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Development of an experimental hepatic encephalopathy in a rabbit model: Biochemical and immunohistochemical study

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Abstract

This study was designed to estimate the biochemical, histochemical, and immunohistochemical aspects of hepatic encephalopathy (HE) induced experimentally by using Thioacetamide (TAA). Twenty-four male rabbits were separated into four main groups (6 each), the Control group (group I) and Group II; rabbits were injected with TAA dissolved in distal water at 200 mg/kg B.W. twice weekly for eight weeks. Group III was given silymarin orally dissolved in saline 200mg/kg B.W. daily for eight weeks. Group IV animals received TAA and Silymarin 200 mg/kg B.W. for eight weeks. The results revealed animals treated with TAA indicated a significant decrease in the level of TSP and a significant increase in the levels of TSB, ALP, ALT, and AST. Histopathological examination of each liver and brain indicates necrosis of the hepatocytes, Cholangitis, biliary duct epithelium hyperplasia and preductular fibrosis, and collagen fiber deposition in the portal triad. Necrosis of the neurons, Purkinjean, and molecular cells with a decrease in granular cells and thickening of meninges. The histochemical examination of the liver revealed the presence of fibrosis in the portal area and the peri-lobular septa and the presence portal to portal bridging fibrosis. The immunohistochemical stain of the liver section revealed a positive reaction for collagen type IV, especially in/and around the portal tried as well as in the septa between the lobules. In conclusion, in rabbit's model, hepatotoxicity to the early stages of the pathogenesis of hepatoencephalopathy.

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Introduction

Hepatic encephalopathy (HE), sometimes referred to as systemic portal encephalopathy (PSE), is a complex neuropsychiatric syndrome occur with substantial hepatic dysfunction. Main hepatic spectrum disorders include acute hepatic failure, massive glomerulonephritis and fibrosis (1,2). Hepatic encephalopathy results from insufficient liver function and/or impaired liver perfusion resulting in the accumulation of neuroactive hypoglycemic intestinal contaminants and toxins, which is a condition that causes temporary deterioration in brain function due to progressive acute or chronic liver disease (3). Normally, the liver can convert toxic constituents into non-toxic substances that are eliminated, When the liver is affected, these toxic materials accumulate in the body and cause injury to various systems, particularly the brain (4,5). Liver Fibrosis is defined as an increase in extracellular matrix and collagen deposition after damage of hepatocytes (6-8). Thioacetamide (TAA) is using as a toxic model for experimentally inducing liver fibrosis and hepatic encephalopathy in in animals (9,10). Thioacetamide is a toxic compound that causes severe necrosis of body cells such as hepatocytes. It is used in laboratories as an alternative to hydrogen sulfide, plasticizer. exposure occurs through inhalation or through the skin (11), and the Global Organization for Investigation on Cancer has

given a classification of 2 / B for TAA, which indicates that it is likely to be a carcinogen to both human and animals (12).

Materials and methods

Ethical approve

The Ethical Committee for Animal Experimentation of the in college of Veterinary Medicine, University of Mosul approved the experimental work No. 1369, dated 1-10-2021.

Induction of acute hepatic encephalopathy

Hepatic encephalopathy was convinced in rabbits using intraperitoneal (i.p.) injections of TAA 200 mg/kg twice weekly for 8 weeks in TAA- water solution 5 ml/kg/day.

Experimental protocol

24 male rabbits were separated into main 4 groups (6 each), the groups are: Control (group I), and TAA (group II), rabbits were orally treated with TAA dissolved in distal water at a dose of 200 mg/kg B.W. twice weekly for 8 weeks, Group III was given silymarin orally dissolved in saline 200 mg/kg B.W. daily for 8 weeks. Group IV, animals receiving TAA and Silymarin 200 mg/kg B.W. for 8 weeks. Toward the end of this investigation, samples of blood are taken for serum tests. liver and brain samples are stored in a formalin solution of 10% neutral buffer for histopathological examination (13).

Assessment of hepatotoxicity

Hepatotoxicity was measured by calculating the total serum proteins (TSP), total serum bilirubin (TSB), alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels in serum. Blood samples were collected from all groups, and collected serum was evaluated by spectrophotometer via a diagnostic kit (BIOLABO /French). The numbers were investigated via the statistical program SPSS, and the mean and standard error were calculated using the ANOVA test (one-way analysis of variance), the significant difference for all tests was at the level of significance of $P<0.05$. Liver samples were kept in a neutral 10% buffered formalin for tissue slide preparation and histopathological examination.

Liver Immunohistopathological examination

Liver tissue was fixed by 10%formalin buffer solution for 48 h, then the specimens were washed away in water, dehydration processing by using ascending concentrate of ethanol, clearing by xylene, and finally embedded in paraffin wax. Sections of 4-µm thickness were prepared and stained with hematoxylin and eosin and Masson's trichrome stain then examined under the light microscope (14). For histochemical staining of the liver sections, specimens were prepared and stained using Masson's trichrome for collagen fiber detection and the immunohistochemical examination according to method of Dako-immunohistochemical processing were slides treated with rabbit-anti-cleaved antigen, for recognition of type IV collagen in liver tissue (15).

Results

Levels of liver enzymes in group II were significantly elevated, and there was an increase in the level of TSB, ALP, AST, and ALT In the TAA-treated rabbits, while there is decrees TSP in contrast, to control and other groups, while in group IV, which represent the treatment with silymarin revealed significantly decreased these enzymes related to TAA group (Figures 1-5).

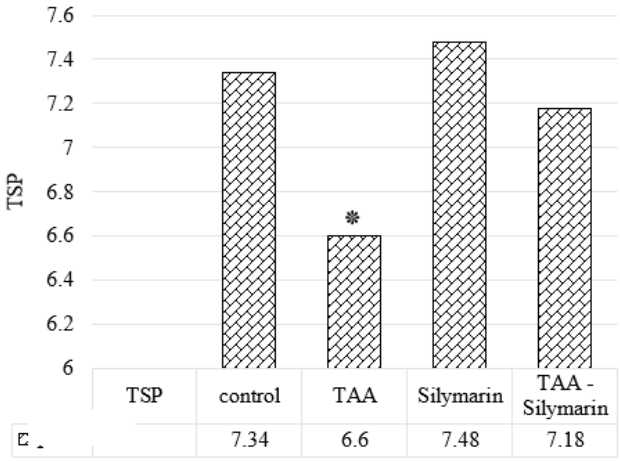

Figure 1: Serum level of TSP were assumed in rabbits treated with TAA comparing to control group and TAA-silymarin group. * mean significant at $P<0.05$.

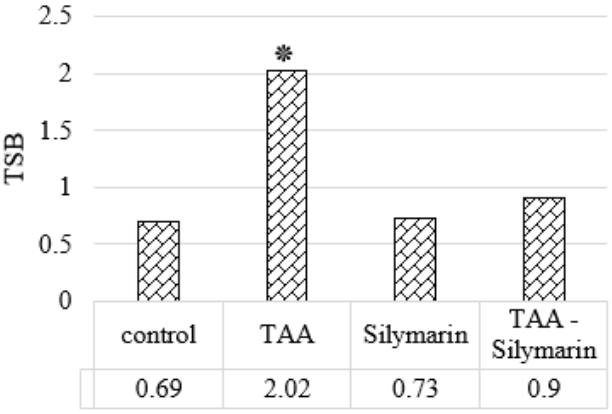

Figure 2: Serum level of TSB were assumed in rabbits treated with TAA comparing to control group and TAA-silymarin group. * mean significant at $P<0.05$.

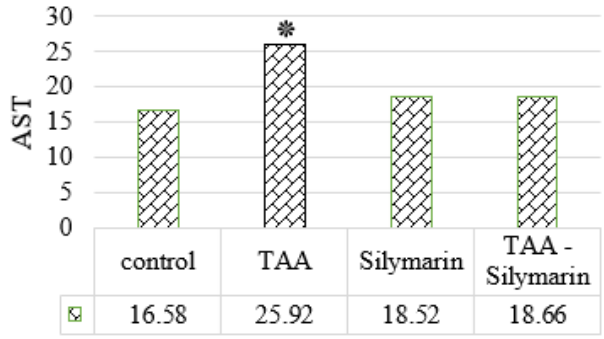

Figure 3: Serum level of AST were assumed in rabbits treated with TAA comparing to control group and TAA-silymarin group. * mean significant at P<0.05.

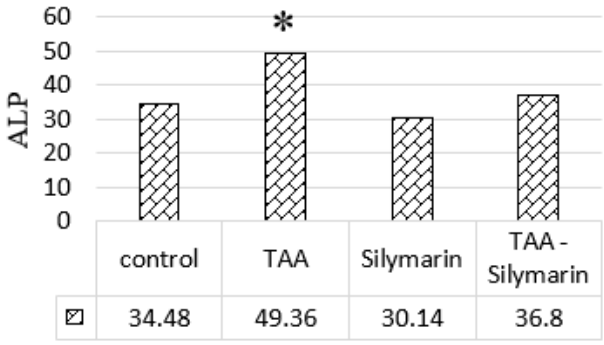

Figure 4: Serum level of ALP were assumed in rabbits treated with TAA comparing to control group and TAA-silymarin group. * mean significant at P<0.05.

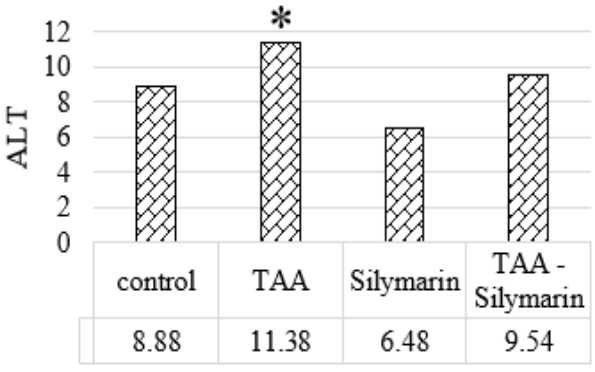

Figure 5: Serum level of ALT were assumed in rabbits treated with TAA comparing to control group and TAA-silymarin group. * Significant at P<0.05.

The histopathological assessment of liver sections demonstrates many pathological changes as a result of treatment with TAA. The deviation in the histology of liver sections in the TAA-treated group a severe centrilobular and periportal hepatocellular vacuolation and necrosis were seen, and dilatation and congestion of central veins are noticed as well. Cholangitis with severe collagen fibers deposition in the portal area with biliary duct epithelium hyperplasia, in addition to the periductular fibrosis and mononuclear inflammatory cells, infiltrate the portal triad. The portal fibrosis extends towards the neighboring portal areas and inside the hepatic lobules (Figures 6-8). Liver sections from group IV displayed minor changes in the histopathological picture in comparison to TAA alone. This group displayed minor portal fibrosis with moderate inflammatory cell accumulation in the portal area. Liver cells illustrate less vacuolation and necrosis. In the brain section, Histopathological; examination revealed congestion of blood vessels with present of vasogenic edema and perivascular cuffing of inflammatory cells. vacuolation and liquefaction of the neurons. In the cerebellum there is necrosis of the Purkinje cells and molecular cells with decrease in granular cells, as well as thickening of meninges (Figures 9-11). Sections of liver tissue stain with Masson's trichrome revealed present of fibrosis in the portal area as well as in the peri-lobular septa and present portal to portal bridging fibrosis (Figures 12-14). The immunohistochemical stain of liver section revealed positive reaction for collagen type IV specially in/and around the portal tried, as well as in the septa between the lobules (Figures 15-17).

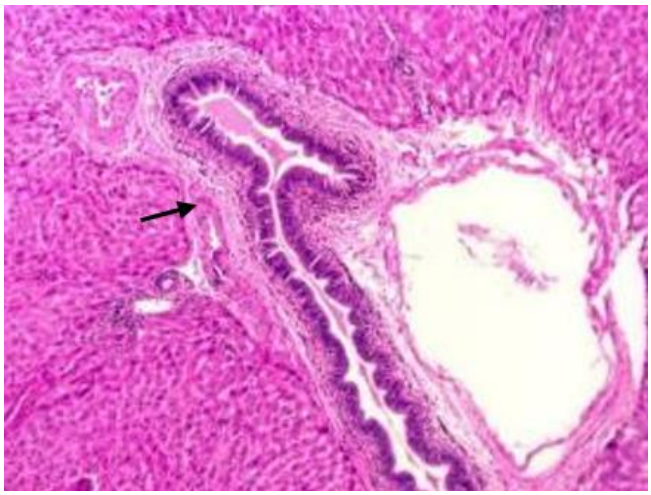

Figure 6: Liver of male rabbits treated with TAA, reveals cholangitis and collagen fiber deposition in portal tried (arrow), with biliary duct epithelium hyperplasia (arrow). H&E, 10x.

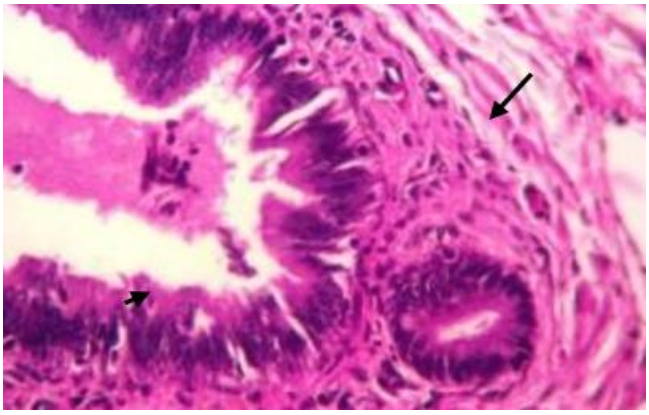

Figure 7: Liver of male rabbits treated with TAA, reveals Severe collagen fibers deposition in the portal area (arrow) with biliary duct epithelium hyperplasia (arrowhead) and periductular fibrosis. H&E, 40x.

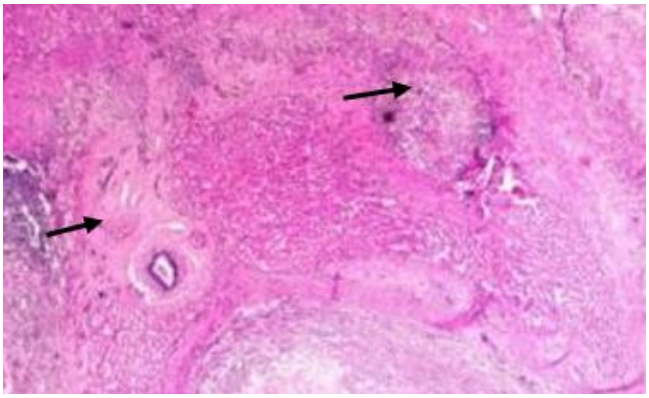

Figure 8: Liver of male rabbits treated with TAA, reveals Severe liver fibrosis and granulation tissue formation (arrow). H&E, 10x.

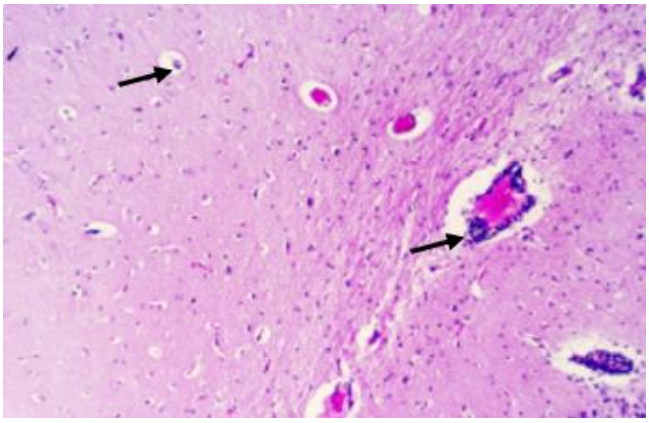

Figure 9: Brain of male rabbits treated with TAA, reveals vacuolation and liquefaction of the neurons and congestion of blood vessels (arrows). H&E, 10x.

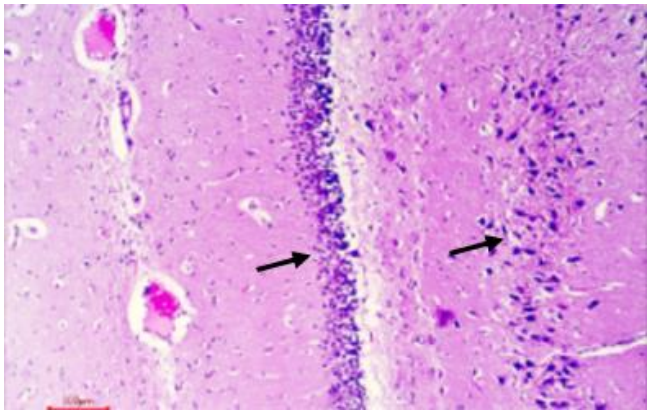

Figure 10: Brain of male rabbits treated with TAA, reveals necrosis of the Purkinjean cells and molecular cells with decrease in granular cells (arrows). H&E, 10x.

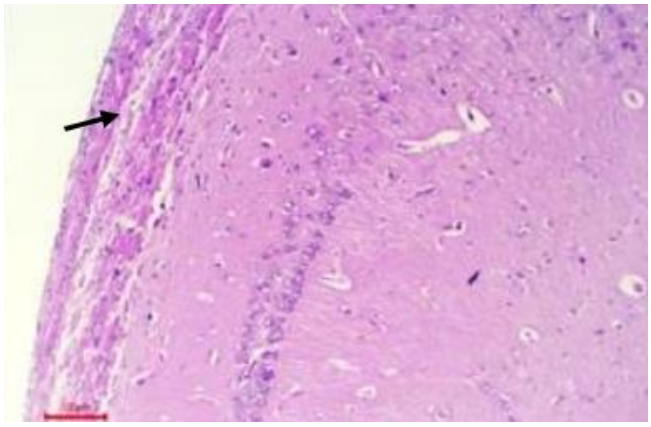

Figure 11: Brain of male rabbits treated with TAA, reveals thickening of meninges (arrows). H&E, 10x.

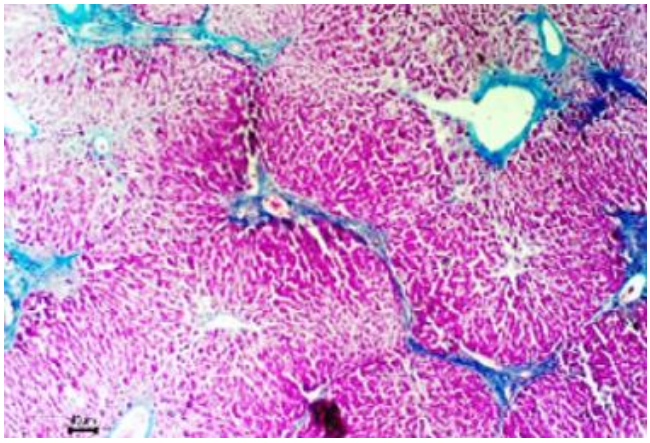

Figure 12: Liver of male rabbits treated with TAA. Reveals fibrosis in the portal area as well as in the peri-lobular septa and present portal to portal bridging fibrosis. Masson's trichrome, 10x.

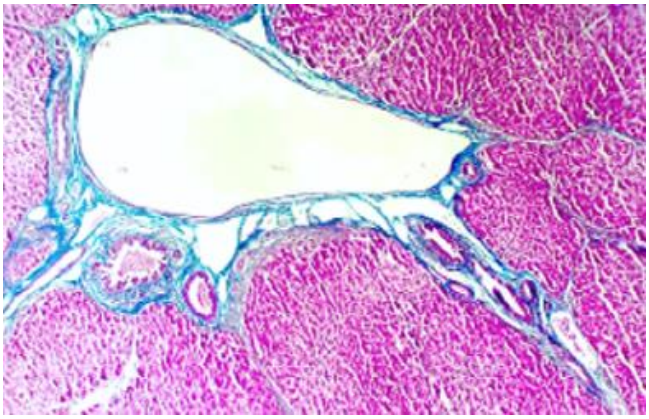

Figure 13: Liver of male rabbits treated with TAA, reveals fibrosis in the portal area as well as in the peri-lobular septa. Masson's trichrome, 10x.

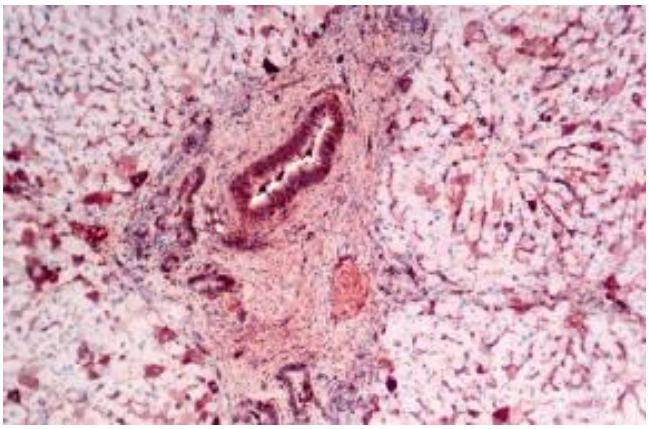

Figure 14: Liver of male rabbits treated with TAA. Moderate positive reaction of collagen IV immunohistochemistry in the portal tried. IHC collagen IV, 10x.

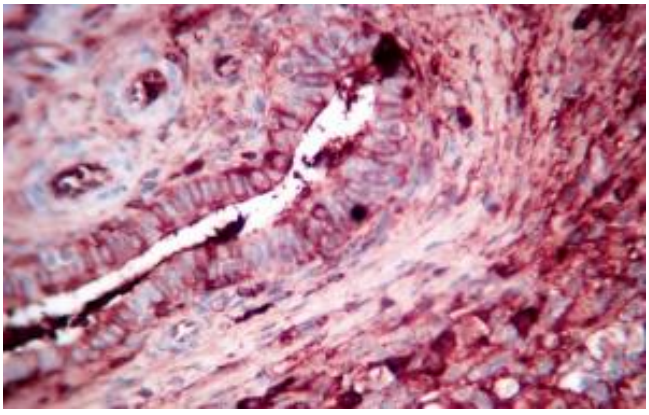

Figure 15: Liver of male rabbits treated with TAA. Severe positive reaction of collagen IV immunohistochemistry specially in/and around the portal tried, as well as in the septa between the lobules. IHC collagen IV, 10x.

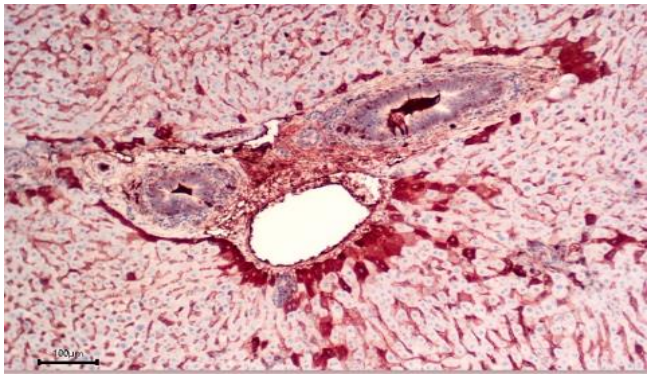

Figure 16: Liver of male rabbits treated with TAA. severe positive reaction of collagen IV immunohistochemistry in the portal tried. IHC collagen IV, 10x.

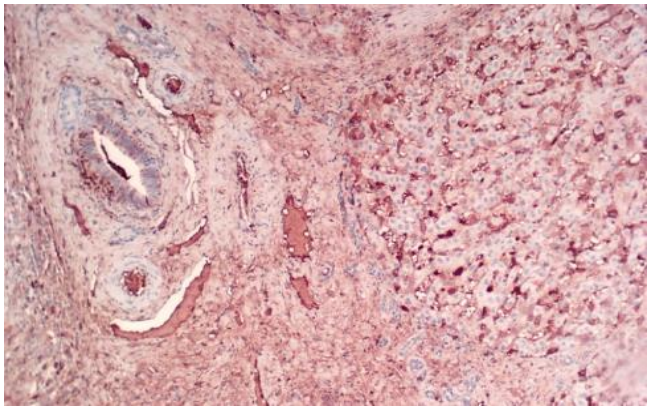

Figure 17: Liver of male rabbits treated with TAA. Mild positive reaction of collagen IV immunohistochemistry in the portal tried. IHC collagen IV, 10x.

Discussion

The liver is one of the most main vital organs in the body, various liver diseases are among the most common diseases, the liver is the target organ for numerous pathogens, but the associated pathological signs are not clear (16). Hepatic encephalopathy (HE) is a principal neurological condition that is a common complication of liver injuries. It is a life-menacing syndrome that causes declined brain function and occurs when the hepatocytes are unable to remove toxic substances from the portal circulation. HE is considered a result of liver disease, which accounts for up to 25% of cases of acute and chronic liver fibrosis (17). This research focused on the follow-up of TAA to inducing hepatic encephalopathy, where the pilot study was used to conclude the chronic dose in rabbits. TAA used as model to cause hepatotoxicity and induced encephalopathy. Various researchers indicated that chronic use of TAA causes severe injuries in the liver, ranging from severe necrosis to fibrosis and that can lead to encephalopathy (18,19).

Several issues were playing in the pathogenesis of encephalopathy and liver fibrosis. oxidative stress is a major of these issue in the pathogenesis of hepatic encephalopathy (20,21). Thioacetamide poisoning has led to impairment of the antioxidant system. This was demonstrated by a reduction in the glutathione (GSH) concentration and in the activity of glutathione peroxidase (GPX), with a proliferation in brain malondialdehyde (MDA) content (22,23). Furthermore, recent research suggested a new mechanism for brain dysfunction in fibrosis, through fibrotic-induced damage in the glymphatic system, a recently revealed comprehensive pathway of brain that assists the removal of numerous accumulated elements in the brain (24-26).

Ammonia plays an important role in causing hepatic encephalopathy as it is one of the toxins that directly affect the brain (27). Different genes Expression were responsible for significant proteins responsible for brain function. Ammonia is generated by the breakdown of urea, amines and amino acids by intestinal bacteria. In liver fibrosis, ammonia created in the intestine bypasses the liver, and large volumes of it spread to the blood circulation (28). In addition, liver damage reduces the transformation of urea-ammonia, which leads to increased accumulation of ammonia in the blood (29,30).

The results of our current study presented a significant enhancement in the activities of the liver enzymes AST, ALT and ALK as well as the levels of total bilirubin in the blood serum after administering silymarin to animals compared with the group of animals treated with TAA. Treating rabbits with TAA caused an increase in the activity of AST, ALT and ALK enzymes, while no increase was observed in animals treated with silymarin, indicating the protective activity of silymarin against TAA (31,32).While Ghosh (33) and Kim (34) showed (33,34) showed that administration of silymarin to mice treated with TAA for a time of 56 days caused a decrease in the activity of ALT, AST and ALK, besides an increase in the activity of anti-oxidant enzymes SOD, MDA and CAT, indicating the effectiveness of silymarin as an antioxidant and a hepatoprotective against the effect of TAA (35,36). Through its role in reducing the programmed death of hepatocytes and stimulating the PI3K-Akt cell survival pathway (37-39).

Conclusions

This study concludes that liver damage induced by TAA, can cause encephalopathy through the biochemical investigation and histopathology of brain and liver sections.

Acknowledgment

We express thanks everyone who offered the probability to end this study, predominantly Veterinary Medicine College, Department Pathology and Poultry Diseases, University of Mosul.

Conflict of interest

The investigator announces there is no conflict of interest exists.

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تطوير نموذج تجريبي للاعتلال الدماغي الكبدي في الأرنب: دراسة كيميائية حيوية وكيميائية نسيجية مناعية

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الخلاصة

صممت هذه الدراسة لتقييم الجوانب الكيميائية الحيوية والكيميائية النسيجية والكيميائية النسيجية المناعية لاعتلال الدماغ الكبدي المحدث تجريبياً عن طريق استخدام الثايواستايماید. ٢٤ أرنب من الذكور قسمت إلى أربع مجموعات رئيسية (٦ لكل مجموعة)، والمجموعات هي: مجموعة السيطرة (المجموعة الأولى)، والمجموعة الثانية، تم حقن الأرانب بالثايواستايماید المذاب في الماء بجرعة ٢٠٠ ملغم / كغم من وزن الجسم مرتين أسبوعيا ولمدة ٨ أسابيع، المجموعة الثالثة أعطيت السيليمارين عن طريق الفم المذاب في محلول ملحي وبجرعة ٢٠٠ملغم / كغم من وزن الجسم يوميا لمدة ثمانية أسابيع. المجموعة الرابعة الحيوانات التي أعطيت الثايواستايماید والسيليمارين سوية لمدة ثمانية أسابيع. أظهرت النتائج أن الحيوانات المعالجة بالثاواستايماید تشير إلى انخفاض معنوي في مستوى الثايواستايماید وزيادة معنوية في مستويات ناقلة أمين الالنين وناقلة امين الاسبارتيت والفوسفاتيز القاعدي وتركيز البليروبين الكلي. اظهر الفحص المجهري لكل من الكبد والدماغ إلى وجود نخر في الخلايا الكبدية والتهاب الأقنية الصفراوية وتضخم ظهارة القناة الصفراوية مع تليف الكبد وترسب ألياف الكولاجين في البوابة الكبدية. تنخر الخلايا العصبية وخلايا بيركنجي والخلايا الجزيئية مع انخفاض في الخلايا الحبيبية وكذلك تثخن في أغشية السحايا. أظهر الفحص الكيميائي النسيجي للكبد وجود التليف في المنطقة البوابية الكبدية وكذلك في الحاجز حول الفصيص الكبدي. أظهر استخدام الصبغة الكيميائية المناعية للكبد تفاعلاً إيجابياً للكولاجين من النوع الرابع خاصة داخل وحول البوابة الكبدية التي وكذلك في الحاجز بين الفصيصات الكبدية. الاستنتاجات سببت السمية الكبدية تطوراً وبصورة سريعة الى اعتلال الكبد والدماغ في الأرانب.