Study of the histopathological and hematological changes due to dimtethoate toxicity in rabbis

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دراسة التغيرات المرضية النسجية والتغيرات الدمية نتيجة التسمم بمادة الدايمثويت في الارانب

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المستخلص:

يعتبر الدايمثويت من اهم المبيدات الفسفورية العضوية التي تستخدم بشكل واسع في الزراعة و في العديد من البلدان خصوصا العراق ,والذي يسبب العديد من الامراض للنبات والحيوان وكذلك الانسان . هدفت الدراسة الى معرفة التغيرات المرضية والتغيرات الدمية لماده الدايموثيت في الارانب حيث قسمت الحيوانات الى اربعة مجاميع حيث اعتبرت المجموعه الاولى مجموعة سيطره اما المجاميع المعالجه الثانية والثالثة والرابعة فقد اعطيت مادة الدايموثيت على التوالي بجرع مختلفة 10, 25, 50mg/kg of B.W. اظهرت النتائج الدمية وجود فرق معنوي في عدد الكلي للكريات الدم الحمر وكذلك فرق معنوي في قيمة خضاب الدم في المجاميع المعالجه مقارنة بمجموعه السيطرة , اما التغيرات المرضية النسيجية فقد اظهرت تغيرات مرضية في مختلفه اعضاء الجسم حيث كانت على اشدها في الكبد والذي تميز بوجود تغيرات تنكسية وتنخر في نسيج الكبد وكذلك لاحظ وجود فرط التنسج والتهاب القنوات الصفراوية للكبد ولوحظ ايضا تشمع الكبد وتليفة خصوصا في مجموعه المعالجه الرابعة وكذلك تبين تغيرات تنكسية وكذلك تنخر في نسيج الكلية والقلب اما الدماغ فتميز بوجود الخزب حول الاعصاب وارتشاح الخلايا الالتهابيه ,الطحال تميزبوجود نزف في منطقه اللب الاحمر للطحال ,الرئة لوحظ ارتشاح الخلايا الالتهابية وكذلك وجود انتفاخ الرئه والخزب والنزف في النسيج الرئوي ,نستنتج من هذه الدراسه ان ماده الدايموثيت تسبب تغيرات مرضية في مختلف اعضاء الجسم حيث كانت على اشدها في الكبد والذي تميز بوجود تغيرات تنكسية وتنخر في نسيج الكبد وكذلك لاحظ وجود فرط التنسج والتهاب القنوات الصفراوية للكبد ولوحظ ايضا تشمع الكبد وتليفه خصوصا في مجموعه المعالجة الرابعة وكذلت تغيرات دمية خصوصا في العدد الكلي للكريات الدم الحمراء وفي قيمه خضاب الدم.

الكلمات المفتاحية: الدايموثيت/ تليف الكبد / تشمع الكبد/ التهاب القناة الصفراوية

Abstract:

The dimethoate is considered as one of most important organophosphorus pesticides that vastly used in agriculture in many countries especially in Iraq which caused different diseases in plants, animals and man. In present study we investigated the histopathological and hematological changes in rabbits resulting from chronic dimethoate intoxication. The treated groups (G2, G3 and G4) received dimethoate orally (10, 25 and 50 mg/kg of B.W.) respectively for two months while the control group (G1) was given water for the same period.

The hematological results showed significant decrease in red blood cells counts and hemoglobin values ($P< 0.05$) in treated groups especially G3 and G4 compared to G1 control group. While the total W.B.Cs counts showed variables values without significant differences between treated groups and control group. The histopathological lesions in organs are dose concerning and include mild hepatocellular degeneration and hepatic necrosis ,hemorrhage with extensive periportal fibrosis, chronic inflammatory cells infiltrations mainly lymphocytes and macrophages in addition to liver fibrosis and cirrhosis and biliary hyperplasia with cholangitis occurred only with toxic doses of dimethoate especially G4, also there degenerative changes and necrosis in kidney and heart, hemosiderosis and hemorrhage with lymphoid depletion in spleen , In brain, there is extensive demyelination and perineruonal edema and perivascular leukocytes cuffing and extensive focal gliosis and the lungs showed congestion with thickened alveolar walls because of slight infiltrations of inflammatory cells mainly lymphocytes and macrophages also there is severe pulmonary hemorrhage and edema with severe emphysematous area and atelectasis in pulmonary tissue .

It was concluded that dimethoate induces different histopathological lesions in different organs in rabbits especially in liver which causes hepatocellular degeneration, biliary hyperplasia and cholangitis with hepatic fibrosis and cirrhosis and causes significant decrease in red blood cells counts and hemoglobin values in treated groups compared to the control.

Keywords: Dimethoate, Liver fibrosis, Liver cirrhosis, Cholangitis.

Introduction

Organoophosphorus compounds have been wildly known as a health hazard because of their wide spread use and release into environment (1). Their effects range from acute mortalities to organ specific lesions and immunorepression , teratogenesis , carcinogenesis and metabolic disorders after chronic exposure (2).The insecticides are commonly used in public health and agriculture which caused severe acute and chronic conditions of human and animal poisoning (3)."The acute toxicity of organphosphorus insecticides are considered to be due to firstly to the inhibition of acetylchonesterase (AChE) performing in an accumulation of acetylcholine (Ach) with a sustained overstimulation of Ach receptors in the clefts of central and peripheral neuronal synapses"(4).The toxicity of organophosphorus insecticides returns in negative effects in different organs and systems like liver, kidney, nervous system respiratory system, reproductive system and immune system (5,6,7,8).

Dimethoate it is consider as one of the organophosphorus insecticides and it is vastly used in agriculture and domestic insect control (1). Chronic exposure of dimethoate has been accompanied with critical excess in hepatopathy and diabetic mellitus and is a probable human carcinogen (9, 10). "Prior studies indicate that the dimethoate intoxication which cause cellular injury and oxidation stress ,finally which leads to lipid peroxidation and free radical production" (11,12)."Recent studies showed that the acute and subchronic exposition to dimethoate change the antioxidant status and alters the histology of liver tissue, brain , kidney and testes of rats (13,14,15) and human red blood cells" (16).

Dimethoate has counter effects on some blood parameters such as erythrocytes and hemoglobin and liver dysfunctions leading to histological changes, these changes induced by dimethoate direct or indirect effect to tissues relying on dose of dimethoate and duration of exposure (17).

The aim of present study to investigate the histopathological and hematological parameters associated with dimethoate intoxication in rabbits.

Materials and methods

Twenty-four local rabbits about 6 months old, weighted between 1500-

2000g were obtain from local market, these animals were housed in cages in the animal house in a room under 12 hours light / 12 hours dark at 22-25 C .

The animals were randomly divided into four groups each group consist of six animals. Group (G1) was the control group and received water only. Group 2 (G2) were exposed to dimethoate (10 mg/kg of body weight (B.W.) / day) for two months, this dose consider as NOEL in rabbits (18). Group 3 (G3) received dimethoate (25 mg/kg of (B.W.) / day) for two months. Group 4 (G4) received dimethoate (50 mg/kg of body weight (B.W.) / day) for two months. All treatments were administered by oral gavage.

"The histopathological study was done after two months, the animals were scarified and dissected were done for all animals, the specimens were taken from all internal organs and the tissues were kept in 10% formaldehyde directly after removal ,following 48 hours of the fixation, the processing was done for a set of increasing alcohol concentrations, the tissues sections were embedded in paraffin blocks, then sectioned by microtome at 5 µm for all tissues ,finally, the tissues were stained with hematoxylin and eosin stain (H and E stains) and the histopathological changes were reading under light microscope" (19).

Hematological counts, fasting blood samples were collected at day 60 of experiment via cardiac puncture technique into EDTA tubes, the blood is used directly for measured complete blood picture (CBC).The Hb was estimated by spectrophotometer (20).RBCs and WBCs counts were calculated by hemocytometer method (21).

Results are expressed as Mean +SE statistical analysis of data were estimated using one way analysis of variance (ANOVA I), differences between groups were estimated by using LSD test at $P<0.05$ (22).

Results and discussion

Hematological findings:

Dimethoate administrated to rabbits in different concentration for two months in rabbits, the results showed significant decrease in red blood cells counts ($P<0.05$) in treated groups especially G3 and G4 compared to G1 control group. The hemoglobin values showed significant decline ($P< 0.05$) in treated rabbits especially G3 and G4 compared with G1 control group. While white blood cells counts produced variable values, without significant differences ($P<0.05$)

between treated groups G2, G3 and G4 compared to G1 control group (Table **1**).

The present study showed that exposure of rabbits to the dimethoate toxicity for two months manifested by significant decrease in red blood cells counts and hemoglobin content values ($P<0.05$) in treated groups especially G3 and G4 compared to G1 control group were supported by Yaqoob *et.al.(*17) and Betrosian *et.al.* (23) who showed that pesticides reducing R.B.Cs. counts and Hb% values due to the poisoning by pesticide residues which leads to evolution of anemia because of interference with Hb biosynthesis and dereliction life span of circulating red blood cells. Our findings are in deal with Jyostana *et. al.* (24) which showed that pesticides reduce R.B.Cs and Hb levels, and Elias and Saif (25), who noticed the decrease of R.B.Cs, Hb, and raise in red blood cells sedimentation rate in rabbits were exposed to the organophosphorus pesticide methidathion in dose of 10mg/kg orally. While the total W.B.Cs counts showed variables values without significant differences between treated groups and control group, similarly, the Baba *et.al.* (26) and Fathia *et.al*. (27) reported similar results when exposing rabbits and mice to dimethoate respectively.

Table (1) Effect of dimethoate toxicity on leukocytes, Erythrocytes and Hemoglobin

Group	W.B.Cs ($X10^3$ mm^3)	R.B.Cs ($X10^6$ mm^3)	Hb (gm/dl)
G1	6.53±0.22 **NS**	5.13± 0.44^{a}	11.21± 0.22 ^{a}
G2	5.98±0.47 **NS**	4.71± 0.45^{ab}	10.95±0.58 ^{ab}
G3	6.10±0.79 **NS**	3. 63± 0.40 ^{bc}	9.05± 0.69 ^{bc}
G4	6.58±0.62 **NS**	3.16±0.67^{c}	8.71± 0.84 ^{c}

indices in rabbits (n=6 for each group) (Mean±S

G1, Control group, G2, received 10 mg/ kg of B.W. of dimethoate for two months
G3, received 25mg/ kg of B.W. of dimethoate for two months,
G4, received 50 mg / kg of B.W. of dimethoate for two months.

*NS= No significant differences between groups $P<0.05$.
*Same latters = No significant differences $P< 0.05$.
* Different letters = significant differences $P<0.05$.

Pathological findings:

Variable pathological lesions were presented in different groups of dimethoate toxicity in rabbits but more extensively seen in group four (G4):

The main histopathological lesion in spleen is extensive hpocellularity in white pulp region of spleen because of sever lymphoid depletions and decreased in macrophages and lymphocytes proliferations in areas around central artery of white pulp, and in remainder areas of red pulp of spleen.In certain section, there is extensive hemorrhage in red pulp of spleen associated with extensive hemosiderosis due to massive deposition of hemosiderin pigments in areas of red pulp **(Fig.1 A, B, C)**. The current observations of microscopic lesion were reported by Elham-Elshewey *et al.*(28), who found hemosiderin pigments present in the spleen under the impact of low concentration of fenthion after giving to *cyprinus carpio* with generation of lymphocytes with elevated concentration ,this occur because of rise in the rate of destruction of red blood cells after exposure to pesticides .It was thought that, these lesions were occurring because of rise rate of breakdown of erythrocytes and/or due to the toxic impact of pesticides on bone marrow (29, 30).

Section of heart, which appeared microscopically as a cloudy swelling in myocardial muscles fibers associated with perinuclear vacuolated edema infiltrated between muscles fibers with increased acidophila of muscles sarcoplasm, in addition to that, there is mild mononuclear cells infiltrations mainly lymphocytes and macrophages in cardiac muscles fibers with severe congestion and hemorrhages in blood vessels of the heart **(Fig.2 A, B).** These results agree with results obtained by Hatice *et.al.* (31)who showed chlorpyrifos pesticides encourage cardiotoxicity when given to rats which lead to degeneration in myocardial fibers and cytoplasmic vacuolization in myocardial cells of heart, these degenerative changes can occur may resulting in raise in reactive oxygen species in heart tissues, the genesis of oxygen free radicals can considered as a major agent in the toxicity of organophosphate pesticides such as dimethoate (32).

Dimethoate toxicity which lead to cellular intoxication and formation of oxidative stress which lead to the

accumulation of lipid peroxidation products in different organs and formation of free radicals ,finally which lead to produce histopathologic lesions in different tissues (33) ."In case of brain, there are severe demyelination with perineruonal and pericellular edema in adjacent glial cells and purkinje cells of brain parenchyma that existing in all examined sections in various groups of animals and in certain cases, there are perivascular leukocytes cuffing with extensive focal gliosis because of proliferation of microglia cells in brain parenchyma" **(Fig.3 A, B)**. Our results are acceptance with Sharma *et .al.* (34) who reported short lived effects of dimethoate toxicity on brain tissue may occur due to vascular injury and formation of oxidative stress and can cause lipid peroxidation which increased in brain.

The lungs showed congestion with thickened alveolar walls because of slight infiltrations of inflammatory cells mainly lymphocytes and macrophages and congestion of alveolar capillaries, in some areas prominent epithelial type II pneumocytes , in other areas of tissue section there is severe pulmonary hemorrhage and edema with severe emphysematous area and atelectasis in pulmonary tissue , in addition to extensive hyperplasia of endothelial cell lining and congestion of blood vessels with hemorrhage ,those lesions were higher in severity in group G4 than other treated and control groups **(Fig.4 A,B,C)**. These pathological finding cooperated with outcomes of Ibtissem *et.al.*(35) as result of dimethoate – encouraged lung oxidative damage. The Baba *et.al.* (26) who showed that the pulmonary emphysema and atelectasis occur due to dimethoate encouraged acetylcholine mediated respiratory trail. "The kidneys were showed acute tubular necrosis in proximal and distal convoluted tubules and slight degenerative changes such as acute cellular swelling in proximal and distal convoluted tubules which appeared star-shaped lumen with swelling of their epithelia with dilation of bowman's space, also there is mild peritubular inflammatory cells infiltrations mainly lymphocytes" **(Fig.5 A,B,C)**. These results are consistent with Benjamin *et.al.*(36) who showed that in severely poisoned rats by insecticides which cause acute tubular epithelium necrosis, hemorrhages in the glomeruli and dilated bowman’s spaces. Kidney necrosis and degeneration may be due to formation of oxidative stress that play a major role to the moderator in variable configuration of

cell membrane ,Finally which lead to the morphologic modification of kidney (37).

Liver is a major organ implicated in xenobiotic metabolism ,and it is considered as the main target for chemical or drug such as dimethoate pesticides, The main lesion in this organ microscopically varies from mild hepatocellular degeneration and acute cellular swelling in group G2 to hepatic necrosiss and hemorrhage with extensive periportal fibrosis, hepatocellular degeneration and loss hepatic architecture and chronic inflammatory cells infiltrations mainly lymphocytes and macrophages in group G3 while the G4 group, appear severe histopathological lesions such as liver fibrosis and liver cirrhosis ,with foci of granulomatous reaction which characterized by accumulation of activated macrophages with lymphocytes and surrounded by fibrosis .Also there is biliary hyperplasia with cholangitis occurred only with toxic doses of dimethoate especially G4 **(Fig.6 A,B,C,D, E,F)**.

These findings are acceptance with that finding by Semanoglu and Akay (38) who reported same histopathological lesions including mononuclear inflammatory cell infiltrations, hydropic degeneration and hepatocellular degeneration in liver of male rats processed with dimethoate, endosulfan and carbaryl. The Sharma *et. al.*(34) and Sharma *et. al* (12) who showed that acute and subchronic exposition to the dimethoate which lead to formation lipid peroxidation and changes the antioxidant status of various tissues in rats and lead to different histopathological lesions in different organs especially liver , brain and other organs .

Conclusions:

This study showed that the dimethoate in rabbits causes significant decrease in red blood cells counts and hemoglobin values in treated groups compared to the control and induced various histopathological lesions in different organs especially liver which appeared microscopically liver cirrhosis and fibrosis with massive biliary hyperplasia and cholangitis .

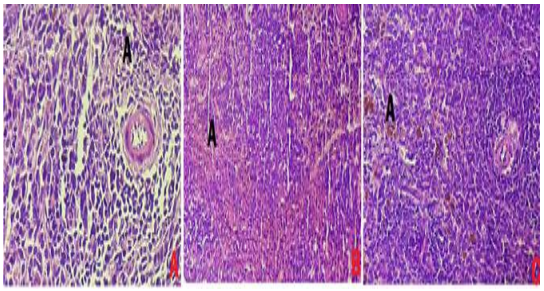

Figure 1: **Spleen**: **A**: There is severe lymphoid depletion and decreased in lymphocytes and macrophages proliferations in areas around the central artery of spleen (A) (H&E stain 400X). B: Extensive hemorrhage in areas of red pulp of spleen (A) (H&E stain 200X). C: Massive hemosiderosis in areas of red pulp of spleen (A) (H&E stain 200X).

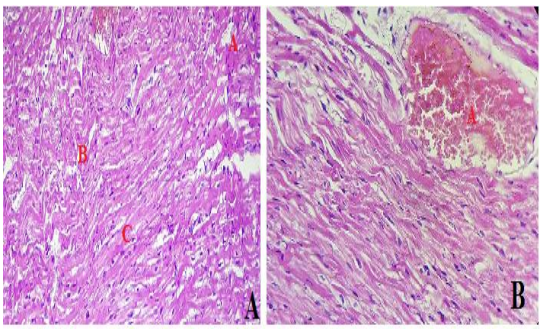

Figure 2: Heart: A: Myocarditis due to slight infiltrations of lymphocytes and macrophages (A), and a cloudy swelling which characterized by perinucler edema infiltrated between muscles fibers (B) with increased acidophilia of muscles sarcoplasm (C) (H&E stain 200X). **B**: Severe hemorrhage and congestion in blood vessels of heart (A) (H&E stain 400X).

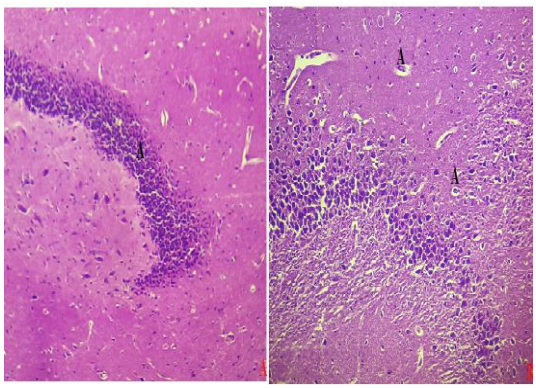

Figure 3: Brain: A: Severe focal gliosis because of focal proliferation of microgli cells in brain parenchyma (A) (H&E stain 200X).

B: Extensive perineuronl edema around glia cells and purkinje cells in brain parenchyma (A) (H&E stain 400X).

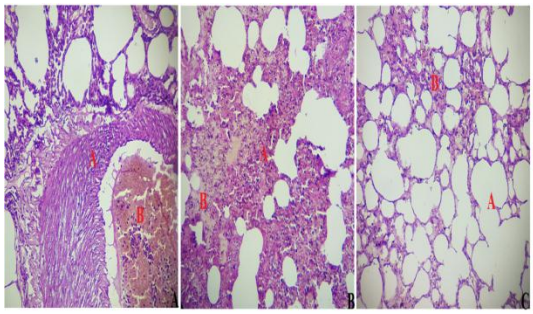

Figure 4: Lung: A: Extensive hyperplasia of endothelial cell lining (A) and congestion of blood vessels with hemorrhage (B) (H&E stain 400X). **B**: Severe pulmonary hemorrhage (A) and edema in pulmonary tissue (B) (H&E stain 200X).**C**: There is severe emphysematous area in pulmonary tissue (A) with interstitial thickening and thickening of alveolar walls because of slight infiltrations of inflammatory cells mainly lymphocytes and macrophages and congestion of alveolar capillaries, with proliferations epithelial type II pneumocytes (B) (H&E stain 400X).

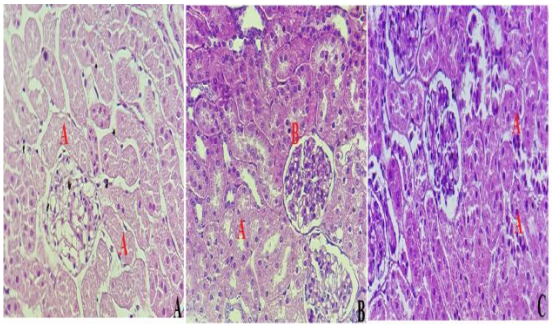

Figure 5: Kideny: A: Acute tubular necrosis in proximal and distal convoluted tubules (A) (H&E stain 400X). **B**: Acute cellular swelling of proximal convoluted tubules appeared star-shaped lumen (A) , swelling of their epithelia with dilation of bowman's space (B) (H&E stain 400X).**C**: There is mild peritubular inflammatory cells infiltrations mainly lymphocytes (A) (H&E stain 400X).

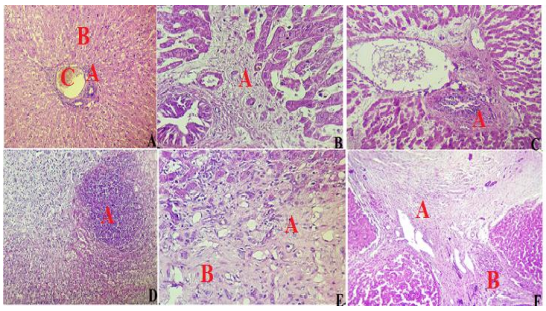

Figure 6: Liver: A: Periportal leukocytes cuffing (A) , Hepatocellular degeneration (B) and congestion of blood vessles (C) (H&E stain 100X). **B**: Extensive periportal fibrosis and hepatocellular degeneration with loss of hepatic archiecture (A) (H&E stain 200X).**C**:There is massive biliary hyperplasia and cholangitis due to inflammatory cells infiltrations mainly lymphocytes (A) (H&E stain 400X).**D**:Granuloma in hepatic tissue which chacterized by activated macrophages inflitrations and lymphocytes suurrounded by fibrosis (A) (H&E stain 400X).**E:** Extensive liver cirrchosis with regenerative nodules of hepatocytes ringed by thick bands of collagenous fibrosis (A) with mononuclear cells infiltrations mainly lymphocytes(B) (H&E stain 400X).**F**: There is extensive liver cirrchosis with fibrosis (A) with mononuclear cells infiltrations mainly lymphocytes and formation of portal-portal fibrous septa (B) (H&E stain 200X)

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