given pregabalin (12.8 mg/kg, orally) for 30 consecutive days. The histological and immunohistochemical features of the brain were investigated. A histomorphometric analysis was also performed, and the rats' weights were determined. The results revealed a variety of histopathological lesions. There was a positive response for GFAP (glial fibrillary acidic protein) expression in the brain. There were histological lesions in the liver, kidney, and brain, as well as differences in the histomorphometric measurements in set II compared to set I. Meaningful elevations in the GOT/AST (aspartate aminotransferase), GPT/ALT (alanine aminotransferase), and creatinine levels were explored, but a non-significant increase in the urea amount was noticed. The medication caused a meaningful elevation in body weight. The results revealed that the drug has toxic effects on the vital organs and their functions and can change their cellular structure if taken for a long time. Therefore, considering its side effects, it must be taken under medical advice.

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Introduction

Anti-seizure drugs were frequently used to help manage physical pain caused by nerve problems. Anti-seizure drugs were specifically developed to treat people suffering from epilepsy (1,2). Anti-seizure drugs inhibit excessive pain signal transmission from injured neurons (neuropathy) or overly sensitive nerves (as in myofascial pain). Pregabalin is a medication used to prevent epilepsy that acts as an anticonvulsant, analgesic, and anxiolytic (3). The drug can be prescribed to treat a variety of illnesses, including arthritis, neuropathic pain, and fibromyalgia (4). According to (5), pregabalin was authorized for use in the United States in 2004.The chemical formula is (S)-3-(aminomethyl)-5-methyl hexanoic acid. The drug company sold pregabalin under the trade names Lyrica and Lyrica Cr (4). This chemical is part of a group of organic molecules called gamma-amino acids and analogs. The gamma carbon atom of this amino acid has a (-NH_2) group linked to it, as well as numerous off-label applications, such as withdrawal effects, stress, and unpredictable emotions (6). Pregabalin is a manufactured-aminobutyric acid structurally reduced form that decreases the release of excitatory neurotransmitters (7). The recommended dosage ranges between 150 and 600 mg. For the treatment of epileptic attacks, more significant amounts of medication are employed. The dosage ought to be periodically increased and reduced (8). The occurrence of consequences associated with pregabalin has already been documented and connected to quantity. The drug is absorbed quickly and thoroughly after an oral dose when fasting, no matter the dosage. Pregabalin absorption is believed to be around 90%. After eight weeks of pregabalin oral

administration daily, female rats may develop reproductive, kidney, lung, and heart fibrosis as a secondary effect of the medication. Studies on animals have aided in identifying the biological processes underlying its anti-hyperalgesic and anti-allodynic effects (9). According to a particular histopathological investigation, the side effects of the drug included significant hepatic alterations (including fibrosis, cirrhosis, vacuolation, karyorrhexis, and programmed cell death) and numerous severe tissue lesions in the kidney and heart. Organ dysfunction and the accumulation of pregabalin-induced fibers were related (7). The medication also influences the body weight of rodents (10). Pregabalin is a biologically distinct derivative of the principal inhibiting transmitter, GABA. The medication neither functionally transforms into GABA or a GABA agonist nor binds to GABAA or GABAB receptors. Because of its pre-synaptic binding to the voltage-gated calcium channel's alpha-2-delta subunit, pregabalin has been shown to have pharmacological effects that limit sodium glutamate output at brain junctions (11). The medication affects the neurological system, particularly the brain, and so many pathological abnormalities are identified, effectively leading to progressive degeneration (12). The drug is considered a central nervous system Depressant and is through mode harmless, but it is thought to involve CNS depression along with cardiac and pulmonary problems. Although the precise mechanisms by which PGB causes cerebellar impairment remain unknown, several findings have shown that PGB may induce the cerebellum to lose some of its functional ability due to a reduction in the excitatory input from the brainstem (13).

Drug poisoning has indeed been linked to excesses taken in association with suicide, pleasure, and unintentional overdose. The research aims to investigate the negative influences of pregabalin on the histological structure of adult white male rats' liver, kidney, and brain, as well as the immunohistochemical properties of the GFAP brain. The study also aimed to discover how the medicine alters the serum's biological components.

Materials and methods

Ethical approve

The research was conducted in an animal's house at the Faculty of Veterinary Medicine at the University of Mosul, Iraq, according to IACUC ethical approval number UM.VET.2022.065 on 1/9/2022.

Animal preparation for experiments

Twenty mature male white albino rats from the laboratory animal house of the College of Veterinary Medicine / University of Mosul were used. Their weights ranged from 244.4 to 266.2 g. Rats were kept in plastic cages, and pellets, and water were supplied (14). After a 1-week adaptation of lighting (24 h. of dark and light), the laboratory temperature at which the breeding was carried out was (25±2°C), and humidity was 50% ±10%.

Pregabalin dose

900 mg of pregabalin (Pioneer Co. for pharmaceutical industries in Iraq) was used. The dose was calculated for 1 kg. Thus, the dose given to the animal became 12.8 mg/kg was dissolved in 5 ml of distilled water; thus, the dose volume was (5 ml/kg). The dose of pregabalin was chosen based on preliminary experiences.

Experiment design

In the present study, 20 male rats were split into two groups, ten each (I and II). Set I was considered a control group treated with distilled water (5 ml/kg b.w, orally). Pregabalin was given to set B throughout 30 days continuously at a dosage of 900 mg/kg orally. Body mass weight was recorded after the treatment (both sets) period (following the process for 30 days).

Biochemical tests

Blood samples were taken after the end of the treatments from rats' ophthalmic venous plexus procedures before dissection, according to Salah (15). The blood was maintained in anticoagulant tubes to evaluate serum glutamic-oxaloacetic transaminase (SGOT /AST), and serum glutamic-pyruvic transaminase (SGPT/ALT) of the liver, Blood urea, and serum creatinine were indicators of renal function. Kits of the Biolabo SA (manufacture Biolabo SA, Les Haults Rivs, 02160, Maizy, France, Biosystems S.A. UREA/ BUN color; Costa Brava30,08030, Barcelona, Spain) were used.

Histopathological processing

After the blood samples were obtained, the animals were killed by euthanasia. Specific organs, such as the liver, kidneys, and brain, were obtained, and then fixed in formalin 10 % for two days. After that, they were rinsed using tap water for several hours. The samples were processed by a routine method in the standard pathological preparation; histological sections were 5 micrometers thick. Samples were stained with routine Delafield's H&E (16). All tissue sections were photographed with an OMAX 8.0 MP digital USB microscopic camera and software to assess the histomorphometric data including the thickness of the cerebral layers, measurements of the sinusoids, and numbers of the Kupffer cells in the liver (in 5 fields 400X), as well as the measurements of the glomeruli, Bowman's space, and diameters of both types of renal tubules (in 5 fields 400X) in the kidney (17). The camera was attached to the Olympus CX31 microscope, outfitted with advanced imaging analysis software (OMAX Toup View 3.7). Using a stage micrometer, the objective lenses were calibrated for the program (18).

Brain immunohistochemistry

Brain sections embedded in paraffin wax were de-paraffinized. The sections were dehydrated by passing through graded concertation of ethyl alcohol and afterward washing in phosphate-buffered saline. To inhibit the inner peroxide reductases (peroxidase), the microscope slides were incubated in 0.3% hydrogen peroxide for thirty minutes, and then coated with a blockage solution for 1 hour. The rabbit polyclonal VEGF Ab-3-coated slides and TNF- Rabbit Polyclonal (dilution 1:100, antibodies Elabscience, USA) were incubated at 4four °C overnight. They were rabbit polyclonal VEGF Ab-3 (dilution 1:200 clone JH121, NeoMarkers). The secondary antibodies were the anti-goat, anti-rabbit, and biotinylated anti-mouse immunoglobulins (LSAB Kit; Dako). For 30 minutes, they were dissolved in phosphate buffer saline. The negative control sections were prepared by incubating them in phosphate-buffered saline without adding primary. After that, the microscopic slides were treated with streptavidin and donor: hydrogen peroxide oxidoreductase EC 1.11. 1.7 (which is known as horseradish peroxidase) in the buffer of Tris-HCl (consisting of 0.015% sodium azide) for half an hour (LSAB Kit; Dako). Immunolabeling,3,3′-diaminobenzidine DAB chromogenic substrate, and haematoxylin stain were applied. The scorers were documented according to Awad (19) and Atarbashe (20).

Statistics evaluation

Rat's body weight, liver, and kidney enzymes, and liver, kidney, and brain variables, were investigated using the statistical program Graph Pad Software, Inc. 5.0 (San Diego, USA). The mean and standard deviation were obtained to express the actions of specific values (SD). T-test was applied to obtain the significant differences between treated and control experimental animals at *P< 0.05, or **P>0.01 and ***P <0.001.

Results

Histopathological findings

The histopathological assessment of the set I brain section revealed normal histological features (Figures 1 and 2). The brain sections of set II rats were inoculated orally with pregabalin at 12.8 mg/kg for 30 consecutive days, revealing some lesions comprising thickening of the leptomeninges with hemorrhage, liquefactive necrosis in the cerebral cortex, gliosis, and perivascular edema (Figure 3). as well as satellitosis, neuronophagia, gliosis, and vacuolation (Figure 4).

The microscopic assessment of the liver sections of the set I revealed normal histological architecture (Figure 5). The microscopic analysis of the hepatic tissue sections of set II revealed vacuoles, degeneration and cell death (necrosis) of the liver cells, cellular infiltration in the porta hepatis, and congestion of the portal vein (Figure 6), as well as cell death (necrosis) of the liver cells, expansion of the hepatic sinusoids, and congestion of the central and portal veins, respectively (Figure 7).

The microscopic assessment of the kidney sections of the set I revealed normal histological structure (Figures 8 and 9). The microscopic assessment of the kidney sections of group II revealed glomeruli cell loss, causing a decrease in organ size (atrophy), expansion of glomerular capsule space, kidney cyst, and hemorrhage (Figure 10). Additionally, congestion of blood vessels, severe hemorrhage, and cellular infiltration were noticed (Figure11). Furthermore, vacuoles in the cytoplasm and cell death of renal epithelia were observed (Figure 12).

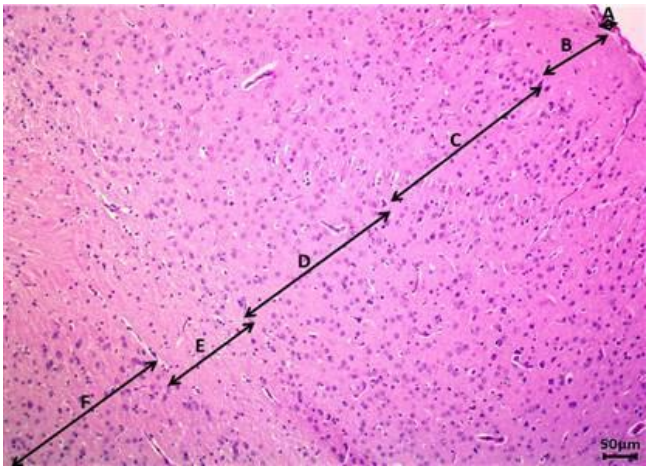

Figure 1: A histological image of rat brain of set I indicating leptomeninges (A) and cerebral cortex layers as: Molecular (plexiform) (B), outer granular (C), outer pyramidal (D), interior granular layer (E) and interior pyramidal layer (F) layers, respectively. Delafield's H&E stain, 100X.

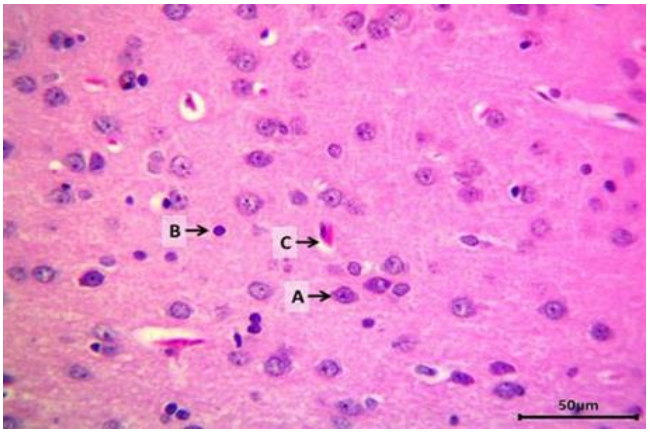

Figure 2: A histological image of the rat brain of set I indicating the cortex of cerebrum with intact nerve cells (A), neuroglia (B), and blood vessels (B). Delafield's H&E stain, 400X.

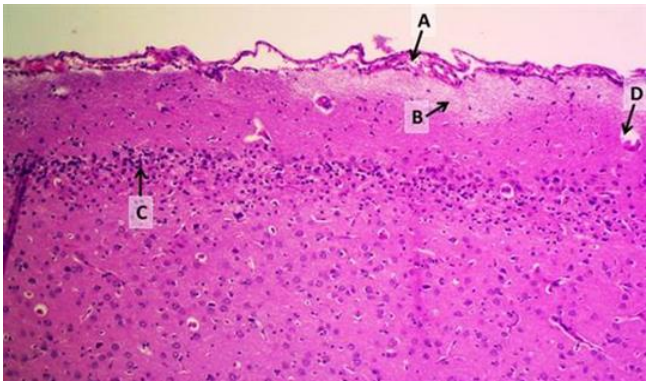

Figure 3: A histological image the of rat brain of set II showing thickening of the leptomeninges with hemorrhage (A), liquefactive necrosis in the cerebral cortex (B), gliosis (C), and perivascular edema (D), Delafield's H&E, 100X.

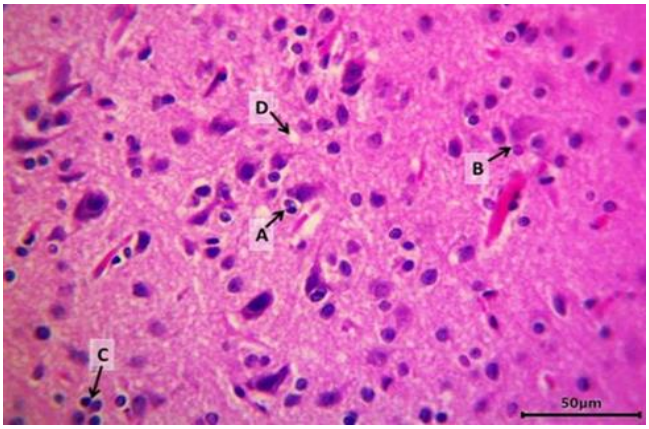

Figure 4: A histological image of the rat brain of set II set indicating satellitosis (A), neuronophagia (B), gliosis (C) and vacuolation (D). Delafield's H&E stain, 400X.

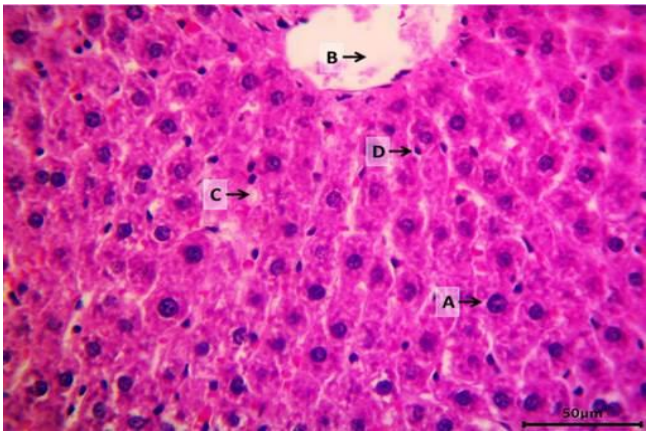

Figure 5: A histological image of rat liver of set I indicates a normal hepatocyte (A), central vein (B), sinusoids (C), and Kupffer cells (D). Delafield's H&E stain, 400X.

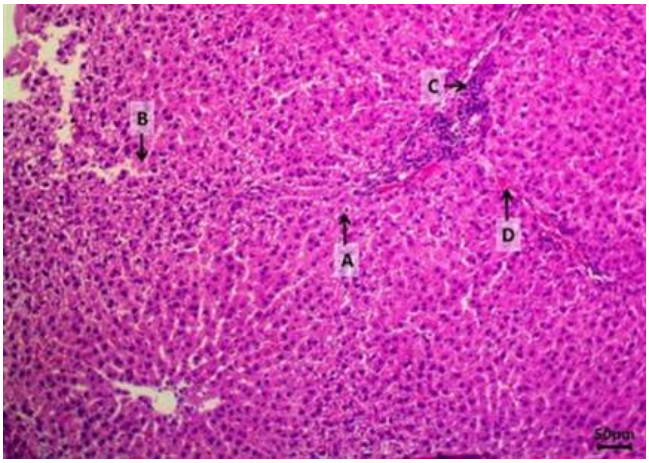

Figure 6: A histological image of the rat liver of the set II group showing vacuolar degeneration (A) and necrosis (B) of the hepatocytes, cellular infiltration in the portal area (C), and congestion of portal vein (D). Delafield's H&E stain, 100X.

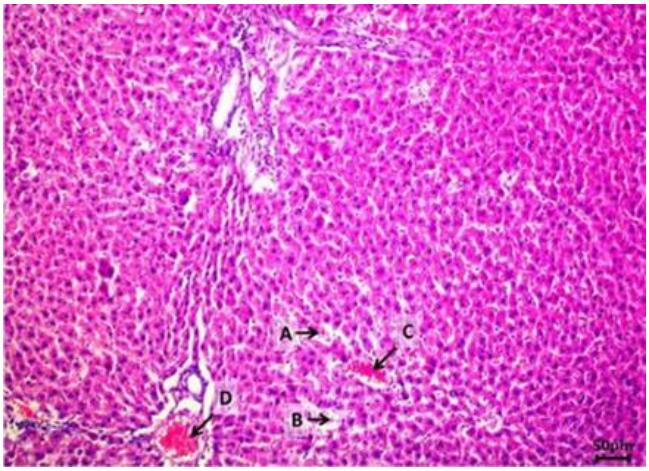

Figure 7: A histological image of the rat liver of set II showing necrosis of the hepatocytes (A), expansion of the sinusoids (B) an excessive or abnormal accumulation of blood in the central vein (C), and hepatic portal vein (D). Delafield's H&E stain, 100X.

Brain immunohistochemistry

The findings of the examination of the brain negative control revealed negative GFAP immunoreactivity (Figure 13). Immunohistochemical sections of the brain (positive control) showed a weak positive GFAP reaction (glial fibrillary acidic protein) in set I (Figure 14). The sections of set II revealed strong positive GFAP expression, indicating fibrillary acidic protein immunostaining was present (Figures 15 and 16). This positive response revealed the extent of damage to the layers of the brain, especially glial cells, and their supporting structures.

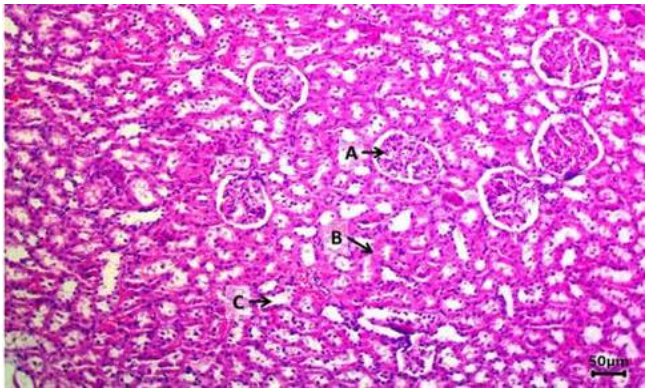

Figure 8: A histological section of the rat kidney of set I indicating typical structure represented by glomeruli (A), proximal convoluted tubule (B), and Distal convoluted tubule (C). Delafield's H&E stain, 100X.

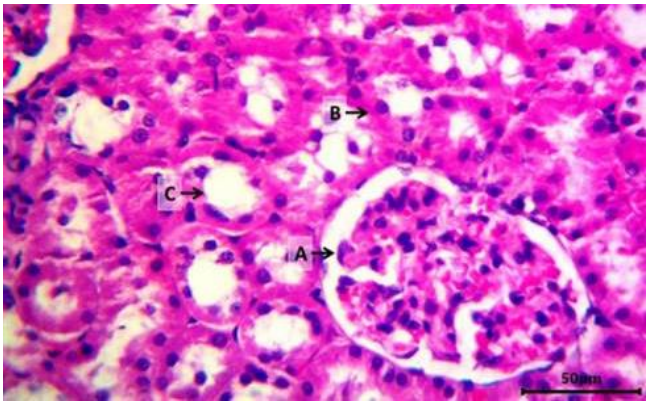

Figure 9: A histological image of a rat kidney of set I shows normal architecture represented by glomeruli (A), proximal convoluted tubules (B), and distal convoluted tubules (C). Delafield's H&E stain, 400X.

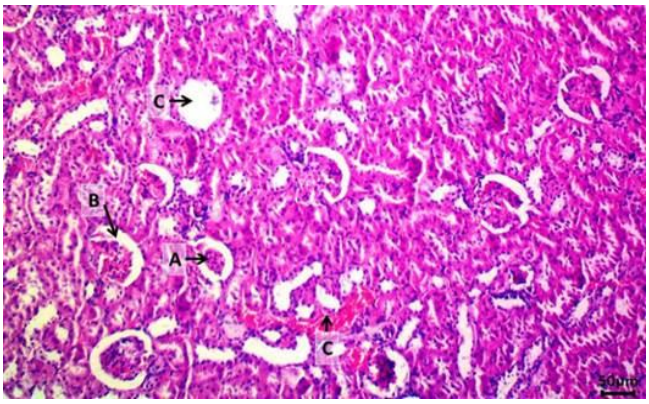

Figure 10: A histological image of a rat kidney of set II showing loss of the glomerulus cells (atrophy) (A), expansion of glomerular capsule space (B), kidney cyst (C), and haemorrhage (D). Delafield's H&E stain, 100X.

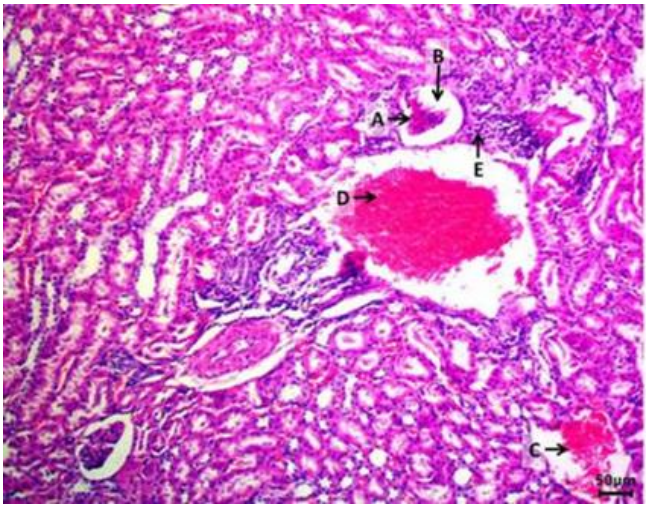

Figure 11: A histological image of rat renal tissue of set II showing loss of the glomerulus cells (atrophy)(A), expansion of glomerular capsule space (B), an excessive or abnormal accumulation of blood in the blood vessels (C), severe haemorrhage (D), and cellular infiltrate (E). Delafield's H&E stain, 100X.

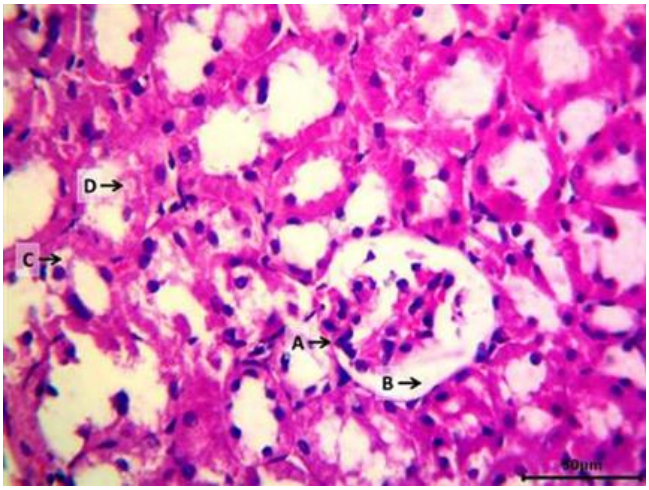

Figure 12: A histological image of a rat kidney of set II showing loss of the glomerulus cells (atrophy) (A), expansion of glomerular capsule space (B), cellular degeneration (C), and cell death (necrosis) of the kidney lining epithelia (D). Delafield's H&E stain, 400X.

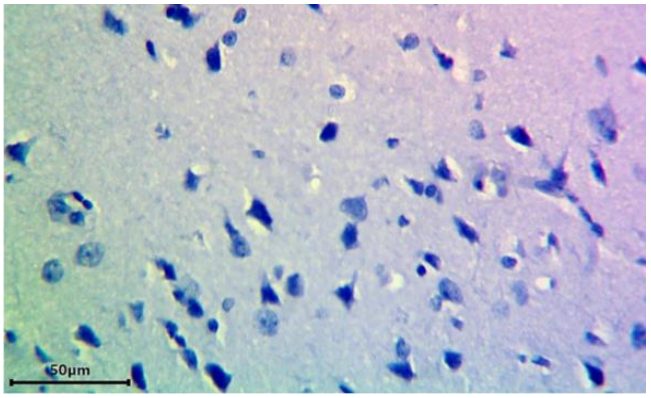

Figure 13: Immunohistochemistry of the GFAP (glial fibrillary acidic protein) expression in the cerebral cortex of the brain of the Negative control for the GFAP expression. (Scale-bar=50µm, 400X).

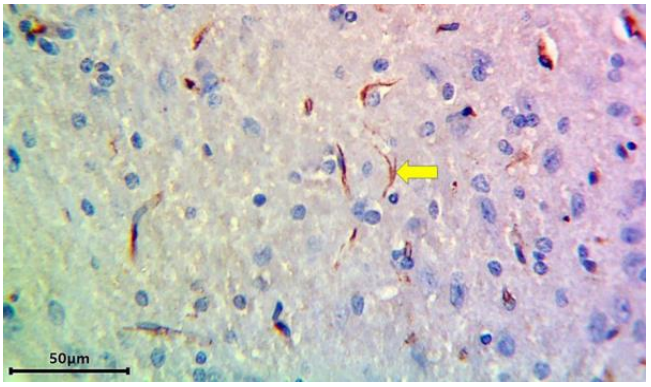

Figure 14: Immunohistochemistry of the GFAP expression in the cerebral cortex of the brain of set I group with weak positive GFAP expression (arrow). (Scale-bar=50µm, 400X).

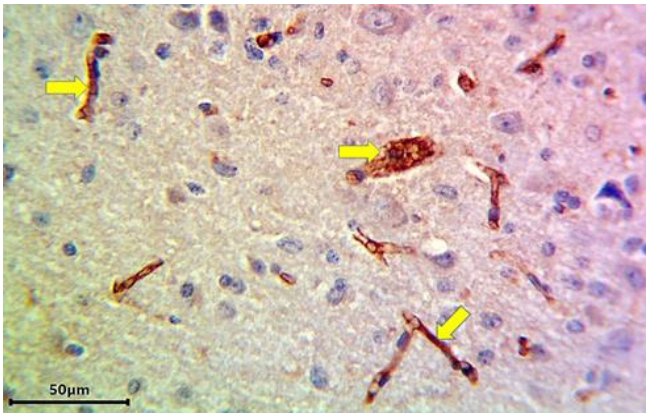

Figure 15: Immunohistochemistry of the GFAP expression in the cerebral cortex of the brain of the set II with strong positive GFAP expression (arrows). (Scale-bar=50µm, 400X).

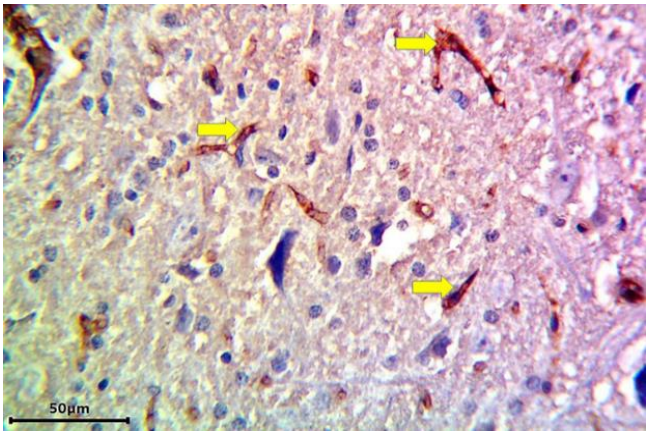

Figure 16: Immunohistochemistry of the GFAP (glial fibrillary acidic protein) expression in the cerebral cortex of the brain of set II with strong positive GFAP expression (arrows). (Scale-bar=50µm, 400X).

Histomorphometry

Histomorphical measurements of the cerebral cortex revealed a remarkable significant increase (P<0.001) in the thickness of the leptomeninges, a meaningful decrease (P>0.05) in the thickness of the Molecular (plexiform) layer, non-significant improvement in the density of the external granular layer, a remarkable significant reduction (P>0.001) in the density of the external pyramidal layer, a highly meaningful (P>0.01) increase in the density of the external pyramidal layer, a significant improvement (P>0.01) in the density of the Internal granular layer, and a significant decrease (P>0.01) in the density of the Internal pyramidal layer (Figure 17).

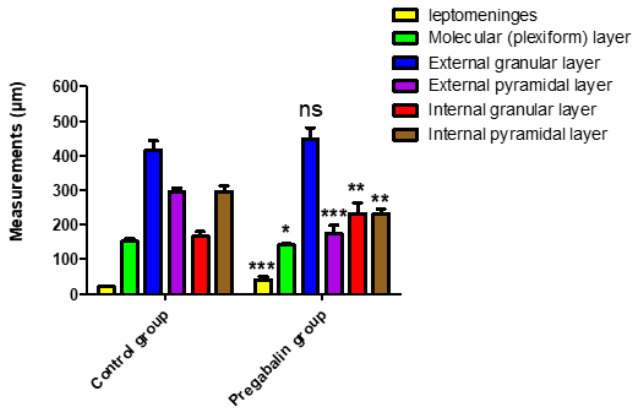

Figure 17: The effect of pregabalin (12.8mg /kg of b.w.) on the density of cerebral layers of the albino rat. The drug was given orally for a month. The findings were presented as (SD), and the experimental group consisted of 10 male albino rats. All values were considered meaningful at *** P<0.001, at **P>0.01, and meaningful at P* <0.05. AT-test was used in the statistical analysis.

The results of the morphometric measurements of the kidneys showed a remarkable and meaningful elevation in the width (diameter) of the glomeruli (P<0.001), and a significant improvement in the (P>0.01) in the diameter of Bowman's space, proximal, and distal renal tubules (Figure18).

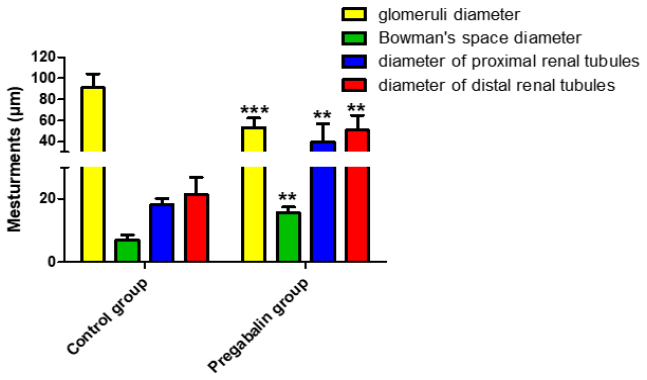

Figure 18: The effect of pregabalin (12.8mg/kg of b.w.) on the diameters of glomeruli, Bowman's space, proximal renal tubules, and distal renal tubules. The experimental group consisted of 10 male albino rats. The drug was given orally for a month. All values were considered meaningful at *** P<0.001, at **P>0.01, and meaningful at P* >0.05. A T-test was used in the statistical analysis.

The morphometric analysis of the liver revealed an extra (highly) meaningful improvement (P<0.01) in the diameter of the sinusoids and a very highly meaningful reduction in the numbers of the Kupffer cells compared to set A (Figuers19 and 20).

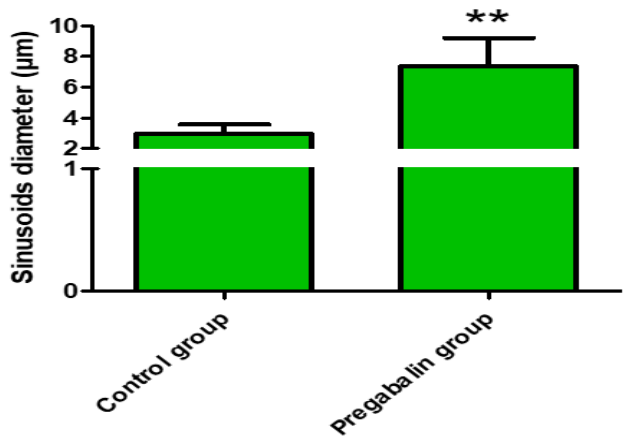

Figure 19: The effect of pregabalin (12.8mg/kg of b.w.) on the diameters of sinusoids in the liver. The experimental group consisted of 10 male albino rats. The drug was given orally for a month.The data were expressed as SD. The value was regarded as highly meaningful at **P>0.01. A T-test was used in the statistical analysis.

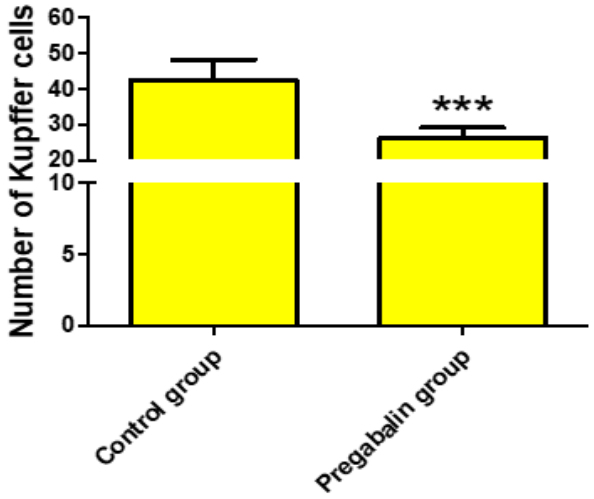

Figure 20: The effect of pregabalin (12.8mg/kg of b.w.) on the number of Kupffer–Browicz cells (Kupffer cells) in the liver. Set B consisted of 10 male white rats. The drug was given orally for a month. The value was regarded as very highly meaningful at* **P> 0.001. AT-test was used in the statistical analysis.

Influence of pregabalin on the rat hepatic and renal functions

The biochemical analysis of the rat blood serum revealed a meaningful (P> 0.05) increase in the GOT level, and GPT amounts in comparison to set I (Figure 21). The outcomes also revealed no meaningful elevation in the urea and a meaningful (P<0.05) improvement in the creatinine amounts compared to set I (Figure 22).

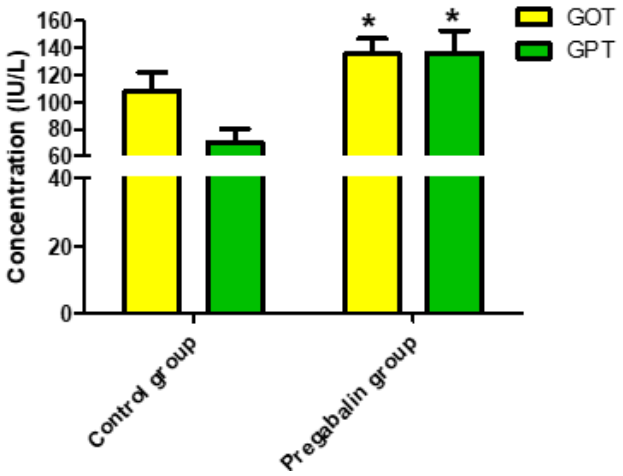

Figure 21: The effect of pregabalin (12.8mg/kg of b.w.) on the levels of GOP and GOT. The experimental group consisted of 10 male albino rats. The drug was given orally for a month. All values were regarded as meaningful * P < 0.05. A T-test was used in the statistical analysis.

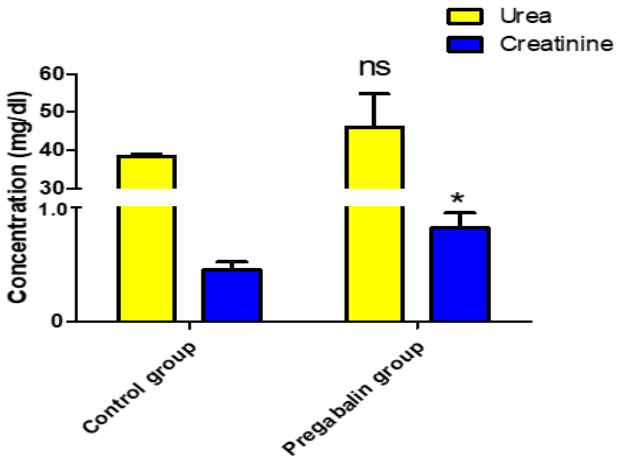

Figure 22: The effect of pregabalin (12.8mg/kg of b.w.) on the amounts of urea and creatinine. The experimental group consisted of 10 male albino rats. The drug was given orally for a month's: which referred to the non-significant increase in the level of urea. The value was regarded as meaningful P <0.05. A T-test was used in the statistical analysis.

Influence of pregabalin on the weight of rats

The experimental animals were weighed for the first 24 hours of the experiment and on the thirtieth day. The results showed a non-significant increase and a significant improvement (P<0.01) in the weight of the body mass at the thirty days compared to set I (Figure 23).

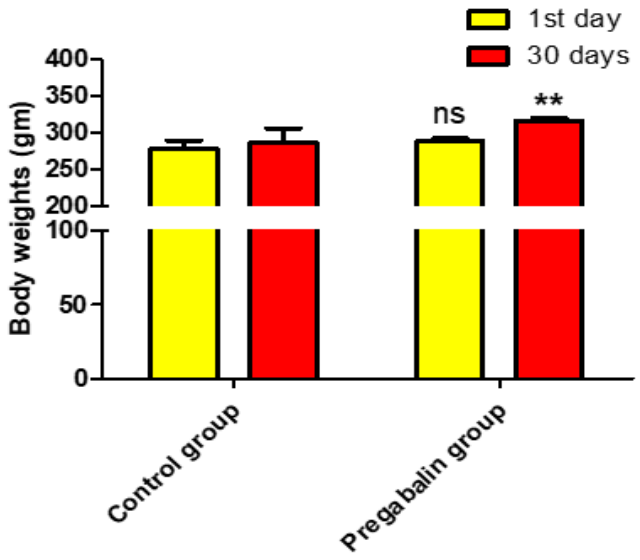

Figure 23: The effect of pregabalin (12.8mg/kg of b.w.) on the weight of male rats. The experimental group consisted of 10 male albino rats. The drug was given orally for a month. The data were presented as SD. The values were regarded as ns: non-significant and significant: ** P>0.01. A T-test was used in the probability (statistical) investigation.

Discussion

The outcomes of the recent study revealed many lesions in the brains of the adult rats that were administrated pregabalin orally at a concentration of 12.8 mg/kg for a month, represented by satellitosis, neuronophagia, gliosis vacuolation, hemorrhage, and perivascular edema. The recent outcomes are close to the outcomes of Awad (19) and Elsukary (21), who reported that long-term usage of pregabalin resulted in brain toxicities such as brain inflammation and controlled cell death. The medicine may have induced the lesions in the current investigation by increasing oxidative stress in the nerve tissue, leading to cell injury (22). The immunohistochemistry outcomes of the brain indicated a solid positive GFAP expression. This outcome was identical to what was found by Elgazzar (23), who indicated a high elevation in the brain part that stained positive for GFAP, referring to more gliosis. Gliosis is a reactionary response to brain damage that indicates that pregabalin is harmful. The results revealed variable lesions in the liver represented by vacuolar degeneration, death of the hepatocytes (necrosis), infiltration of inflammatory cells in the hepatic portal region, accumulation of excessive amounts of blood (congestion) in the portal vein, sinusoidal expansion, and congestion of the central vein. The recent finding was comparable to the findings of Livne (24) that giving a high dose of pregabalin to rats can cause dilatation, hepatic central vein congestion, and cellular infiltration in the liver tissue. The findings are also like those of Ismail (25). The appearance of the current pathological lesions may be because medication poisonousness is handled in hepatic tissue and eliminated through the renal tissue; systemic toxicity appears to be detectable by both kidney and liver histopathology assessments (26). The recent observations revealed many histological changes in the kidney represented by loss (atrophy) of the glomeruli cells, expansion of glomerular capsule space, kidney cyst, hemorrhage, cellular infiltrate, vacuolar degeneration, and necrosis of the renal epithelia. These outcomes did not agree with observations of Hassan (13) and Sewelam (27), while the findings were comparable to those of Ebrahim (10) and Salem (28). Prior lesions could have formed because of drug and metabolite buildup among individuals with persistent renal failure and restricted mesangial activity. Pregabalin is primarily eliminated in the urine by the kidneys Lee (29). The results showed that the drug affected the thickness of the layers of the brain, as it caused an increase in the thickness of some of them and a decrease in the thickness of others.

The recent findings are like those of Salem (28) Bockbrader (30). The previous changes may be due to the drug dose and Sinusoids diameter (µm) treatment period. The outcomes also revealed statistically meaningful differences in the increase of the diameters of glomeruli, Bowman's space, and proximal and distal renal tubules. These observations were somewhat close to what had been

found Parekh (31) and Farrage (32). Bowman's space expansion might be due to increased water pressure within Bowman's capsule due to mesangial hyperfiltration or to capillary puffball shrinkage due to loss of function. The increase in the proximal and distal renal tubules may be due to cell damage from drug-toxic effects (32). The recent study indicated an extra (highly) meaningful improvement in the diameter of the sinusoids and a very highly meaningful ($P>0.001$) reduction in the number of Kupffer cells. Our latest observations were similar partly to the conclusions of Al-Yassiri (33), who indicated that treating rats with high doses of pregabalin caused a proliferation of van Kupffer cells and hepatotoxicity. The increase in the number of these cells may be due to tissue damage in the liver as well as inflammation (34). The levels of GOT and GPT significantly improved, according to what was found concerning the biochemical evaluation of liver functions, the impaired liver biochemistry testing results are generally the first indication of liver dysfunction (33). According to many studies, complications caused by antiepileptic drugs would be observed in increased liver enzyme activities, which can result in hazardous liver injury (35). The results also revealed an insignificant rise in urea and a substantial rise in creatinine, which was incompatible with the results of Preece (36) and Mohamed (37). The elevation in urea and creatinine levels may be due to the tissue damage that affected the renal tubules, which caused renal dysfunction (38). The findings also indicated an extra (highly) meaningful improvement in the body mass of male rats at the beginning and the end of the experiment. Our present data are dissimilar to those of Valdivieso (11) and Elsukary (22). Pregabalin may have contributed to the weight gain by increasing food consumption by suppressing dopaminergic processes in the brain's hypothalamus, encouraging eating (39).

Conclusions

Currently, epileptic conditions and femoral nerve pain are both treated with pregabalin. The drug negatively affects the liver, kidneys, and brain histology. The medication increases the G FAP expression in the brain, especially in the glial cells and degenerated neuronal axons. The drug affects the physiological functions of the kidneys and liver by raising the level of urea and keratin in the kidneys and liver enzymes if used for relatively long periods at specific doses Therefore, it must be taken with caution and under medical advice

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Conflict of interest

No potential conflicts of interest exist.

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التغيرات النسجية للكبد، الكلية والدماغ المحدثة بواسطة عقار البريكابلين في الجرذان البيض

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الخلاصة

البريكابلين عقار شائع الاستعمال لعلاج الألم المرافق لحالات التهاب العصب ولكن كان هناك قلة في الأبحاث التي تناولت التأثيرات الضارة له. هذه الدراسة قسمت ٢٠ ذكر بالغ من الجرذان الى مجموعتين الأولى والثانية. المجموعة الأولى أعطيت ماء مقطر (٥ مل /كغم، فمويا)، بينما المجموعة الثانية أعطيت البريكابلين (١٢,٨ ملغم /كغم، فمويا) لمدة ٣٠ يوم متوالية. درست المظاهر النسجية، الكيميائية المناعية النسجية في الدماغ، القياسات النسجية، فضلا عن أوزان الجرذان. أظهرت النتائج أفات مرضية نسجية مختلفة. كان هناك فعالية موجبة للبروتين الدبقي الليفي الحامضي في الدماغ. وكان هناك آفات نسجية في الكبد، الكلية، والدماغ، فضلا عن القياسات النسجية في المجموعة الثانية مقارنة بالمجموعة الأولى. لوحظ ارتفاع معنوي في مستوي ناقلة الأمين اسبارتيت وناقلة الأمين الألنين، فضلا عن التحري عن مستوي الكيراتينين ولكن لوحظ زيادة غير معنوية في كمية اليوريا. سبب العقار ارتفاع معنوي في وزن الجسم. وأشارت النتائج أن العقار له تأثير سام على الأعضاء الحيوية ووظائفها وانه يمكنه أن يغير في التركيب الخلوي إذا ما تم أخذه لفترة طويلة. وبهذا وبالأخذ بنظر الاعتبار الأثار الجانبية له فيجب أخذه تحت الوصاية الطبية.