



Histopathological evaluation of lesions induced by dimethyl hydrazine in male rats

E.K. Al-Hamdany , K.H. Al-Mallah  and H.Kh. Ismail 

Department of Veterinary Pathology and Poultry Diseases, College of Veterinary Medicine, University of Mosul, Mosul, Iraq

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Correspondence:

K.H. Al-Mallah
karamyahya74@uomosul.edu.iq

Abstract

This study evaluated dimethylhydrazines' carcinogenic and toxic effect (DMH) in male rats; 30 albino rats were divided into three groups, randomly ten rats for each one. Group 1 control group was lifted for water only, group 2 was treated with DMH at a dose of 10 mg /kg bw in 0.9% sodium chloride subcutaneously once weekly for eight weeks, and group 3 was treated with DMH at a dose of 20 mg /kg bw in 0.9% NaCl subcutaneously once weekly for eight weeks. Liver grossly congested with pinpoint hemorrhage in a dose of 10 mg/kg of bw and enlarged in a dose of 20 mg/kg bw. Congestion of blood vessels in the heart with hypertrophy of myocardium in a dose of 20 mg/kg bw. Kidney grossly appears normal in both doses. Lesions of the liver treated with DMH in the dose 10 mg/kg BW show discontinuation of hepatocytes, infiltrations of inflammatory cells, and vacuolar degeneration of hepatocytes with apoptotic bodies. Section of the liver treated with DMH in the dose 20 mg/kg BW shows acute hemorrhage and focal necrosis of hepatocytes with edema. Heart treated with DMH in a dose of 10 mg/kg BW shows discontinuation of myocardial muscle fibers and infiltrations of inflammatory cells. In contrast, lesions in the dose 20 mg/kg bw show foci of inflammatory cells with cardiomyopathies of myocardium and congestion of blood vessels. Kidney treated with DMH in a dose of 10 mg/kg BW shows degeneration of epithelial cells lining renal tubule, infiltrations of inflammatory cells, hyaline cast with atrophy of glomerular tuft, increased space of Bauman's, and cloudy swelling. The kidney section treated with DMH in a dose of 20 mg/kg bw shows hemorrhage between renal tubules, congestion of blood vessels, infiltrations of inflammatory cells, a renal cyst, and degeneration of glomeruli.

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Introduction

Dimethylhydrazine (DMH) occurs as 1,1-dimethylhydrazine and 1,2-dimethylhydrazine isomers they are acutely toxic and carcinogens also it causes cancer in animals after cutaneous exposure, both are colorless, clear, liquids, they are a component of rocket fuels and jet used as absorbent to acid gas, a plant-growth control agent and feedstock in chemical synthesis, as an additive for lubricants, as an antioxidant and present in rubber products (1-3). Hydrazine was used recently in the preparation of agricultural chemicals, corrosion inhibitor and in heat

systems as oxygen scavenger, about 45,000 metric tons were Annually synthesis as hydrazine, 1,1-dimethylhydrazine and monomethyl hydrazine (4,5). Exposure to derivatives of hydrazine in small amounts leads to pulmonary injury, seizures, tissue injury finally death (6-8). Also, exposure of skin to hydrazine derivatives can cause caustic injuries, dermatitis and erythema then progressed to edema and papules (9-11). Intra peritoneal or subcutaneous injections of dimethylhydrazine cause tumors in the rectum and colon in mice and rat, however a chronic poisoning lead to mild fatty change in liver and an increase in enzyme alanine transaminase (12,13). Activation of DMH in liver occurs

through a series of reactions by intermediates methylazoxymethanol and azoxymethane, which are then transported through bile into the colon which in turn induce oxidative stress in the colon, the alkalization of DNA to induce gene mutation and carcinogenic metabolite occurs by reactive methyl diazonium ions in liver (14,15). Toxicological and pathological effects of dimethylhydrazines by various routes of administration were observed in laboratory animals including, heart, central nervous system, lungs, kidneys and liver (16,17). A researchers reported that hemangiosarcoma were induced after administration of many of chemicals including dimethylhydrazine in rat (18-21). A nephrotoxic effect of DMH manifested by acute reductions in rate of renal tubular reabsorption of glucose and glomerular filtration rate but the mechanism for either effect remains to be clarified by further experiments, however hydrazine cause real a threat to environment, human life and animals (22,23).

This study was indicated to determine and evaluate lesions in hepatic, renal and heart tissues in rats that may follow an acute exposure to DMH and because of little study on this substance cause air pollution of environment and the atmosphere surrounding humans and animals.

Materials and methods

Ethical approve

The experiments were conducted in accordance to approval of the Ethics Committee of the College of Veterinary Medicine, University of Mosul, Mosul, Iraq, with the IACUC ethical approve number UM.VET.202204 at 11/1/2022.

Animals

30 albino male rats of 10-week-old and weighing 150 - 250 gm were brought from the animal house, College of Veterinary Medicine, University of Mosul. Animals were free access to commercial water and diet throughout the experimental period. The experiments were conducted in accordance to approval of the Ethics Committee of the College of Veterinary Medicine, University of Mosul, Mosul, Iraq.

Chemical

Dimethyl hydrazine supplied from (Sigma, USA, 161608-100 G). DMH was dissolved in 0.9% sodium chloride.

Experimental design of animals

Rats were divided randomly after one week of acclimatization period in to three groups 10 rates for each one. Group one, control group rats were lifted for water and food only. Group two the rats treated with DMH at dose 10 mg /kg bw (24) in 0.9% sodium chloride subcutaneously once weekly for 8 weeks. Group three the rats treated with

DMH at dose 20 mg /kg bw (25) in 0.9% sodium chloride subcutaneously once weekly for 8 weeks.

Sampling, tissue fixation and histopathological evaluations

After 8 weeks at the end of experiment including the week of acclimatization, rats were killed by ether inhalation. The liver, kidney and heart were excised, cleaned, rinsing with saline and dried on filter paper. For histopathological study, 10% neutral buffered formalin were used for fixation of specimens for more than 72 hours, then serial concentrations of alcohol were used for dehydration, clearing with xylene and paraffin wax embedding, cut at 6 micrometer thickness, stained with hematoxylin and eosin and assessed by using light microscope (24).

Results

Liver grossly congested with rounded edge in animals treated with DMH in a dose 10 mg/kg while in liver is enlarged in rat treated with 20 mg/kg of DMH shows congestion and enlargement of organs (Figure 1). Heart of rats treated with 10 mg/kg of DMH shows mild congestion while those treated with 20 mg/kg reveals hypertrophy of heart and sever congestion of blood vessels (Figure 2). Histopathological the examined livers treated with 10 mg/kg DMH for 8 weeks show discontinuation of hepatocytes with infiltrations of inflammatory cells and edema (Figure 3). Some rat liver section reveals vacuolar degeneration of hepatocytes, focal necrosis of few hepatocytes, congestion of portal vein and thickening of the central vein wall with pericentral apoptotic bodies (Figure 4). While liver sections of rats treated with 20 mg/kg DMH for 8 weeks revealed more sever lesions like necrosis of hepatocytes with infiltrations of inflammatory cells in the hepatic tissue, sever hemorrhage with dilatation of sinusoids and edema (Figure 5). Heart sections in rats treated with 10 mg/kg DMH shows disarrangement of muscle fibers, edema with focal myocarditis and hemorrhage (Figures 6 and 7). While sections of rat's hearts treated with 20 mg/kg DMH shows more sever lesions like acute hemorrhage and cardiomyopathies, hyalinization with infiltrate of many numbers of inflammatory cells and necrotic foci surrounded by inflammatory cells and calcium deposition with blood vessels congestion in some sections (Figures 8 and 9). Kidneys sections in rats treated with 10 mg/kg DMH for 8 weeks reveals vacuolar degeneration of epithelial lining renal tubules, cloudy swelling and hyaline cast in some lumens of renal tubules with infiltration of inflammatory cells (Figures 10 and 11). While sections treated with 20 mg/kg DMH shows congestion of blood vessels, hemorrhage, atrophy in glomerular tuft, expansion of bowman's capsule and presences of some renal cysts (Figures 12 and 13).

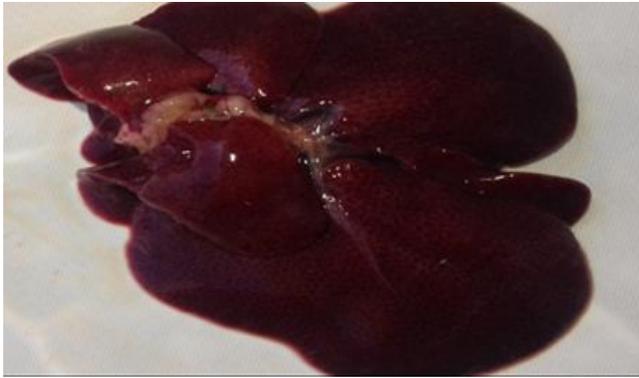


Figure 1: rat liver treated with DMH in a dose 20 mg/kg BW shows congestion and enlargement of organ.

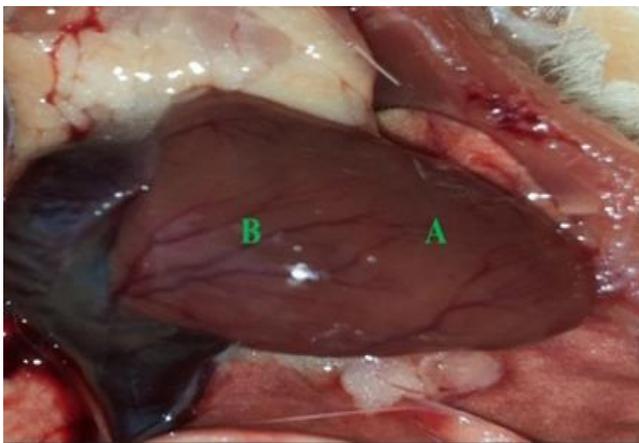


Figure 2: rat heart treated with DMH in a dose 20 mg/kg BW shows hypertrophy of myocardium (A), and congestion of blood vessels (B).

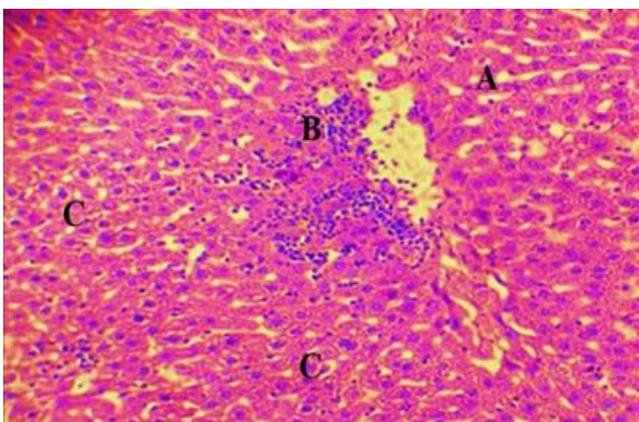


Figure 3: A photomicrograph of rat liver treated with DMH in a dose 10mg/kg BW shows (A) discontinuation of hepatocytes, (B) infiltrations of inflammatory cells, (C) vacuolar degeneration of hepatocyte. Hematoxylin and eosin. 100X.

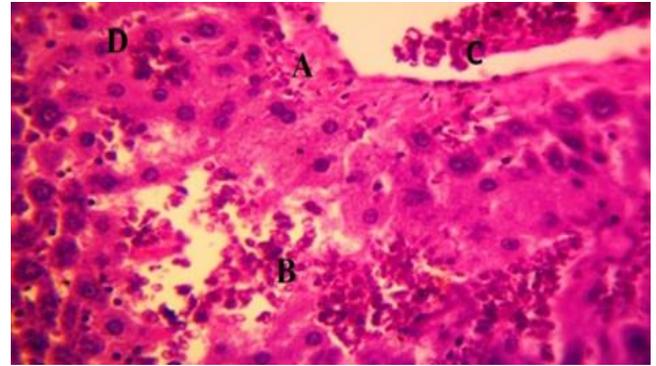


Figure 4: A photomicrograph of rat liver treated with DMH in a dose 10mg/kg BW show (A) thickening in wall of the blood, (B) infiltrations of inflammatory cells, (C) congestion of blood vessels, (D) pericentral apoptotic bodies. Hematoxylin and eosin. 400X.

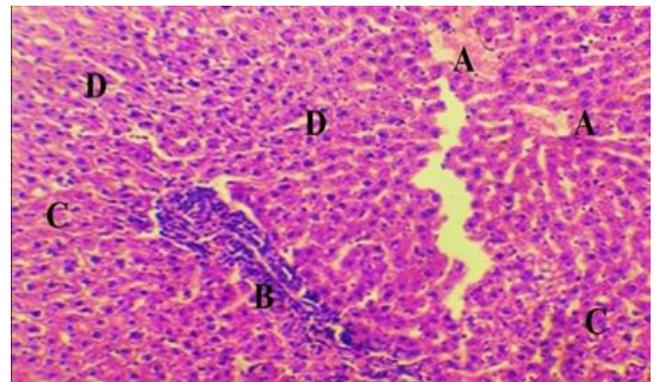


Figure 5: A photomicrograph of rat liver treated with DMH in a dose 20mg/kg BW shows (A) acute hemorrhage, (B) infiltrations of large number of inflammatory cells, (C) vacuolar degeneration of hepatocyte, (D) edema. Hematoxylin and eosin. 100X.

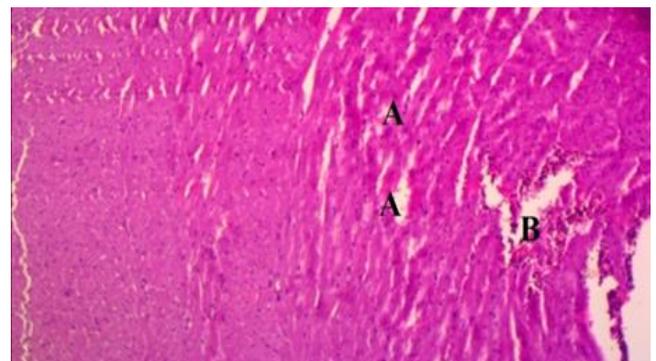


Figure 6: A photomicrograph of rat heart treated with DMH in a dose 10mg/kg BW shows (A) disarrangement of myocardial muscle fibers, (B) infiltrations of inflammatory cells. Hematoxylin and eosin. 100X.

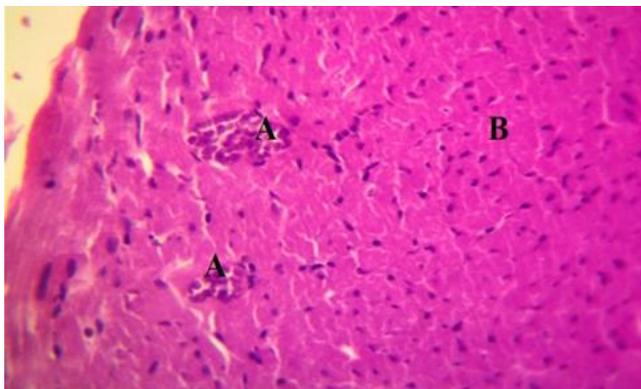


Figure 7: A photomicrograph of rat heart treated with DMH in a dose 10mg/kg BW shows (A) focal myocarditis, (B) cardiomyopathies. Hematoxylin and eosin. 150X.

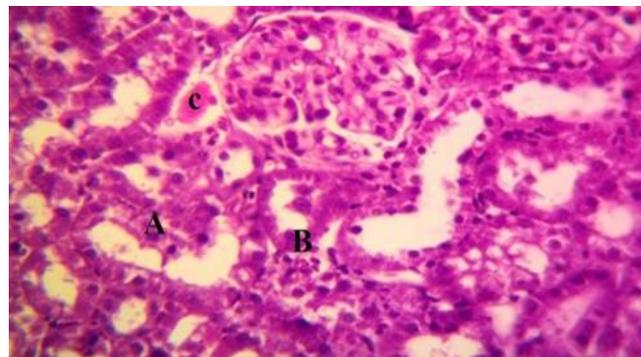


Figure 10: A photomicrograph of rat kidney treated with DMH in a dose 10mg/kg BW shows (A) degeneration of epithelial cells lining renal tubules, (B) infiltration of inflammatory cells, (C) hyaline cast. Hematoxylin and eosin. 400X.

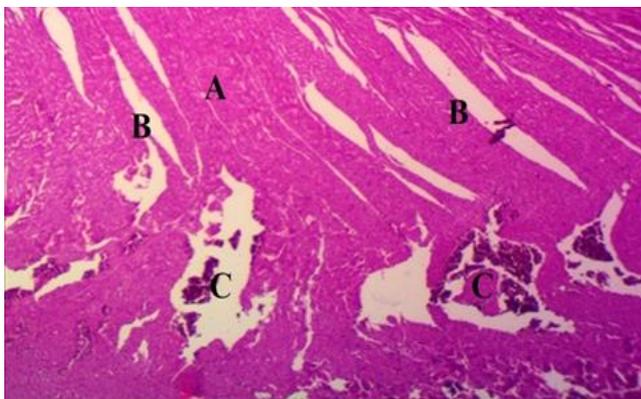


Figure 8: A photomicrograph of rat heart treated with DMH in a dose 20 mg/kg BW shows (A) cardiomyopathy, hyalinization and loss of striation, (B) edema between myocardial muscle fibers, (C) deposition of calcium salts. Hematoxylin and eosin. 100X.

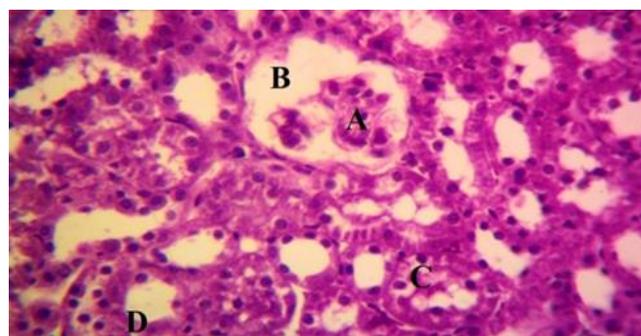


Figure 11: A photomicrograph of rat kidney treated with DMH in a dose 10mg/kg BW shows (A) shrinkage of glomerular tuft, (B) increase space of Bauman's capsule, (C) vacuolar degeneration of epithelial cells, (D) cloudy swelling. Hematoxylin and eosin. 400X.

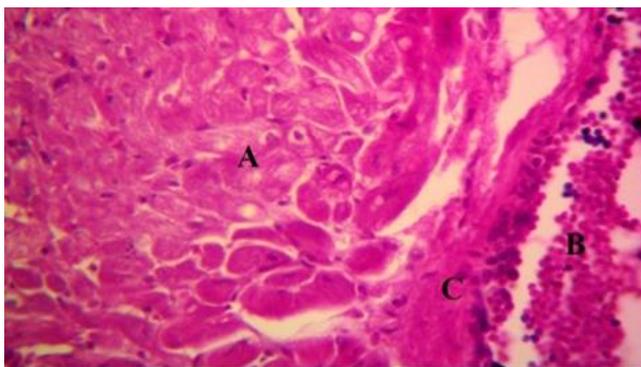


Figure 9: A photomicrograph of rat heart treated with DMH in a dose 20 mg/kg BW shows (A) cardiomyopathy, (B) congestion of blood vessels, (C) infiltration of inflammatory cells. Hematoxylin and eosin. 400X.

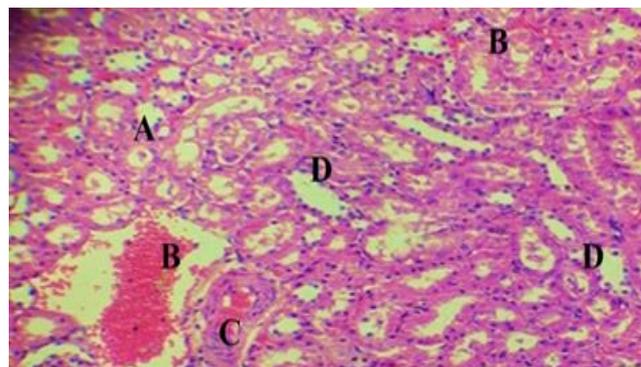


Figure 12: A photomicrograph of rat kidney treated with DMH in a dose 20mg/kg BW shows (A) degeneration of epithelial cells lining renal tubules, (B) hemorrhages between renal tubules, (C) congestion of blood vessels, (D) infiltrations of inflammatory cells. Hematoxylin and eosin. 150X.

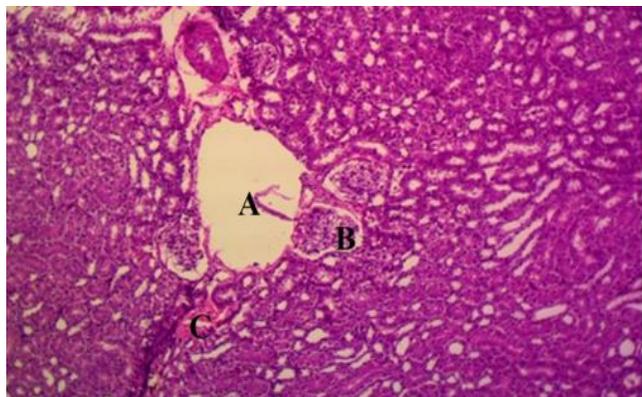


Figure 13: A photomicrograph of rat kidney treated with DMH in a dose 20 mg/kg BW shows (A) renal cyst, (B) degeneration of glomeruli, (C) hemorrhage. Hematoxylin and eosin. 100X.

Discussions

As we know hydrazine derivatives cause protein denaturation and saponifying adipose tissue, the results indicate that rats' livers treated with DMH in a dose of 10 and 20 mg/kg bw reveals vacuolar degeneration, necrosis, hemorrhage and infiltration of inflammatory cells this lesion occurs due to a toxic free-radical that produced by the dimethylhydrazine administration this indicated by increased serum level of AST and ALT which cause liver injury (25-27). DMH consider a stronger hepatic and colonic carcinogen cause hepatic tissue injury, oxidative stress and mutation of DNA which metabolized in liver to carbonium ion and oxy radicals that leads to Wnt signaling pathway activation this in turn cause increased proliferation and inflammation of hepatocyte that indicated by increased level of cyclooxygenase 2 enzyme (COX-2) (8). Animals that Exposed to hydrazine derivatives in both acute and chronic phase can exhibit hepatic damage this damage can demonstrated by histopathological lesions and increased liver enzymes (28-31). The researcher (17) reported that inhalational exposure to derivatives of hydrazine can elevate level of aspartate aminotransferase and alanine aminotransferase during 5 hours after induction and lasting up to a week (16). some studies in animals indicated that hydrazine cause cell degeneration and focal hepatic necrosis because of their interfering in hepatic tissue with pyridoxine dependent enzymes (32-34). Also, hepatic injury occur because of DMH is a potent reducing agent and because of depletion of reduced glutathione and oxidative stress (26,35).

Heart sections in rat treated with 10 and 20 mg/kg DMH shows edema, Zenker's necrosis, discontinuation of muscle fibers with foci of infiltration of inflammatory cells and hemorrhage but more sever lesions in dose 20 mg/kg some studies indicated that there are a vasoconstriction occur in the coronary vessels of heart after Acute exposure to DMH

(20), heart lesions occurs because of toxic effect of DMH and free radicle that release whereas DMH needs bio activations to induce its mutagenic effects and induce its hepatotoxic effects so its activated metabolically in liver by several steps of reactions to carcinogenic and toxic metabolite through intermediates methylazoxymethanol and azoxymethane and these metabolite affect cardiac muscles and cause cardiomyopathies (18,36,37).because of DMH is a potent colonic and hepatic carcinogen many tumors that occur in colon cause release of H_2O_2 which is under go detoxification in liver and distributed in all tissues by circulation including heart and many generations of H_2O_2 are produced from this tumors thus induce cardiomyopathies and continuous injury to rat tissues (38,39). Kidneys sections in rats treated with 10 and 20 mg/kg DMH for 8 weeks reveals vacuolar degeneration of epithelial lining renal tubules with cloudy swelling and hyaline casts in some lumen of renal tubules because of application of hydrazine derivates is nephrotoxic and leads to an impairment in renal tubules, decreasing glomerular filtration rate and function (11,40,41), a numbers of animals studies on hydrazine and it derivatives are hypothesized that toxicity is exerted by interfering in urea cycle this occurred by increased levels $N\alpha$ -acetyl citrulline and arginosuccinate (42-45).

Conclusion

In conclusions, our results provide experimental evidence about the toxic and carcinogenic effects of dimethylhydrazines (DMH) on liver, kidney and heart of rats this revealed by cardiomyopathy, hepatotoxic and nephrotoxic effects that occurred in these organs also the severity of the changes are dose and time depended indicating that DMH induce its effect on the tissues by increasing time and dose.

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Conflict of interest

The authors announce there is no conflict of interest.

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التقييم المرضي النسيجي للآفات المحدثة بثنائي مثيل الهيدرازين في ذكور الجرذان

انتصار خزعل الحمداني، كرم هاشم الملاح و هناء خليل إسماعيل

فرع الأمراض وأمراض الدواجن، كلية الطب البيطري، جامعة الموصل، الموصل، العراق

الخلاصة

أجريت الدراسة الحالية لتقييم التأثير المسرطن والسمي لثنائي مثيل هيدرازين في ذكور الجرذان، استخدمت في التجربة ٣٠ جرذاً من نوع ألبينو مقسمة إلى ٣ مجموعات عشوائياً ١٠ جرذ لكل مجموعة. المجموعة الأولى مجموعة السيطرة تركت على الماء والطعام فقط أما المجموعة الثانية تم معاملة بمركب ثنائي مثيل الهيدرازين بجرعة ١٠ ملغم/كغم من وزن الجسم مذاب في ٩,٠٪ كلوريد الصوديوم مرة أسبوعياً تحت الجلد لمدة ٨ أسابيع والمجموعة الثالثة تم إعطائها مركب ثنائي مثيل الهيدرازين بجرعة ٢٠ ملغم/كغم من وزن الجسم مذاب في ٩,٠٪ كلوريد الصوديوم مرة أسبوعياً تحت الجلد لمدة ٨ أسابيع. أظهرت النتائج الفحص العياني وجود احتقان شديد في الكبد مع نزف حبري عند الجرعة ١٠ ملغم / كجم من وزن الجسم وتضخم في الكبد عند جرعة ٢٠ ملغم/كغم من وزن الجسم. كذلك بينت النتائج حصول احتقان الأوعية الدموية في القلب مع تضخم عضلة القلب في ٢٠ ملغم/كغم من وزن الجسم، في حين عينات الكلى ظهرت بشكل طبيعي عيانياً في كلتا الجرعتين. بينت المقاطع النسيجية للكبد المعاملة بثنائي مثيل الهيدرازين بجرعة ١٠ ملغم/كغم من وزن الجسم عدم انتظام الخلايا الكبدية، ارتشاح الخلايا الالتهابية والتنكس الفجوي للخلايا الكبدية وكذلك حدوث الموت الخلوي المبرمج لبعض الخلايا الكبدية. في حين بينت عينات الكبد المعاملة بثنائي مثيل الهيدرازين في جرعة ٢٠ ملغم/كغم من وزن الجسم وجود نزيف حاد، تنخر بؤري لخلايا الكبد مع الوذمة. أظهرت عينات القلب المعاملة بثنائي مثيل الهيدرازين عند جرعة ١٠ ملغم/كغم من وزن الجسم عدم انتظام في ألياف عضلة القلب مع الوذمة وارتشاح كثيف للخلايا الالتهابية، أما عند جرعة ٢٠ ملغم/كغم من وزن الجسم أظهرت المقاطع وجود بؤر للخلايا الالتهابية مع اعتلال عضلة القلب واحتقان الأوعية الدموية. في حين بينت المقاطع النسيجية لعينات الكلى المعاملة بثنائي مثيل الهيدرازين عند جرعة ١٠ ملغم/كغم من وزن الجسم التنكس الفجوي في الخلايا الظهارية المبطنة للنبيبات الكلوية مع ارتشاح للخلايا الالتهابية فضلاً عن وجود القوالب الزجاجية، ضمور اللمة الكبيبية، توسع في فسحة بومان مع التورم الغيمي. كما وأظهرت مقاطع أخرى معاملة بثنائي مثيل الهيدرازين في ٢٠ ملغم/كغم من وزن الجسم حصول نزيف بين النبيبات الكلوية واحتقان الأوعية الدموية مع ارتشاح في الخلايا الالتهابية ووجود كيس كلوي وتنكس الكبيبات الكلوية.