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Biological effects of different doses of Piroxicam in albino males rats

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Abstract

Current study aimed to investigate the effect of piroxicam on some hematological and biochemcal parameters. For this reason forty males mature *Sprage Dawlley* rats were divided into four equal groups. control group administrated distilled water (G1), and three groups administrated (20mg/kg,30mg/kg,40mg/kg) body weight of piroxicam for 45 days. The results showed significant decrease ($P<0.05$) in hemoglobin (Hb) and packed ceq volume (PCV) in groups treated with (30,40)mg/kg of piroxicam, while the treated groups produced significant increease ($P<0.05$) in the total white blood cell count (WBC). On the serum biochemical porameters, Piroxicam caused increase in the level of liver enzyme amunotans ferase (ALT) and aspartate amintou (AST) Also recorded significant changes in the level of kidney function (creatinine, blood urea, uric acid). Histological studies appeared piroxicam caused more severe damage to the liver included depletion of glycoprotein, nearosis congestion, fatty change and inflammatory cell infiltration, kidney section appeared shrink of glomeruli, dilated renal tubules and necrosis were noticed in the renal tubules. Also the testes section appeared no effect in all the treatment groups except in the group which treated with piroxicam _40mg/kg) which showed thickening of somniferous tubules, shrink of leyding cells and necrosis of germ cells. This study shows that the toxic effect of piroxicam depends on time and conceutration of dose administration.

Keywords: Piroxicam, Liver Enzymes, Kidney Function.

التأثيرات الحيوية لجرعات مختلفة للبايروكسيكام في ذكور الجرذان البيض

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الخلاصة

تهدف الدراسة الحالية الى دراسة تأثير البايروكسكام في بعض معايير الدم و المعايير الكيموحياتية تم اخذ 40 من ذكور الجرذان البيض وقسمت الى اربعة مجاميع متساوية جرعت المجموعة الاولى ،مجموعة السيطرة بالماء المقطر ، اما المجاميع الثلاث الاخرى فجرعت بعقار piroxicam بتراكيز (20 ملغم/كغم، 30 ملغم/كغم، 40 ملغم/كغم) لمدة 45 يوما . اظهرت النتائج انخفاضا معنويا في ($p<0.05$) في (Hb) و (PCV) في المجموعتين المعاملة بالبايروكسكام (30mg/kg, 40mg/kg) بينما اظهرت النتائج حصول ارتفاعا معنويا ($p<0.05$) في معدل (WBC) في المجاميع المعاملة بالبايروكسيكام بينما اظهرت النتائج الكيموحياتية ان البايروكسيكام يسبب ارتفاعا في معدل مستويات (ALT) و (AST) ، ايضا سجل ارتفاعا في مستويات الكرياتنين و اليوريا و حامض اليوريك . اظهرت الدراسة النسجية ان البايروكسيكام يسبب اضرار لنسيج الكبد منها استنفاذ شديد في البروتينات السكرية نغيرات في الدهون ، ارتشاح الخلايا الكبدية ، اظهرت انكماش في الكبيبة مع توسع الانابيب الكلوية مع ارتشاح الخلايا الالتهابية، كذلك اظهرت مفاطع الخصية عدم

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وجود اي تأثير في نسيج الخصية ما عدا المجموعة المعاملة بالبايروكسيكام بتركيز 40mg/kg و التي اظهرت تسمك النبيبات المنوية، و انكماش في خلايا ليدنك lyding cells و تنخر في الخلايا الجرثوية germ cells ، هذه الدراسة اظهرت ان سمية البايروكسيكام تعتمد على الجرعة و الزمن المعطاة.

Introduction

Rheumatic arthritis and osteo arthritis spread around the world causing many medical problems (Zvaifler.,1988)and many people suffering from those diseases . Many companies began to search solutions for those problems and then they discover many drugs one of these drugs (NSAIDs) are different chemical classes which introduce for clinical use. [1, 2] Piroxicam is one of the (NSAIDs) types which used for healing osteo arthritis. and Rheumatic arthritis , but many pupils start using this drugs without consulting doctors in different doses from low to high concentrations, because Piroxicam has analgesic , antipyretic and anti inflammatory activity [3]. At present time [4] found that agreat of growing and indention of apoptosis happen when Piroxicam is employed in high level concentration that rose maximum need doses. The taking of high concentrations of Piroxicam will effect on the functions of kidney, liver and testes [5] damages their tissues, for this reason our present study was designed to investigate the physiological and hematological effects of piroxicam on the liver and kidney and histological effects of piroxicam on liver, kidney and testes of labratory albino rats treated with Piroxicam .

Materials and Methods

Forty male mature *Sprage-Dawelly* Albino rats of an average body (200-225)gm Animals divided into four equal groups, control group (G1) administrated distilled water (D.W), second group administrated 20mg/kg of piroxicam (G2), third group administrated 30mg/kg of piroxicam (G3). fourth group administrated 40mg/kg of piroxicam (G4) the route of administration was oral intubation for every other day for 45 days . in the end of experiment, period the animals were anaesthetized using diethyl ether and blood obtained by heart puncture for hematological and serum , biochemical studies , heamoglobin (Hb) packed cell volume (PCV) and white blood cell (WBC) counts were measured, Serum enzymes aspartate aminotransferse (AST) and alanine aminotrusferase (ALT) were determine by kit (Reflotron kit, Germany) , (blood urea, creatinine and uric acid) were determine by kit (Urea kit, LINEAR. Spain), Then the animals were disected and the organs (liver kidney and testes) , laminate for studying histopathological changes, the histological section were made according to [6], the organs were fixed by 10% formalin and then subjected to histological procedures.

Results

The results showed significant hematological changes ($P<0.05$) after administration of piroxicam. These changes in clued a significant decrease ($P<0.05$) in (Hb) and (PCV) in animals groups which administrated (30mg/kg,40kg,mg) of piroxicam, while the group treated with (20mg/kg) of piroxicam showed non-significant ($p>0.05$) difference as compared with control group Table-1. Also the results in Table-1 shoed significantly increased ($P<0.05$) levels of total WBC in all groups treated.

The results in Table-2 showed significant increased ($P<0.05$) levels of (ALT) and (AST) . Also appeared significantly changes in kidney function, these changes include a significant increased ($P<0.05$) level of (creatinin, blood urea, uric acid).

Table 1-values of hematological parameters changes of rats administrated treated with Piroxicam for 45 days

Treated groups	Hb gm/dl M±SE	PCV% M±SE	WBC cell/ml^3 M±SE
Control group(G1)	12.66±1.05	39.62±0.24	8.601±371.2
G2 (20mg/kg)	12.20±1.24	38.41±0.34	11.35±310*
G3 (30mg/kg)	9.6±0.31	34.69±1.58*	13.600±482.9*
G4 (40mg/kg)	9.3±0.8	32.9±1.21*	14.86±611*

*significant ($P<0.05$)

Table 2- values of biochemical parameters changes of rats administrated treated with Piroxicam for 45 days.

Treated group	ALT Iu/L M±SE	AST Iu/L M±SE	Blood urea mg/dl M±SE	Creatinine mg/dl M±SE	Uric acid mg/dl M±SE
Control group (G1)	15.9±0.01	31.21±0.03	27.25±0.4	0.531±0.03	2.33±0.22
G2 (20mg/kg)	17±0.07	34.12±1.1	29.01±0.25	0.650±0.02	3.52±0.19
G3 (30mg/kg)	23±0.02*	40.43±0.05*	33.00±0.12*	0.897±0.03*	4.04±0.22*
G4 (40mg/kg)	25.20±0.07*	38±0.07*	37.5±0.67*	0.905±0.02*	5.19±0.16*

*significant (P<0.05)

The histological changes in liver, kidney and testes

Liver

The present histopathological study of liver cells of control group (G1) showed a normal hepatocytes arrange as plates around the central vein with sinusoid between the liver plate Figure- 1(a, b). Section of liver cells of (G2), showed slight dilatation of sinusoid while other cells lock like normal appearance (Figure- 2(a, b). Section for the liver cells of (G3), showed slight depletion of glycoprotein granules, near portal area Figure- 3(a, b) while section of liver cells of (G4), showed congestion to the central vein, severe depletion of glycoprotein and near portal area Figure- 4(b) increased inflammatory cells infiltrate necrosis to heptocytes and fatty changes in the given section Figure- 4(a).

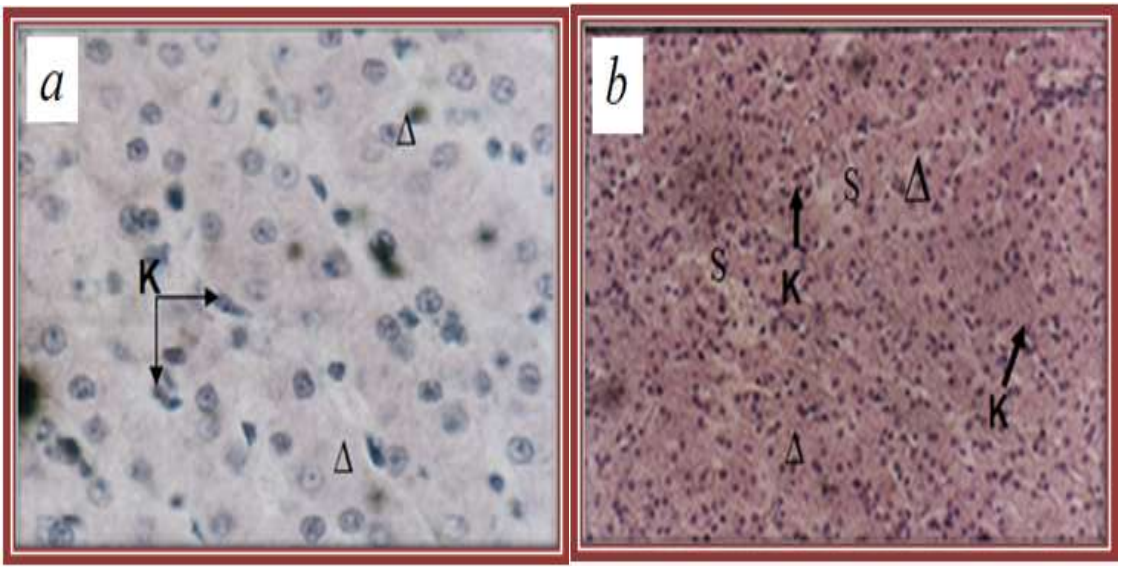

Figure 1- sections of liver from control group (G1) a: liver cells of control group (G1) showed a normal hepatocytes (Δ**)** arrange as plates around the central vein between the liver plate and numerous of kupffer (k) .(H&E)(400X) b: liver cells of control group (G1) showed a normal hepatocytes (Δ**)** arrange as plates around the central vein with sinusoid (s) between the liver plate and numerous of kupffer (k) .(H&E)(200X)

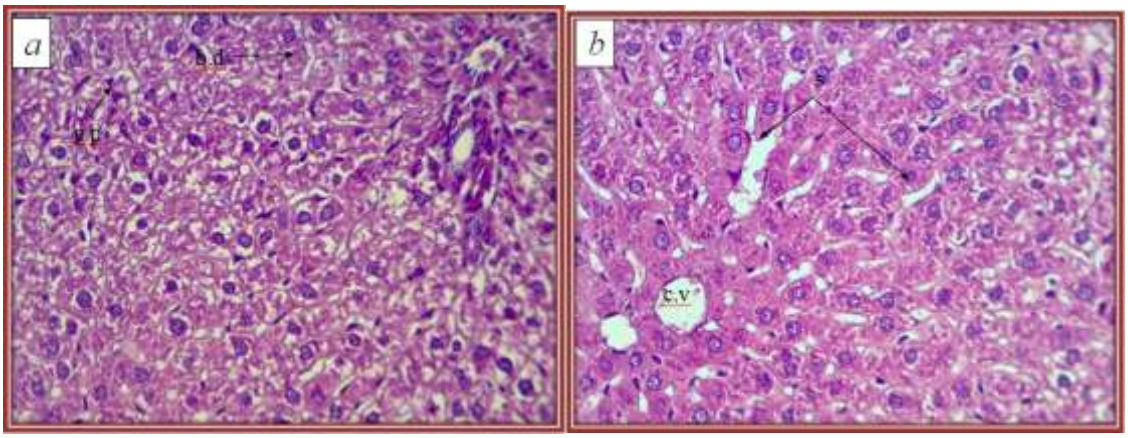

Figure 2- sections of liver from group (G2) (20mg/kg) a: liver cells of treated group (20 mg/kg/day) (G2) section show mild depletion of glycoprotein (g.p) granules, bile ducts (b.d) (H & E) (400x) b: liver cells of treated group (20 mg/kg/day) (G2) section show mild dilation of sinusoid (s) while other cells look like normal appearance, central vein (c.v) (H & E) (400x)

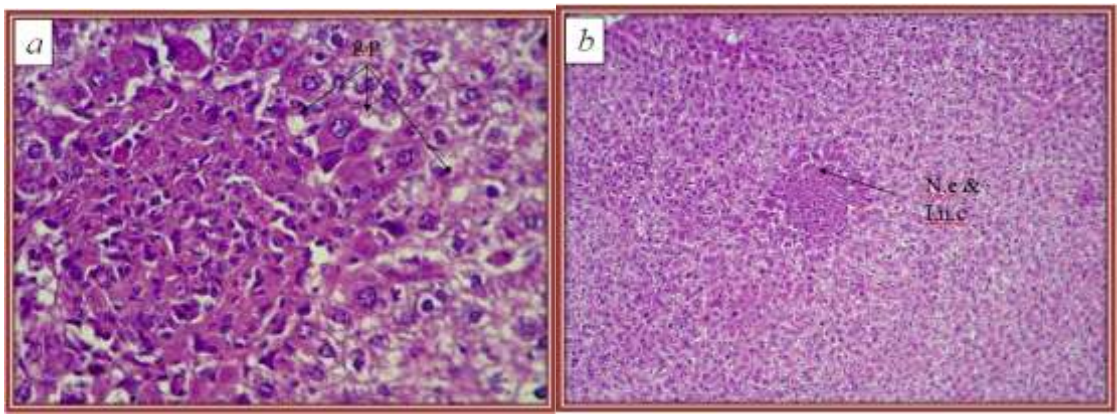

Figure 3- of liver from group (G3) a: liver cells of treated group (30 mg/kg/day) (G3) section show depletion of glycoprotein (g.p) (H & E) (400x) b: liver cells of treated group (30 mg/kg/day) (G3) section show focal area of necrosis (Ne) and inflammatory cells (I.n.c) infiltrate (H & E) (200x)

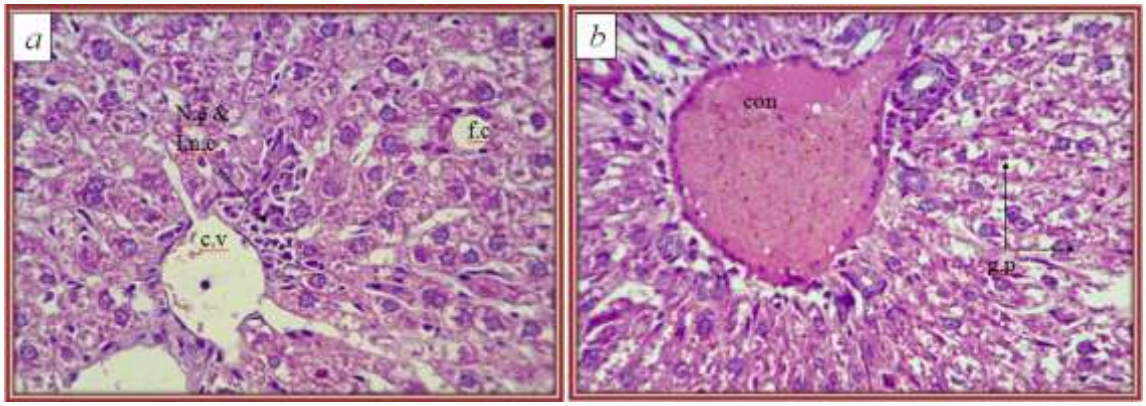

Figure 4- sections of liver from group (G4) a: liver cells of treated group (40 mg/kg/day) (G4) section show focal area of necrosis (N.e) and inflammatory cells (I.n.c), central vain (c.v), fatty change (f.c) (H & E) (400x) b: liver cells of treated group (40 mg/kg/day) (G4) section show congestion (con), severe depletion of glycoprotein granules near portal area (g.p) (H & E) (400x)

Kidney

The section of kidney of control group (G1), showed a normal structure of glomerulus with a normal bowman's and bowman's space, also showed normal structure of convoluted tubules Figure- 5(a,b). Section of kidney of (G2) and (G3) showed shrinkage of glomerilus with dilates of

renal tubules Figure- 6 (a, b) Figure- 7 (a, b) While section of kidney of (G4) showed dilated renal tubules with focal disperse area of necrosis in renal tubules with inflammatory cells infiltral Figure- 8 (a, b).

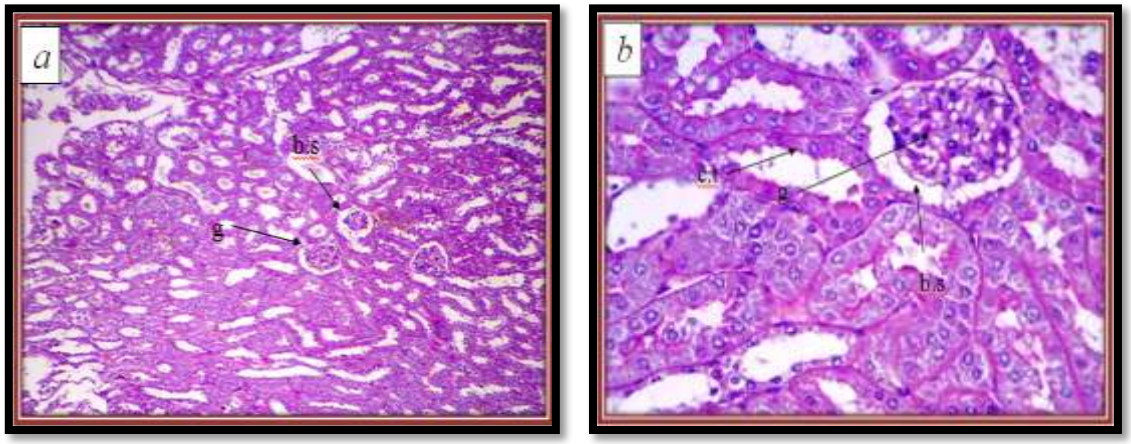

Figure 5- sections of Kidney from control group (G1) a: kidney cells of treated group (G1) section show glomerulus , bowman's space (g) (H & E) (200x) b: kidney cells of control group (G1) section show glomerulus (g), convoluted tubules (c.t), bowman's space (b.s) (H & E) (400x)

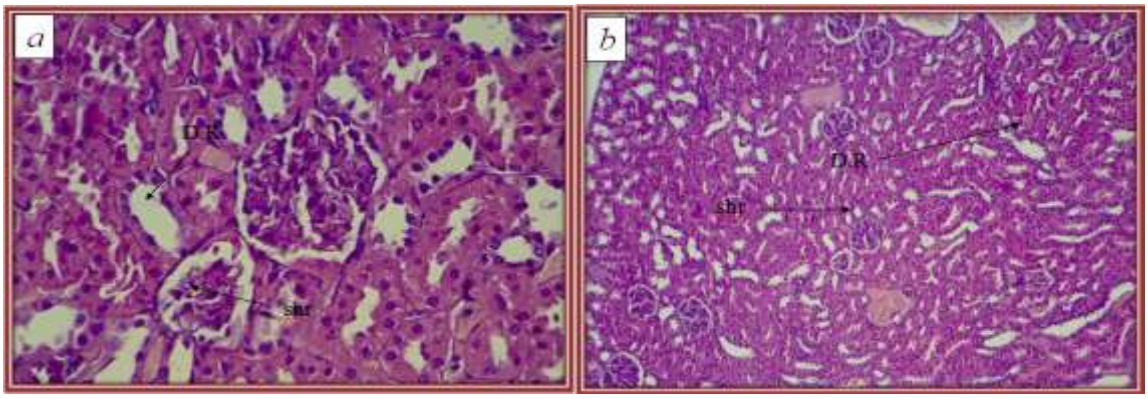

Figure 6- sections of Kidney from group (G2) a: kidney cells of treated group (20 mg/kg/day) (G2) section show shrinkage glomeruli (shr) & dilated renal tubules (D.R) (H & E) (400x) b: kidney cells of treated group (20 mg/kg/day) (G2) section show shrinkage glomeruli (shr) & dilated renal tubules (D.R) (H & E) (200x)

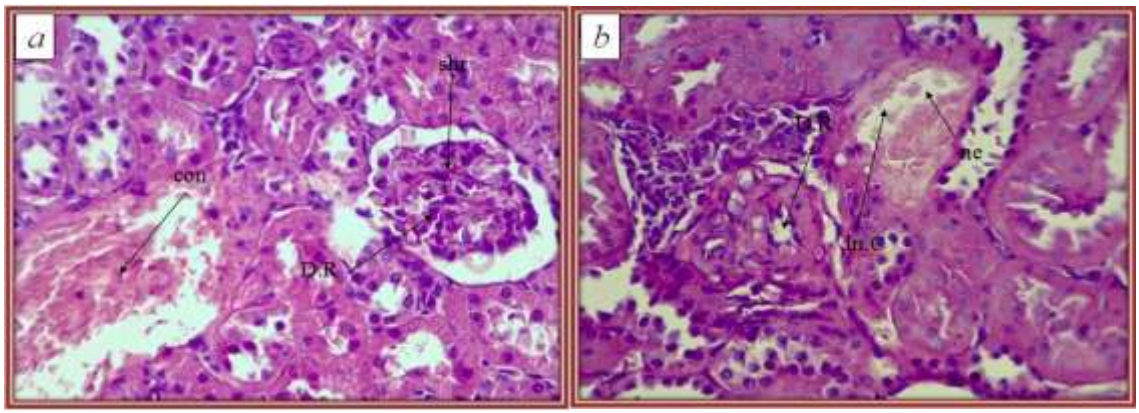

Figure 7- sections of Kidney from group (G3) (30mg/kg) a: kidney cells of treated group (30 mg/kg/day) (G3) section show shrinkage glomeruli (shr) with dilated renal tubules (D.R), congestion (con) (H & E) (400x) b: kidney cells of treated group (30 mg/kg/day) (G3) section show dilated renal (D.R) tubules with focal dispersed area of necrosis (ne) in renal tubes with inflammatory cells (In.C) infiltrate(H & E) (400x)

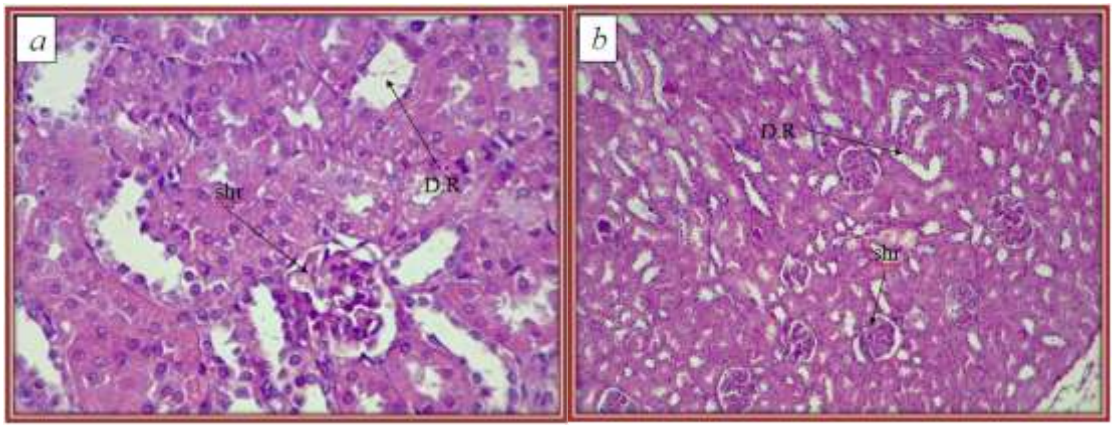

Figure 8- sections of Kidney from group (G4) a: kidney section of treated with piroxicam group (40 mg/kg/day) (G4) section show shrinkage of glomeruli (shr) with dilated renal tubules (D.R) (H & E) (400x) b: kidney cells of treated group (40 mg/kg/day) (G4) section show shrinkage of glomeruli (shr) with dilated renal tubules (D.R) (H & E) (400x)

Testes

The histological effects of Piroxicam on the testicular tissue of the male rats are evident. Result of this study revealed that this drug has damaging effects in the 40 mg/kg , these changes were observed as thickening of seminephreus tubular basement membrane with certain germ cell necrosis, no mature of spermatogoni cells, therefore presence of necrotic debrism also shrinkage of leyding cells Figure- 12 (a, b) section through the testis of control (G1) rats showing normal somniferous tubules, normal lumen of somniferous tubule and germinal layers normal interstitum Figure-9 (a, b) while histopathological sections in (G2) and (G3) (treated with 20mg/kg b.w, 30 mg/kg b.w) respectively reveals normal structure appearance of seminephrous tubules with maturate of spermatogoni and presence of sperms inside the lumen , with normal like structure of leyding cells Figure- 10(a, b) Figure- 11(a, b).

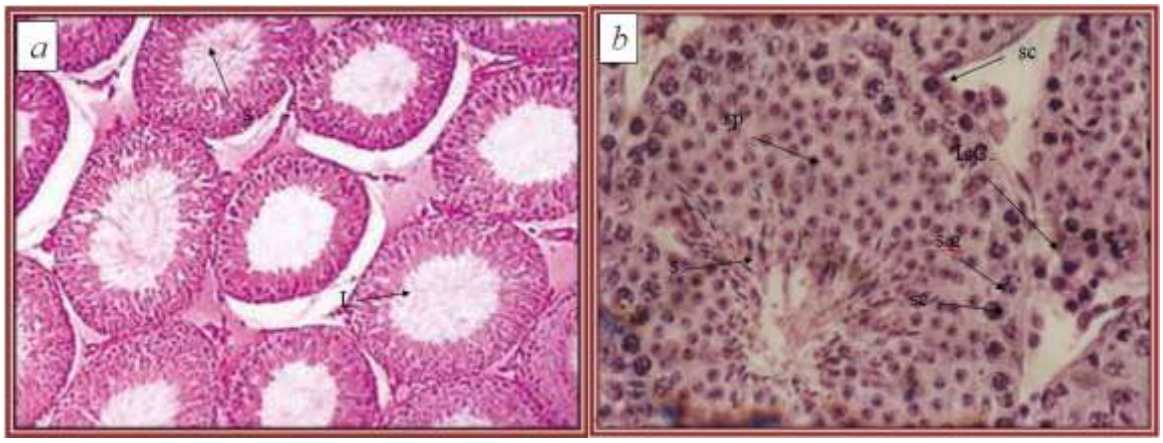

Figure 9- of testes from control group (G1) a: section through the testes of control group (G1) section of normal appearance which consist of seminephrous tubular with sperms (s) inside the lumen (L) (x200) (H & E) b: section through the testes of control group (G1) section in a control group testis showing spermatogonia (s.g), primary spermatocytes (sc), spermatids (sp) and sperms (s). Sertoli cells (Sc). Leydig cells (L.C.). (x400) (H & E)

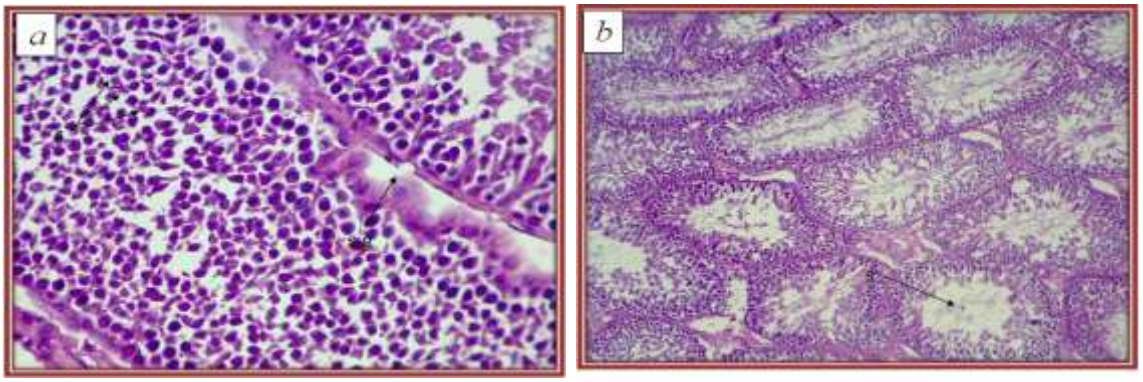

Figure 10- sections of testes from group (G2) (20mg/kg) a: section through the testes of treated group (20 mg/kg/day) (G2) section show the well mature semineferous (s) tubules and spermatogonia (s.g) with presence of sperms (H & E) (400x) b: section through the testes of treated group (20 mg/kg/day) (G2) section look like normal appearance which consist of seminephrous tubular with sperms (s) inside the lumen (H & E) (200x)

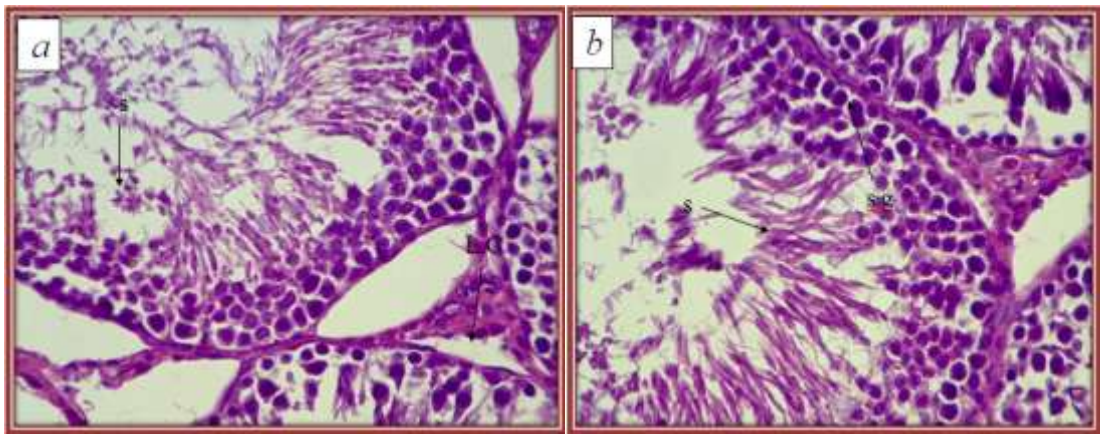

Figure 11- sections of testes from group (G3) (30mg/kg)a: section through the testes of treated group (30 mg/kg/day) (G3) section show the normal like structure of Leyding cells (L.C.) (H & E) (400x) b: section through the testes of treated group (30 mg/kg/day) (G3) section look like normal appearance which consist of semineferous tubules with mature spermtogonia (s.g) and presence of spearms (s) inside the lumen (H & E) (400x)

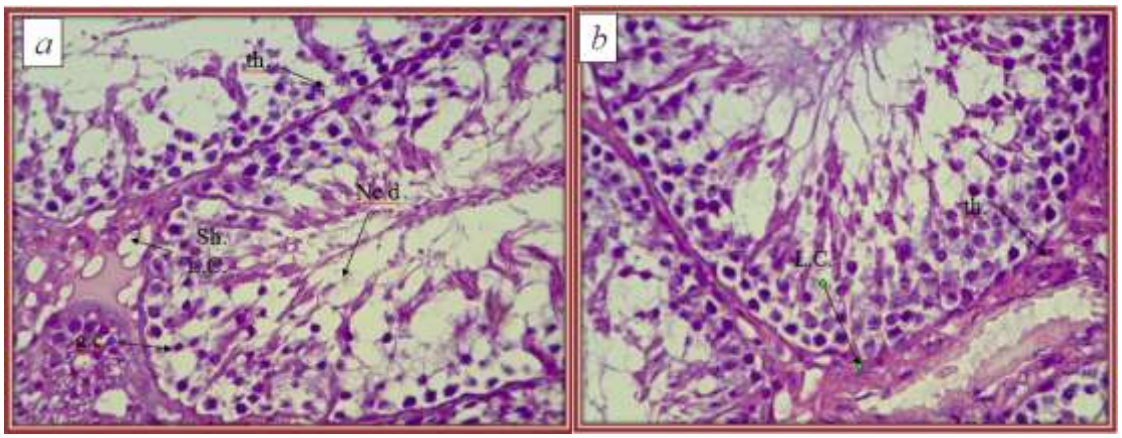

Figure 12- sections of testes from group (G4) (40mg/kg) a: section through the testes of treated group (40 mg/kg/day) (G4) presence of necrotic debris (Ne.b) and no sperms inside the lumen, with shrinkage of Leyding cells (Sh. L.C), germ cells (g.c) and thickening of seminephrous tubular (th) (H & E) (400x) b: section through the testes of treated group (40 mg/kg/day) (G4) section show thickening (th) of semineferous tubules basement membrane with germ cells necrosis and no mature of spermatogoni cells(L.C.) (H & E) (400x)

Discussion

The piroxicam effect in our study, on liver, kidney functions and hematological and histological variation depend on different constrictions of this drug. There was increased effects with elevation of dose administration NSAIDs cause injury to liver, and this lead to increase in level serum ALT and AST has been associated with bile duct damage . Abnormal bile flow due to is disruption of transport pumps leading to cholestasis and jaundice that was other case leading to hepato toxicity [7]. There result are in agreement with [8]. Similar change were also noticed by [4] who referred that a significant inhibition of proliferation and induction of apoptosis occur when piroxicam is used in concentrations that exceed maximum recommended doses. Regarding the histochical changes observed in this study under piroxicam administration . These changes were consistent with those induced histopathologically for (G2), (G3) and (G4) groups, increasing evidence of hepatotoxicity suggests that these toxic metabolites can induce oxidative stress in the liver in rat [9]. Also these results are in agreement with [10] observed that the Piroxicam may caused liver toxicity by reduction of poly saccharine, and total protein in the liver tissue, the decrease in carbohydrate content may be due to increased stress in organs.

The result for kidney function showed increasing the level of blood urea creatinine and uric acid . Significant increase associated with renal damage which is the most common effect of this compared as mention in previous studies of [12, 13-14]. These result are in agreement with [10] who were attributed that the Piroxicam caused renal injury in the experiment animal mostly the damaging of Proximal convoluted tubules , on the other hand [11] said that these effects may be appeared because the drugs cause severe organ toxicities throng the metabolic activation to highly reactive free radicals including the superoxidase and oxygen reactive species. Also this result in agreement with [15] who reported that the administration of NSAIDs drug may cause renal papillary necrosis and other renal injury.

There were decreasing in Hb and PCV values this may be due to effect of Piroxicam in synthesis of DNA which effect on protein synthesis [16], due to side effect of piroxicam This result are in agreement with [20] after administration of some NSAIDs drugs.

And there was increasing in WBC value this results due to ,elucidate inflammatory response of WBC toward piroxicam, this result agreement with several previous studies [17,18-19] whose suggested that abundance of leucocytes are prominent response of body tissues facing any injurious impact, or may be cell when intake .

The results of our histological study was corresponded with biochemical (liver, and kidney functions) results, that the histological changes increased especially in (G3) and (G4) treated groups, so we observed, the pathogenesis of drug or toxin induced liver injury usually involves the participation of toxic metabolites, drug metabolites can undergo a variety of chemical reaction including covalent binding, depletion of reduced glutathione, oxidative stress with consequent effect on protein . These chemical can directly effect in organelles such as mitochondria, endoplasmic reticulum cytoskeleton and nucleus or may be indirectly the activation or inhibition of gene expression lead to cell death either through shrinking or apoptotic process or necrosis [21] and that cell death lead to liver injury.

Administration of Piroxicam produces pathological changes may lead to impaired liver function which interferes with secretion of plasma proteins , this lead to decreased blood osmotic pressure with subsequent decreased drainage of tissue which caused due to congestion, similar result were reordered [22-23] . Treated group of liver (G3) and (G4) showed congestion to the central vein and fatty changes in the cytoplasm of the hepatocytes, depletion of glycoprotein and increased inflammatory cell infiltration in the hepatocytes. Particularly in the group (G4).Similar degenerative changes were also noticed by [10]. Administration of Piroxicam caused peripheral hepatic necrosis may be due to loss of basophilic DNA of endoplasmic reticulum damaged [24] or may occur because significant increase in the level ALT and AST [23], These results be in agreement with [25]. Results also showed a remarkable cellular infiltration in the hepatic tissue the infiltration was caused due to increased permeability of blood vessels that occurs when the contraction of the endothelial cells of blood vessels in response to certain chemicals or as a result of lose of particles desmosomes, which lies between the endothelial cells, which allows the passage of blood vessels [26].When blood vessels expand caused the rush of inflammatory cells from the center to the periphery endothelial lining the blood of to find its away out of the vessel [27] The results of the present study accordance with the

previous studies such as that reported by [28-29]who used paracetamol indomethacin and diclofenac drugs in the treatment of rats.

The same results in kidney in treated group (G3),(G4) due to increasing of the drug concentrations in the blood is affected by capillary constriction leading to a decrease in glomerular filtration of that drug, this may affect the shrinkage of the glomerullus, these result were in agreement with previous results of [10]. Mechanisms for decreased glomerular filtration appear to involve capillary hydrostatic pressure and glomerular ultra filtration coefficient. Prominent features of tubular injury are initial necrosis of the terminal segment of the Proximal tubule with subsequent involvement of distal tube [30]. the histological changes increased especially in (G3) and (G4) treated groups, so we observed the tubular lesion were accompanied by invasion inflammatory cells to the intertubular tissues. Some of these external stressors apparently caused the tubular lesions, which may suggest that the main target of Piroxicam is the convoluted and collecting tubules, Similar finding had been presented by [12-31]. Histopathology examination showed that the Piroxicam causes severe damage in the kidney of rat, similar results were recorded by [32,10-14] who were attributed that the Piroxicam caused renal injury in the experimental animal mostly the damaging of the proximal convoluted tubules, these effects may be appeared because the drug inhibits both Na^+ transport- depended and Na^+- in depended adenosine triphosphate ATP utilization as well as mitochondrial oxidative phosphorelation in the renal proximal tubules. The results of the present study are in accordance with the previous studies such as that reported by [33,37-25]. who used indomethacin, Piroxicam, dicholenac drug in the treatment of rats.

Also in testes , the histological changes increased with the increasing of the constriction of piroxicam drug similar result were recorder by (34,29,14-25). Who were attributed that Piroxicam caused many histological alterations in the experimental animal mostly the damaging of seminiferous tubules .Also these effects could be appeared because the NSAIDs drugs inhibits of the cyclooxygenase enzyme (Cox) pathway, in addition reducing the production of prostaglandin (PGH,PGE,PGF)[38].

Apoptosis in germ cell, spermatogonia, primary spermatocytes and speranatids which showed in (G4) may reflect the disturbance of microenvironment of the sertoli cells that effect the protein synthesis, these protein are secreted in level in normal testes during spermatids elongation and spermation. [35].Also this result are in agreement with[36]who referred that the indomethacin may caused germ cells apoptosis, degeneration deplete in number of seminiferous tubules due to ability of the drug inhibiting prostoglandin synthesis.

References

1. Zvaifler, NJ. **1988**. New perspectives on the pathogenesis of rheumatoid arthritis. *Am J Med*, **85**: 12.
2. Cooke, JD., Scudamore, RA. **1989**. Studies on the pathogenesis of rheumatoid arithritis. *Br J Rheumatol*, **28**: 243.
3. Insel, PA. **1991**. *Analgesic- antipyretics and antiinflammatory agents*: Drugs employed in the treatment of rheumatoid arthritis and gout. Gilman AG, Rall TW, Nies AS, Taylor P, editors. The Pharmacological Basis of Therapeutics. 8th ed. New York: Pergamon press; 638.
4. Knottenbelt, C., Chambers, G., Gault, E., Argyle, DJ. **2006**. The in vitro effects of piroxicam and meloxicam on canine cell lines. *J Small Anim Pract*, **47**(1): 14-20.
5. Humson, C. L. **1972**. *Animal tissue techniques*, 3rd ed, W.H. Freeman company, 641pp.
6. Miura, S., Suematsu, M., Tanaka, S., Nagata, H., Houzawa, Sl., Suzuki, M., Kurose, I., Serizawa, H. and Tsuchiya, M. **1991.** Microcirculatory distrubance in indomethacin- induced intestinal ulcer. *Am J Physiol*. **24**: 213–309.
7. Duncan, J. R., Prasse, K. W. and Mahaffey, E. A. **1994**. *Veterinary Laboratory Medicine. Clinical Pathology*. 3rd Ed. Iowa State University Press, Ames, Iowa.
8. Lapeyre-Mestre, M., de Castro, AM., Bareille, MP., Del Pozo, JG., Requejo, AA., Arias, LM., Montastruc, JL., Carvajal, A. **2006**. Non-steroidal antiinflammatory drug-related hepatic damage in France and Spain: analysis from national spontaneous reporting systems. *Fundam Clin Pharmacol*, **20**(4): 391-395.
9. Chen, X., Xu, j., Zhang, C.,Y4, T. and Wang, G. **2011**. The protective of deoxychdic acid on isoniazid plus rifampicin induced liver injury in mice. *Eur. J. Pharmacol*. **659**: 53-60.

10. Ebiad, H., Dkhil, M., Danfour, M., Tohamy, A. and Gabry, M. **2007**. Piroxicam induced hepatic and renal histopatholo -gical changes in mice. *L.J.M*., **2**(2): 82-89.
11. Abrahams, C., Levinson, E. **1970**. Ultrastructure of the renal papilla in experimentally induced analgesic nephritis in rats. *S Afr Med H*., **44**(3): 63–65.
12. El-Banhawy, MA., Mohallal, EM., Hamdy, MH., Attia, TNN. **1992**. The toxic impacts of the narcotic drug (flunitrazepam) on the rat kidney tissues. *Zaq J Med Physiol*. **1**(3): 233–239.
13. Ibrahim, MA. **1999**. A study of the histochemical changes in some mammalian tissues induced by a NSAID (Diclofenac). M.Sc. Thesis. Fac Sci Helwan Univ.
14. Modi, C. M., Mody, H. B., Patel,G. B., Dudhatra,G. B., Kumar, A. and Avale, M. **2012**. Toxico pathological overview of analgesic anti inflammatory drug in animals. *J. of Applied pharmaceulical Sience*, **2**(1): 149-157.
15. Jameson, J. Larry, and Loscalzo, Joseph. **2013**. *Harrisons Nephrology and Acid-Base Disorders.* 2nd Edition McGraw-Hill Medical, 978-0-07-181497-3.
16. Hechtman, DH., Kroll, MH., Gimbrone, MA. Jr., Schafer, AI. **1991.** Platelet interaction with vascular smooth muscle in synthesis of prostacyclin. *Am 1 Physiol*, **260**: H1544-H1551.
17. Miura, S., Suematsu, M., Tanaka, S., Nagata, H., Houzawa, Sl., Suzuki, M., Kurose, I., Serizawa H. and Tsuchiya, M. **1991.** Microcirculatory distrubance in indomethacin- induced intestinal ulcer. *Am J Physiol*. **24**: 213–309.
18. El-Banhawy, MA., Ilham, IS., Mohamed, AS., Ramadan, AR. **1994**. The toxic impacts of the anti-inflammatory drug (Indomethacin) on the mice kidney tissues. *J Egypt Ger Zool*. **14**(C): 177–201.
19. McCafferty, D., Granger, DN. and Wallace, JL. **1995**. Indomethacin-induced gastric injury and leukocyte adherence in arthritic versus healthy rats. *Gastroenterol*. **109**: 1173–1180.
20. Abatan, M. O., Lattef, I. and Taiwov, O. **2006**. Toxic effects of non-steroidal Anti-inflammatory Agents in Rats. *African Journal of Biomedical research*. **9**: 219-223.
21. Knapp, DW., Glickman, NW., Widmer, WR., DeNicola, DB., Adams, LG., Kuczek, T. et al. **2000**. Cisplatin versus cisplatin combined with piroxicam in a canine model of human invasive urinary bladder cancer. *Cancer Chemother Pharmacol*, **46**: 221–226.
22. Lacroix, I., Lapeyre-Mestre, M., Bagheri, H., Pathak, A., Montastruc, JL. **2004**. Nonsteroidal antiinflammatory drug-induced liver injury: a casecontrol study in primary care. *Fundam Clin Pharmacol*. **18**(2): 201-206
23. Young, B., Stewart, W. and Odowd, D. **2011**. Wheater's basic pathology a text attas and review of histopathology. 15thed. Interanational edition. PP 174-175.
24. Schaumloffel, N. and Gebel, T. **1998**. Heterogenicity of the DNA damage Provoked by antimony and arsnic. Mutagensis. **13**(3): 281-286.
25. Clària, J. **2005**. Safety of short-term administration of celecoxib in decompensated cirrhosis. *Hepatology*, **42:** 238.
26. Cotran, R. S, Kumar,V. and Colline, T. **1999**. *Morphological features of a poptosis in: Robin pathology basis of Disease*. Ch.1,6th edn., W.B Saunders co., pp:1-30.
27. Kumar, V, Abbas, A.K., Fausto, Nand, and Mitchell, R.N. **2007**. *Robbins Basic Pathology*. 8th ed. Saunders Elsevier., PP:2,9, 632-634.
28. Mohamed, AD. **1999**. Histological and cytogenetic effect of piroxicam induced in vivo mammalian system. M.Sc. Thesis. Egypt: Helwan University.
29. Subramanian, S. **2009**. Diclofenac induced toxic manifestation on adjuvant induced arthritic rats pheripheral and reproductive organ of male wistar rats rattus norvegicus. *J.of Toxicology & Envi - ronmental Health Sciences*. **1**(1): 12-21.
30. Diamod, G.L. **1989**. Biological consequenced Soluble form of natural uranium-Radiation protection, *Dosimen try*. **26**: 23-33.
31. Al-Thani, AS. **1993**. The side effects of chloramphenicol on some histological, histochemical and ultra-strucutral aspects of the liver and kidney of the white rat Ph.D. Thesis. Faculty of Science. Cairo, Egypt: Ain Shams University.
32. Chen,X., Xu, J., Zhang,C., Y4, T. and Wang, G. **2011**. The protective of deoxychdic acid on isoniazid plus rifampicin induced liver injury in mice. *Eur. J. Pharmacol*. **659**: 53-60.
33. Bach, P.H. **1997**. The renal medulla and distal nephron toxicity, in sipes IG, McQueen CA, Gandolfi A J, (eds): Comprehensive Toxicology, Vol. 7. Oxford England Elsevier, pp279-298.

34. Peti-Peterdi, J., Komlosi, P., Fuson, A.L., Guan, Y., Schneider, A., Qi, Z., Redha, R., Rosivall, L., Breyer, M.D., Bell, P.D. **2003**. Luminal NaCl delivery regulates basolateral PGE2 release from macula densa cells. *J. Clin. Invest.*, **112**: 76–82.

35. Saeed, S., Anwar, N., Khan, M. and Sarfras, N. **2009**. Effect of chronic treatment with cyclooxygeneas inhibiter on reproductive male rat. *J.Aub.Med .Coll .Abottabad*, **21**(3): 66-71.

36. Manivannan, B., Mittal, R., Goyals, S., Ansari, AS. And Lohiya, NK. **2009**.Sperm charac- teristics & ultrastructure of testis after long- term treatment with the methanol sub fraction of carica papaya seeds . *Asian J. Androlo*., **11**: 583-599.

37. Mogliner, J., Lurie, M., Coran, A., Nativ, O., Shiloni, E. and Sukhotnik, I. **2006**. Effect of diclofenac on germ cells apoptosis following testicular ischemia – reperfusion injury in rat. Pediatri. *Surgury Int*.**22**: 99-105.

38. Singh, S.K., Srivastawa, A.K and Kumar, S. **2011**. Diclofenac toxixity in experimental Japanese quails-egg quality and pathological studies. *Induan, J, Veter pathology*. **3s**(1):102-107.

39. Beak, S.G., Willson, L.G., Lee, C. and Eling,TE. **2002**. Dual function of NSAIDs in inhibition cyclooxygeneas and induction NSAIDs – activated gene. *J.P.ET*., **301**: 1126 -1131.