Histopathological Changes in Some Internal Organs Of White Mice Due To Treatment With Pentoxifylline

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Summary

The aim of the study was to make knowledge on the histopathological changes in some internal organs (liver, kidney and spleen) of albino mice after treatment with therapeutic dose(16mg/kg BW/day) of pentoxifylline (PTX). Thirty albino mice which are approximately at same age (8week) and body weight were, randomly divided into three equal groups, group 1:Received tape water along the period of experiment and considered as a control group, Group 2:Treated with Pentoxifylline (16 mg /kgBW/day)for 30 days Group 3:Treated with Pentoxifylline (16 mg/kgBW/days)for 60 day. The histopathological findings of liver, kidney and spleen, showed infiltration of mononuclear cells within the liver parenchyma and portal areas and in the interstitial tissue of the kidney with perivascular lymphocytic cuffing and mild degenerative changes represented by acute cellular swelling of hepatocytes and epithelial cells lining the cortical renal tubules in addition to congestion of blood vessels Spleen showed lymphoid hyperplasia of white pulp with congestion and infiltration of lymphocytes in red pulp.

Key words: Pentoxifylline, mononuclear cells , lumen system, spleen, liver, kidney.

دراسة التغيرات المرضية النسجية في بعض الاعضاء الداخلية للفئران المهقاء بعد المعالجة بعقار البنتوكسفيلين

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الخلاصة

هدفت الدراسة الى معرفة التغيرات المرضية النسجية لبعض الاعضاء الداخلية (الكبد, الكلية والطحال في الفئران المهقاء بعد اعطاء الجرعة العلاجية لعقار البنتوكسفيلين(16ملغم\كغم وزن الجسم) اجريت التجربة على 30 فار ابيض بعمر 8اسابيع وذات اوزان متقاربة. قسمت الحيوانات الى ثلاثة مجاميع متساوية وكما ياتي:المجموعة الاولى اعطيت ماء شرب وعدت مجموعة سيطرة المجموعة الثانية جرعت 16 ملغم\كغم من وزن الجسم من عقارالبنتوكسفيلين ولمدة 30 يوم المجموعة الثالثة جرعت 16ملغم\كغم من وزن الجسم من عقار البنتوكسفيلين ولمدة 60يوم لقد اظهر الفحص المجهري للاعضاء الداخلية (الكبد الكلية الطحال) ارتشاح بؤري للخلايا وحيدة النواة في متن الكبد والباحات البابية والنسيج الخلالي للكلية مع حصول استكفاف لمفاوي حول الاوعية

الدموية مع حصول بعض التنكسات الطفيفة متمثلة بالتورم الخلوي الحاد لكل من خلايا الكبد والخلايا المبطنة للنبيبات الكلوية للقشرة اضافة الى احتقان الاوعية الدموية اما الطحال فقد اظهر فرط التنسج اللمفاوي للب الابيض مع احتقان اللب الاحمر وارتشاحه بالخلايا اللمفاوية.

Introduction

Pentoxifylline (PTX) is an orally active hemorheological agent for the treatment of peripheral vascular disease cerebrovascular disease and a number of other conditions involving a defective regional microcirculation (1). It acts primarily by improving red blood cell deformability reducing blood viscosity and by decreasing the potential for platelet aggregation and thrombus formaton (2). PTX is also used in the treatment of male infertility in human by enhancing sperm motility both in vivo and in vitro (3and4) in cases of normozoospermia and asthenozoospermia (5). Also administration of (PTX) cause elevation in the values of reproductive hormones and increase folliculogenesis and improve ovulation in female mice (6). Like other methylated xanthine derivatives PTX is both a competitive nonselective phosphodiesterase inhibitor (7). Which raises intracellular cAMP activates protein kines (PKA) and inhibits TNF-alpha (8) and leukotriene synthesis and reduce inflammation (9). Furthermore the phosphodiesterase inhibitor (PTX) exerts multiple beneficial immunomodulatory effects in states of hyperinflammation (10). It seems that inflammatory cytokines specially tumor necrosis factor alpha (TNF-a) which were produced by activated macrophage**s** have an important role in pathology of endometriosis based on this theoryant TNF- drugs like PTX are suggested as new drugs for endometriosis (11and 12), little to our knowledge has attempted to show the pathological changes in internal organs. Therefore the aim of this study is to accomplish this task and study the pathological changes in liver kidney and spleen.

Materials and methods

Thirty albino mice (Age 8 weeks) and were weighed(25-52gm) divided into three equal groups. The first group treated orally with tape water and considered as control. The second group treated orally with 16mg/kgBW/day for 1 month. The third group treated with16mg/kgBW/day for 2months. Trental® is presented in the form of coated tablets containing 400mg (Aventis USA)160 mg of the coated tablets were dissolved in 100 ml of tap water to obtain a stock solution from which 01 ml was given orally to each 10 gm of living body weight of the experimental mice. This amount of the solution will provide a dose of 16 mg/kg BW/ day of the drug .This dose was individually adjusted according to body weight of each animal and

given via a fine plastic stomach tube. After 1and 2month mice of all experimental groups were sacrificed under anesthesia. Tissue specimens' from liver, kidney and spleen were taken for histopathological examination using 10% neutral buffered formalin as a fixativethen processed routinely in histokinettecut at5µm thickness by rotine microtome and stained with hemotoxylin and eosin stain then examind under light microscope (14). After 2 month animals of group 3 were dissected in the same manner as those sacrified after 1month

Results and Discussion

Histopathological findings:-

Control group:- There are no Pathological changes present in the liver kidney and spleen.

Treated group (One month period):

Liver:- Dilation and congestion of central veins with kupffer cells proliferation and acute cellular swelling of hepatocytes (figure1), were aggregation of mononuclear cells beside the central vein (figure 2).

Kidney:- Acute cellular swelling of epithelial cells lining of cortical and medulla renal tubules (figure3), perivascular cuffing of renal blood vessel (figure 4).

Spleen:- Moderate hyperplasia of lymphoid tissue of white pulp(Figure5) and infiltration of lymphocytes within the blood sinuses of red pulp

Treated group (Two month period):

Liver:- Focal infiltration of mononuclear cells within the parenchyma (figur6), infiltration of mononuclear cells in the portal areas around the bile ductules and portal vessels (figure7).

kidney:- Focal infiltration of mononuclear cells within the interstitial tissue and in periglomerular area (figure8).

Spleen:- Moderate hyperplasia of lymphoid tissue of white pulp (with infiltration of lymphocytes Within the blood sinuses of red pulp.

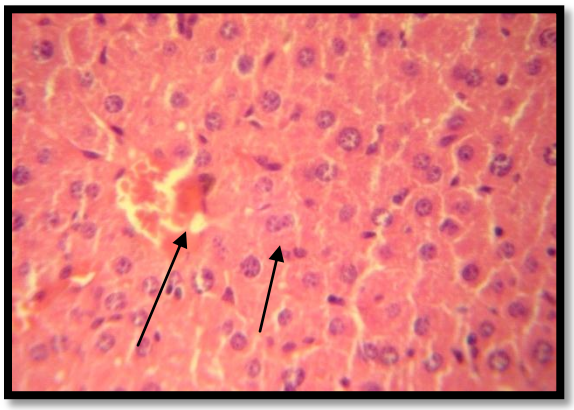


Figure 1: Histopathopathological section of the liver of the mouse treated with 16mg/kgbw of pentoxifylline for1month showing dilation and congertion of central veins(⟶) with kupffer cell prolifration (⟶) (H&EX40)

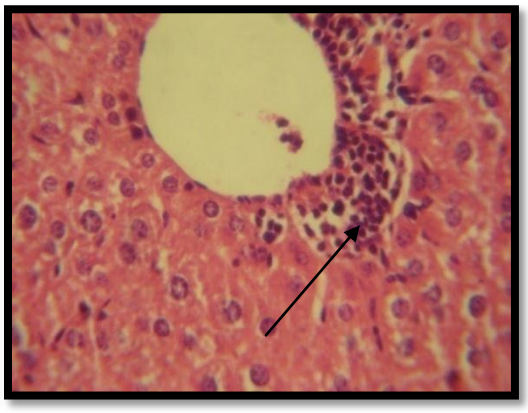


Figure 2: Liver of mouse treated with 16mg/kgbw of pentoxifylline for1month showing aggregation of mononuclear cells beside the central vein (⟶) (H&EX40).

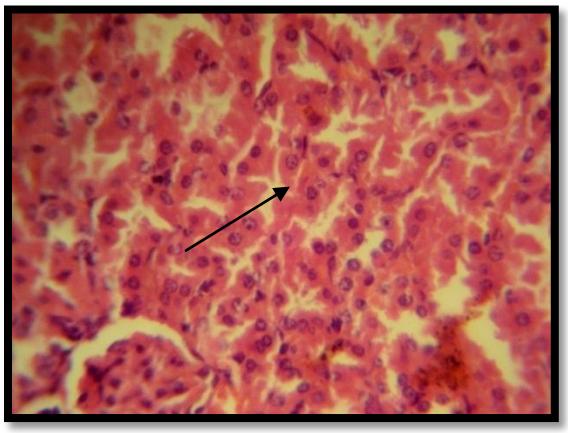


Figure 3: Kidney of the mouse treated with16mg/kgbw for 1month showing acute cellular swelling of epithelial cells lining of cortical and medula renal tubules (⟶) (H&EX40)

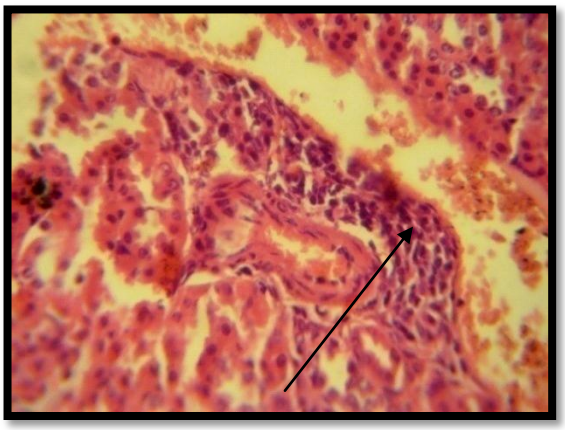


Figure4: Kidney of the mouse treated with 16mg/kgbw of pentoxifylline for 1month showing perivascular cuffing(⟶) (H&EX40)

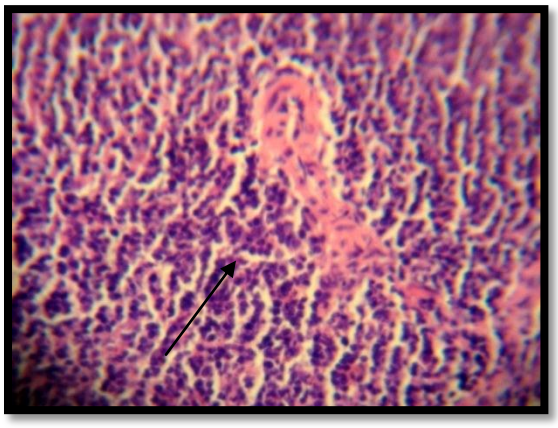


Figure5: Spleen of mouse treated with 16mg/kg bw of pentoxifylline for1month showing moderate hyperplasia of lymphoid tissue of white pulp (⟶) (H&EX40)

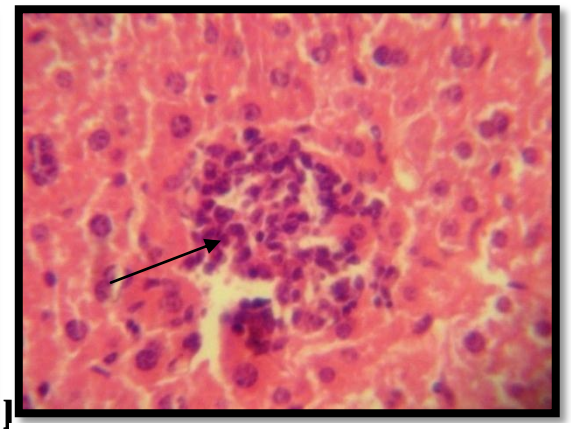
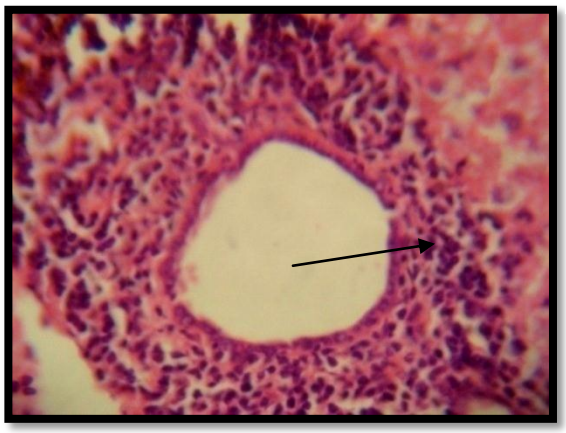
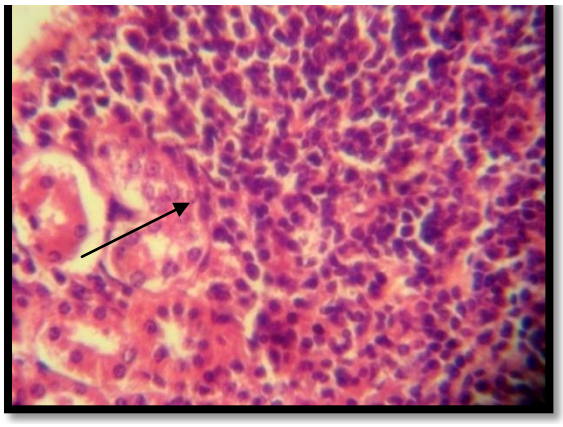


Figure 6: Liver of mouse treated with 16mg/kgbw of pentoxifylline for2month showing infiltration of mononuclear cells within parenchyma(⟶) (H&EX40)



Fgure7: Liver of mouse treated with 16mg/kg bw of pentoxifylline for 2month showing infiltration of mononuclear cells in portal areas around the bile ductules (⟶) (H&EX40)



Fgure8 : Kidney of mouse treated with 16mg/kg bw of pentoxifylline for 2month showing infiltration of mononuclear cell within the interstitial tissue and in periglomerular area(⟶) (H&EX40)

Focal infiltration of mononuclear cells and perivascular cuffing were seen in liver and kidney of treated groups of both duration of exiperimentThese results indicate that PTX increase the defense mechanism and immune response and that agreed with several studies explained (10,11and 12), that PTX which is phosphodiesterase inhibitor has immunodulatory effects in addition to its bettier known rheologic effects (14), and can work as a pharmacological immune adjuvant (15). However, the exact mechanism of action still remains exclusive and the clinical effects of PTX cannot be reliably predicted (16). In common clinical use PTX enhances long –term persistence of T cells response including protective response to a bacterial

immunogen *Salmonella Typhimurium*via a cAMP- dependent protein kinase A-mediated effect on T cells if given to mice for a brief period during immunization PTX inhibits activation – mediated loss of super antigen-reactive CD4 as well as CD8 T cells in vivo without significantly affecting their activation and inhibits activation induced death and caspase induction in stimulated CD4 as well as CD8T cells in vitro without preventing the induction of activation markers consistent with this ability to prevent activation-induced death is not only CD4 but also CD8T cells PTX also enhances the persistence of CD8T cells response in vivo. Thus, specific inhibition of activation-induced T cells apoptosis transiently during immune priming is likely to enhance the persistence of CD4 and CD8T cells response to vaccination and pharmacological modulators of the cAMP pathway already in clinical use can be used for this purpose as immunological adjuvents (15). Small granulomatous lesion in liver were seen in the 3 rd group. That may attributed to central role of the liver in transforming and clearing chemicals and the susceptibility to the toxicity for these agents.

In addition to the dose relationship with the GI tract since 70% of blood coming to the liver arrives directly from G1 organs which bring drugs in near-undiluted (17). Stated that certain medicinal agent when taken in over doses and sometimes even when introduced within therapeutic range may injury the organ and they refer that more than 900 drugs has been implicated in causing liver injury.

The proliferation of kupffer cells may be related to their function against blood materials entering the liver. Furthermore (18) identified a receptor present in kupffer cellsthe complement receptor of the immunoglobulin family (CRIG)and is a critical component of the innate immune system.

The marked hyperplasia of spleen white pulp may be due to increased mitotic index of splenocyte during immune response (19). PTX may act as immune stimulation and increased splenocyte proliferation. There is mild degenerative changes (acute cellular swelling hepatocytes and epithelial cell lining the proximal and distal convoluted tubules of kidney) by (20). Many chemicals damage mitochondria, its and releasing excessive amount of oxidents which in turn injure hepatic cells and interfere with activity of some enzymes in the cytochome P-450 system such as CYP2EI also lead to oxidative stress.

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