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Study the Toxic Effect of Different Doses of Duprost in Liver and Blood of Albino Mice

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Abstract

The aim of this study is to investigate the effect of different doses of Duprost in the liver and blood of albino mice. The current study included twenty one albino mice, obtained and grouped into 3 groups: control (3 mice), acute group (12 mice) and chronic group (6 mice). The acute group was subdivided into 4 groups and each group of 3mice, was given a lonely oral dose of (0.25ml, 0.15ml, 0.1 ml and 0.05ml respectively) for 24 hours. Whereas the third group was subdivided into 2 groups and each set was given a daily dose of (0.15ml and 0.05 ml respectively) for 30 days. After the mentioned periods, blood samples from each animal were taken for blood analysis. Then, the mice of all groups were sacrificed and the livers were removed, processed, sectioned and stained for histological analysis. In acute group, all mice that dosed with (0.25 ml) dose, died after 15 minutes of dosing. Blood results showed significant decrease in Hb level, WBC's and platelets' count among acute subgroups in comparison with chronic subgroups which showed significant increase in WBC and platelets' count, but a significant decrease in Hb levels. The histological analysis of liver in acute subgroups showed different forms of liver inflammation among acute subgroups, in comparison with chronic subgroups which showed formation of granulomatous lesions in the liver parenchyma in high dose(0.15ml) but there were inflammatory cells' aggregation in liver parenchyma among lower doses.

Keywords: *Benign prostatic hyperplasia, duprost, dutasteride*

دراسة التاثير السمي للجرع المختلفة من عقار Duprost في كبد ودم الفئران البيض

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الخلاصة

تهدف هذه الدراسة الى التحري عن تاثير الجرع المختلفة من عقار Duprost في كبد ودم الفئران البيض. شملت الدراسة 21 فارا تم تقسيمها الى ثلاث مجاميع هي : مجموعة السيطرة (3) فئران، مجموعة الاصابة الحادة (12) فأرا والتي قسمت بدورها الى 4 مجاميع ثانوية اعطيت كل مجموعة منها جرعة فموية واحدة من الحجوم التالية (0.25ml, 0.15ml, 0.1 ml, 0.05ml على الترتيب) لمدة 24 ساعة. اما المجموعة الثالثة مجموعة الاصابة المزمنة ضمت (6) فئران والتي قسمت بدورها الى مجموعتين ثانويتين كل منهما ضمت 3 فئران وتم تجريعها يوميا بجرعة فموية واحدة من الجرع التالية (0.15ml, 0.05ml) لمدة 30 يوم. بعد انقضاء المدة المحددة لكل مجموعة تم سحب عينات الدم من كل فأر لاجراء التحاليل المختلفة

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وايضا تم تشريح الحيوانات واستخراج الكبد وتقطيعه الى شرائح وتصبيغها لغرض الدراسة النسيجية. اظهرت نتائج مجموعة الاصابة الحادة موت جميع الفئران التي جرعت بجرعة (0.25 ml) من الدواء بعد 15 دقيقة من التجريع. بينما اظهرت نتائج الدم حدوث انخفاض معنوي في مستوى الهيموغلوبين وكذلك تعداد الكريات البيض والصفيحات الدموية في مجموعة الاصابة الحادة مقارنة بمجموعة الاصابة المزمنة التي اظهرت ارتفاعا في مستويات الكريات البيض والصفيحات بينما كان هناك انخفاض في مستوى الهيموغلوبين فيها. اما نتائج الدراسة النسيجية في مجموعة الاصابة الحادة فقد اظهرت وجود اشكال مختلفة من الالتهاب في نسيج الكبد بين مجاميعها الثانوية بمجموعة الاصابة المزمنة التي اظهرت وجود اورام حبيبية في النسيج الحشوي للكبد عند الجرع العالية من الدواء في حين كان هناك تجمع للخلايا الالتهابية عند الجرع الاوطأ.

Introduction

Benign prostatic hyperplasia (BPH) is a common cause of difficult lower urinary tract symptoms. It is a condition of enlargement of the prostate which is common among aging men, with an incidence of 90 % by the age of 85 years [1].

This illness is a progressive condition, with growth in prostate size accompanied by lower urinary tract symptoms that can result in long-term complications and need for enlarged prostate-related surgery [2]. Current pharmacologic treatment options include alpha-blockers (like: alfuzosin, doxazosin, tamsulosin, and terazosin) and 5-alpha-reductase inhibitors (5ARIs) (include finasteride and dutasteride) [3].

Duprost (scientific name: Dutasteride) capsules (0.5mg) are used to treat BPH. This medicine helps to shrink the prostate and reduce the risk of urinary retention caused by restricted urine flow as the prostate gland becomes enlarged and presses against the urethra which helps urine to flow more easily, prevents urine backlog in the bladder and restores bladder control [4]. This drug is also used to treat male pattern hair loss by increasing hair growth and preventing further hair loss from all areas of the scalp, including the front [5].

The active ingredient Dutasteride inhibits the action of both forms (type I and type II) of the enzyme 5α-reductase that convert the male hormone testosterone to dihydrotestosterone (DHT) in the skin and the liver [6]. DHT is the androgen primarily responsible for development and growth of the prostate gland and also causes BPH.

The action of Dutasteride is to reduce the levels of DHT in the blood, so that prostate growth is no longer stimulated in men with BPH allowing the enlarged prostate to shrink [7].

DHT, which is also found in hair follicles, is responsible for hair loss, as it causes hair follicles in the scalp to gradually shrink producing smaller and thinner hairs, which eventually do not emerge from the follicle; therefore Dutasteride reverses the balding process as it blocks the buildup of DHT in the hair follicles of the scalp, allowing the hair to grow normally [8].

The most commonly reported side effects when taking this drug includes: temporary impotence (whilst continuing on treatment) and low libido. Less common side effects include breast tenderness and enlargement (gynecomastia) and itchy skin rash, while the effect of this brand on liver is not studied [9, 10]. The aim of this study is to investigate some hematological and histological changes in the blood and liver of mice dosed orally with different doses and concentrations of Duprost.

Materials and methods

1. Experimental Animals

Twenty one, 6-week-old male mice, weight 20-25gm were purchased from National Center for Drug Control and Research in Baghdad, and kept under standardized environmental conditions; constant temperature, moisture and with a 12-hr. light regime without stress factors. Mice were allowed to take laboratory food and water.

2. Design of the study:

Mice were randomized into three groups, and treatment was carried out according to the following groups:

A. Group I: Control Group**;** contains 3 mice, received standardized lab food and water without treatment.

B. Group II: Acute group; contains 12 mice, divided into 4 subgroups of 3 mice per each, received a lonely oral dose of following doses:

- Subgroup1: dosed orally with 0.25ml (0.5mg\kg) of drug, all died after 15 minutes of dosing.
- Subgroup2: dosed orally with 0.15ml (0.12mg\kg) of drug.
- Subgroup3: dosed orally with 0.1 ml (0.08mg\kg) of drug
- Subgroup 4: dosed orally with 0.05ml (0.04mg\kg) of drug.

After 24 hours of dosing, 1 ml of blood was obtained from each mouse in last three subgroups by heart puncture. Then, mice were euthanized; livers were carefully removed and fixed in 10% buffered formaldehyde solution. Then, the fixed biopsies were embedded in paraffin and cut into 5µm slices. The slices were mounted on glass slides and stained with hematoxylin and eosin for histological analysis. The images were examined under light microscope.

C. Group III: Chronic group; contains 6 mice, divided into 2 subgroups of 3 animals per each, received one daily oral dose of following doses:

- **Subgroup1:** dosed orally with 0.15ml (0.12mg\kg) of drug per day, one of them died after the fifth dose while the second died after 21 days of dosing.
- **Subgroup2:** dosed orally with 0.05ml (0.04mg\kg) of drug per day.

During the dosing period, all mice were observed behaviorally and morphologically, and notes were recorded. After 30 days of dosing, the residual mice were sacrificed as done with acute groups; 1 ml of blood was obtained from each mouse by heart puncture as well as the livers for histological study.

3. Statistical Analysis

The Statistical Analysis System (SAS, 2012) program was used to effect of difference factors in study parameters. Least significant difference (LSD) test was used to significant comparison between means in this study. Statistical tests were approved by assuming a null hypothesis of no difference between variables, a probability was considered statistically significant when P values ≤ 0.05.

Results

During the dosing period, mice of chronic subgroups seemed to have appetite & weight loss, as well as aggressive behavior.

I: Blood Analysis:

a) Acute group:

Results of blood examination of acute group showed a significant decrease of Hemoglobin (Hb) levels among subgroups; 0.05ml (12.00gm\100ml±0.52), 0.1 ml (11.30 gm\100ml±0.62) and 0.15 ml (11g\100ml ± 0.37). As well as, there was a high significant decrease in WBC count; 0.05ml (7.80 cell\mm^3 ± 0.32); 0.1 ml (5.90 cell\mm^3±0.21); 0.15ml (3.10cell\mm^3±0.27). Furthermore, there were a significant decrease in Platelets' count; 0.05ml(84.00 cell\mm^3±2.91); 0.1ml(80.00 cell\mm^3 ± 3.68);0.15 ml(63.00 cell\mm^3 ± 2.56) among subgroups, with significant differences (P<0.05; P<0.01) when compared with levels of control group (Table- 1).

Table1- Comparison of Hb, WBC and Platelets' counts among acute subgroups.

Groups	Mean ± SE		
	Hemoglobin (gm/100 ml)	WBC count cell\mm^3.	Platelets count cell\mm^3.
Control	13.60 ±0.49	7.90 ± 0.52	220.00±18.46
0.05	12.00 ±0.52	7.80 ± 0.32	84.00 ± 2.91
0.1	11.30 ±0.62	5.90 ± 0.21	80.00 ± 3.68
0.15	11.00 ± 0.37	3.10 ± 0.27	63.00 ± 2.56
LSD value	2.054 *	2.107 **	52.926 **
P-value	0.0461*	0.0109**	0.0026**
* (P<0.05), ** (P<0.01)			

Additionally, results of differential count of WBC among acute subgroups showed significant decrease of granulocytes' count (0.05ml: 4.6 % ± 0.33 ; 0.1ml: 3.6 % ± 0.26 ; 0.15ml: 3.0 % ± 0.19) and lymphocytes' count(0.05ml: 83.1% ± 3.42; 0.1ml: 83.5% ± 3.26; 0.15ml: 75.7% ± 2.09) in comparison with control group (7.6% ± 0.52 and 90.6% ± 3.69) respectively. But there was a significant increase in Monocytes' count(0.05ml: 12.3% ± 0.16; 0.1ml: 12.9% ± 0.22; 0.15ml: 21.3% ± 0.35) when compared with control group (1.8 ± .04) as shown in (Table- 2).

Table 2-Comparisons of Differential WBC count among acute subgroups.

Groups	Mean ± SE		
	Granulocytes %	**Lymphocytes %**	**Monocytes %**
Control	7.6 ± 0.52	90.6 ± 3.69	1.8 ± .04
0.05	4.6 ± 0.33	83.1 ± 3.42	12.3 ± 0.16
0.1	3.6 ± 0.26	83.5 ± 3.26	12.9 ± 0.22
0.15	3.0 ± 0.19	75.7 ± 2.09	21.3 ± 0.35
LSD value	2.063 *	8.225 *	4.578 *
P- value	0.0496*	0.0372*	0.0335*
* (P<0.05).			

b) Chronic group:

As illustrated in (Table- 3), results of blood tests showed significant decrease of Hb levels among chronic subgroups (0.15ml: 9.33gm\100ml ± 0.48; 0.05ml: 10.00gm\100ml ± 0.52) when compared with control group (12.60 ± 0.67). While there were significant increases in WBC count (0.15ml: 13.20 cell\mm^3 ± 0.58; 0.05ml: 6.53 cell\mm^3 ± 0.26) as well as in platelets' count (0.15ml: 410.00 cell\mm^3 ± 17.92; 0.05ml: 240.52 cell\mm^3 ± 15.84) when compared with control group (6.200 cell\mm^3 ± 0.09and 125.00 cell\mm^3 ± 8.63)respectively.

Table 3-Comparison of Hb, WBC and Platelets' counts among chronic subgroups.

Groups	Mean ± SE		
	Hemoglobin(Hb)(gm/100ml)	**WBC count cell\mm^3**	**Platelets count cell\mm^3**
Control	12.60 ± 0.67	6.200 ± 0.09	125.00 ± 8.63
0.15	9.33 ± 0.48	13.20 ± 0.58	410.00 ± 17.92
0.05	10.00 ± 0.52	6.53 ± 0.26	240.52 ± 15.84
LSDvalue	1.882 *	4.632 **	63.266 **
P-value	0.0438*	0.0441*	0.0011**
* (P<0.05), ** (P<0.01).			

Moreover, results of differential count of WBC among chronic subgroups showed significant increase in neutrophil's count(0.05ml: 72.08% ± 2.48; 0.15ml: 75 % ± 3.59) in comparison with control group (23% ± 1.86), while there was high significant decrease in lymphocytes' count(0.05ml: 23.37% ± 1.72; 0.15ml: 23% ± 2.42) in comparison with control group (74% ± 4.62). In other hand, there was significant elevation of monocytes' count in 0.05 ml group as shown in (Table- 4).

Table 4- Comparisons of Differential WBC count among chronic groups.

Groups	Mean ± SE			
	Neutrophil%	**Lymphocyte%**	**Monocyte%**	**Eosinophil%**
Control	23.00 ± 1.86	74.00 ± 4.62	1.00 ± 0.006	2.00 ± 0.008
0.05	72.08 ± 2.48	23.37 ± 1.72	3.67 ± 0.05	1.33 ± 0.002
0.15	75.00 ± 3.59	23.00 ± 2.42	1.00 ± 0.005	1.00 ± 0.00
LSD value	12.674 **	9.526 **	1.724 *	1.245 NS
P-value	0.0113**	0.0037**	0.0437*	0.094NS
* (P<0.05), ** (P<0.01), NS: Non significant.				

II. Histological analysis:

1. Normal structure of liver:

The parenchymal cells of livers are hepatocytes. These polygonal cells are joined to one another in plates, with borders that face either the sinusoids or adjacent hepatocytes. Hepatocytes make contact with blood sinusoids, which are distensible vascular channels lined with highly fenestrated endothelial cells and populated with phagocytic Kupffer cells [11] (Figure-1).

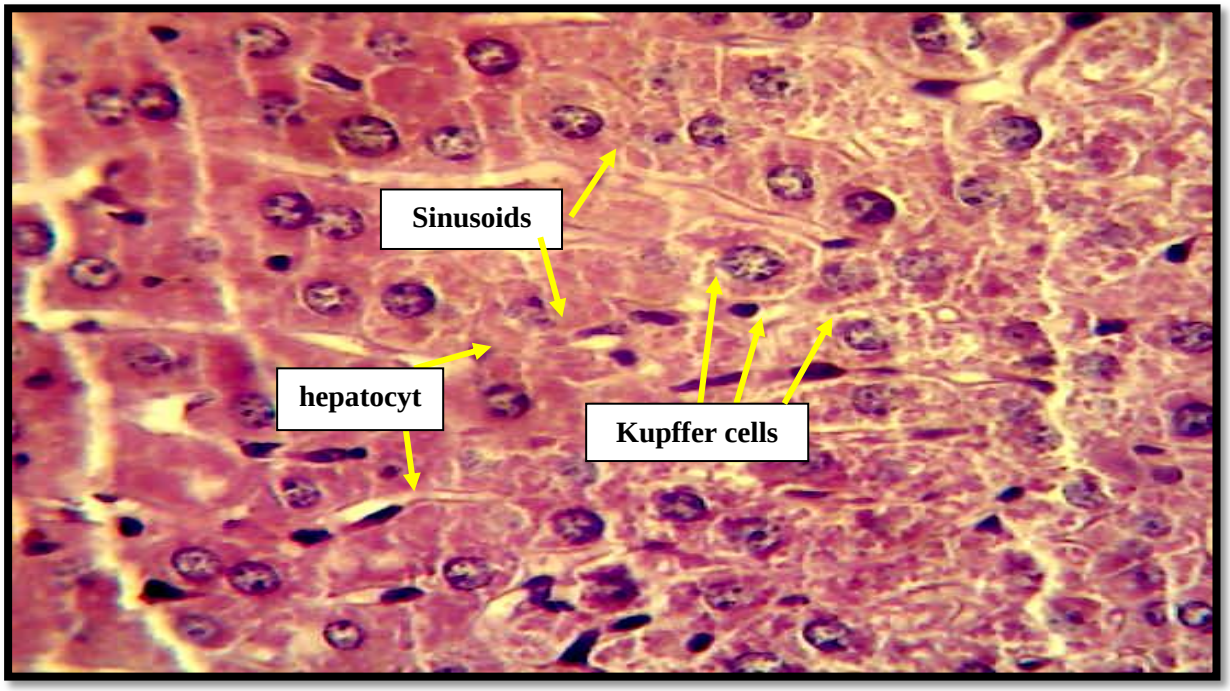

Figure 1- Section in the liver from control mice shows normal structure(H&E stain 400X)

2. Histological changes of liver in acute subgroups:

a) Effect of 0.15ml dose of Duprost:

The section of liver obtained from mice dosed with 0.15 ml of duprost after 24hrs, showed mononuclear inflammatory cell infiltrates into hepatic parenchyma and proliferation of kupffer cells (Figure- 2).

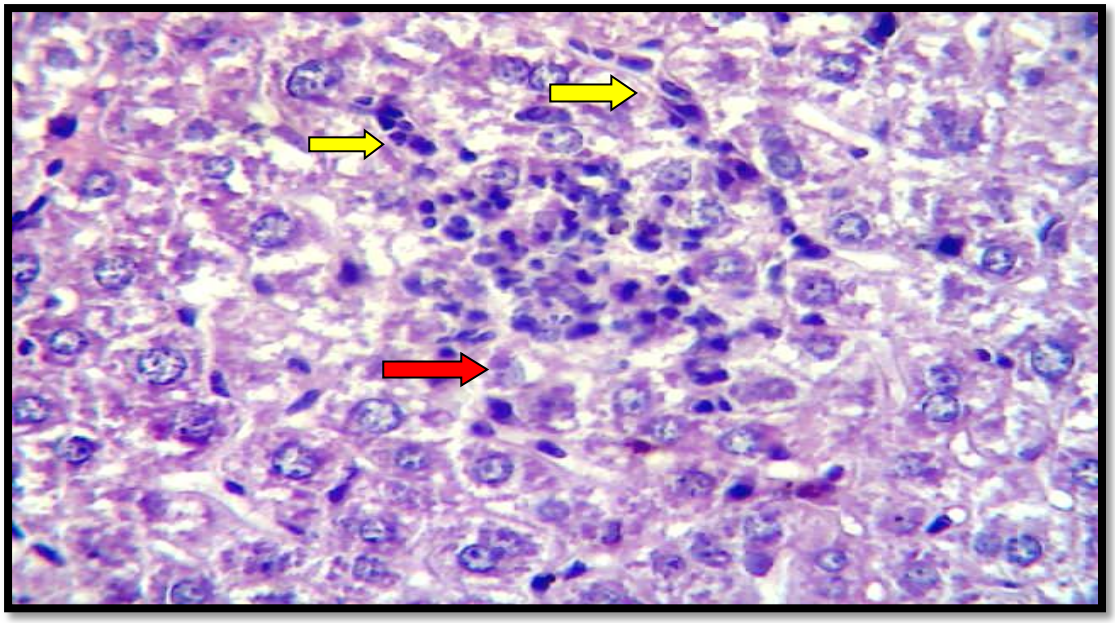

Figure 2- Section of the liver from animal dosed with (0.15 ml) of Duprost, shows mononuclear inflammatory cell infiltrates into hepatic parenchyma (red arrow) and proliferation of kupffer cells(yelow arrows) (H&E stain 400X)

b) Effect of 0.1ml dose of Duprost:

The section of liver obtained from mice dosed with 0.1 ml of duprost after 24hrs, showed aggregation of mononuclear inflammatory cell (macrophage and lymphocytes) into hepatic parenchyma and in the sinusoids, with tendency to form granuloma.(Figure- 3).

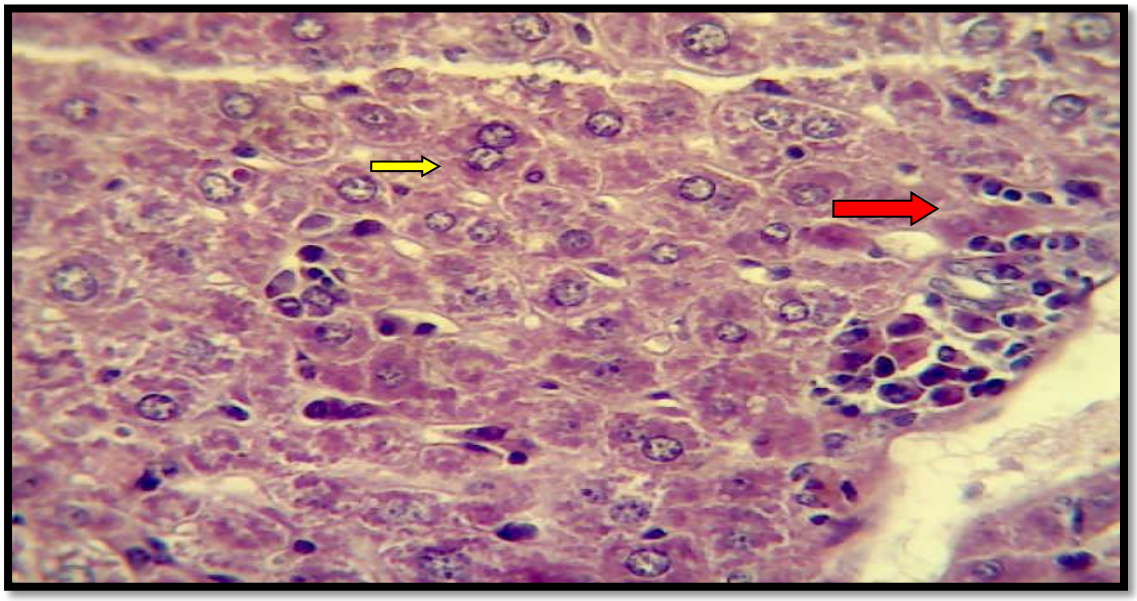

Figure 3-Section in the liver from animal dosed with(0.1ml) of Duprost, shows aggregation of mononuclear inflammatory cell (macrophage and lymphocytes) into hepatic parenchyma, with tendency to form granuloma (red arrow), and in the sinusoids (yellow arrow) H&E stain 400X).

c) Effect of 0.05 ml dose of Duprost:

The section of liver taken from animal dosed with 0.05 ml of duprost after 24hrs showed mononuclear cells aggregation in the liver parenchyma(Figure- 4).

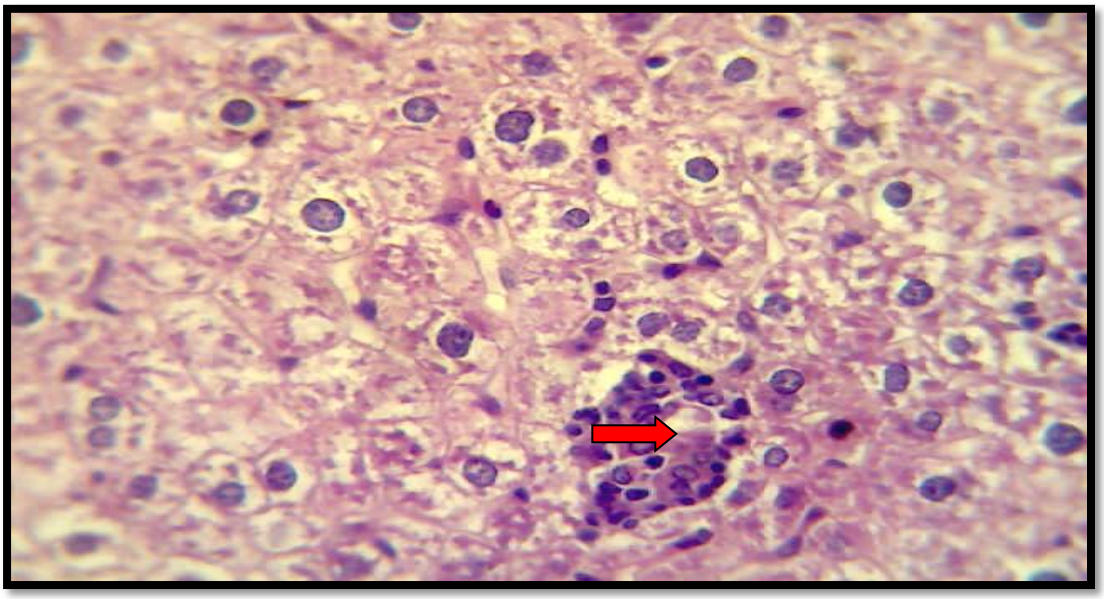

Figure 4-Section in the liver of animal dosed with(0.05ml) of Duprost, shows mononuclear cells aggregation in the liver parenchyma (red arrow) (H&E stain 400X).

3. Histological changes of liver in chronic subgroups:

a) Effect of 0.15 ml dose of Duprost:

The section of liver obtained from mice dosed with (0.15 ml) of duprost for 30 days, showed granulomatous lesions in the liver parenchyma (Figure 5), inflammatory cells (polymorphs and momonuclear cells) in dilated sinusoids (Figure- 6), and inflammatory cells aggregation close to the wall of the blood vessels (Figure- 7).

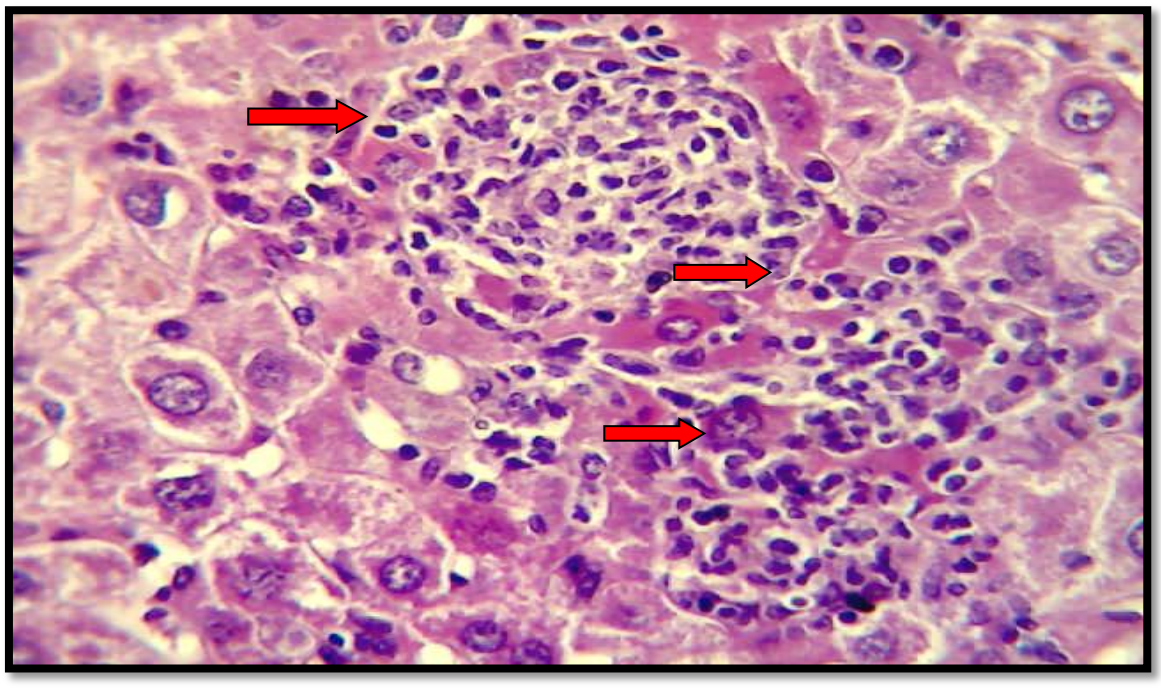

Figure5- Section in the liver of animal at 5 chronic (0.15ml) of Duprost, showed granulomatous lesions in the liver parenchyma (red arrows) (H&E stain 400X).

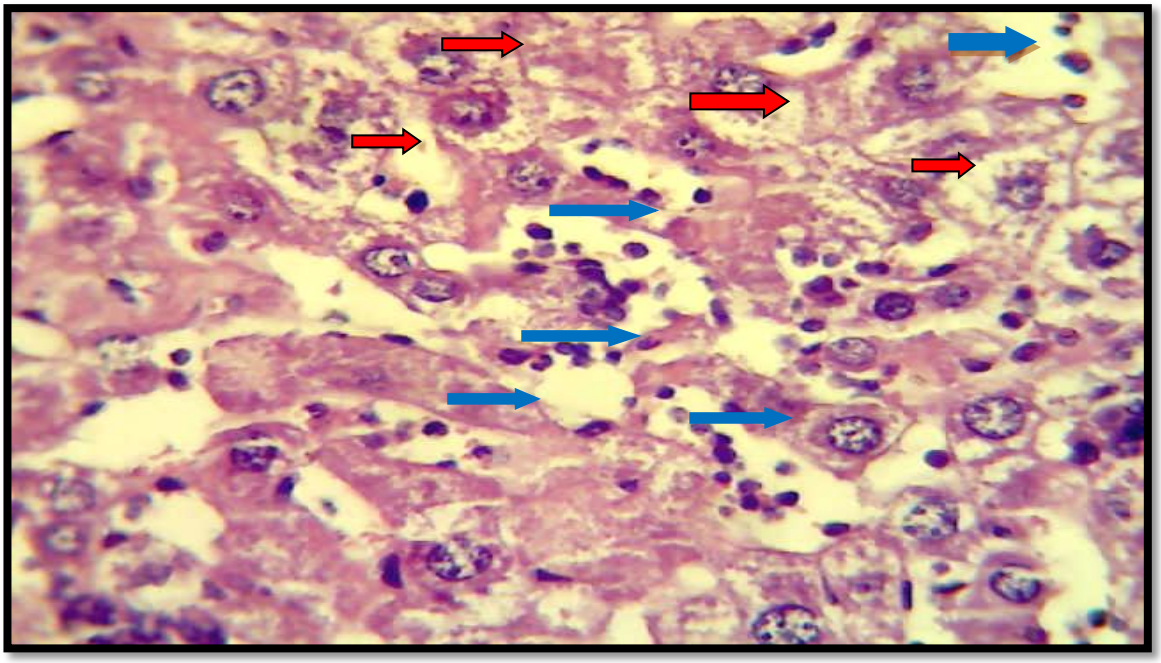

Figure 6- Section in the liver of animal dosed with (0.15ml) of Duprost, shows degenerated hepatocytes (red arrows) and inflammatory cells infiltrates (polymorphs and momonuclear cells) in dilated sinusoids (blue arrows) (H&E stain 400X).

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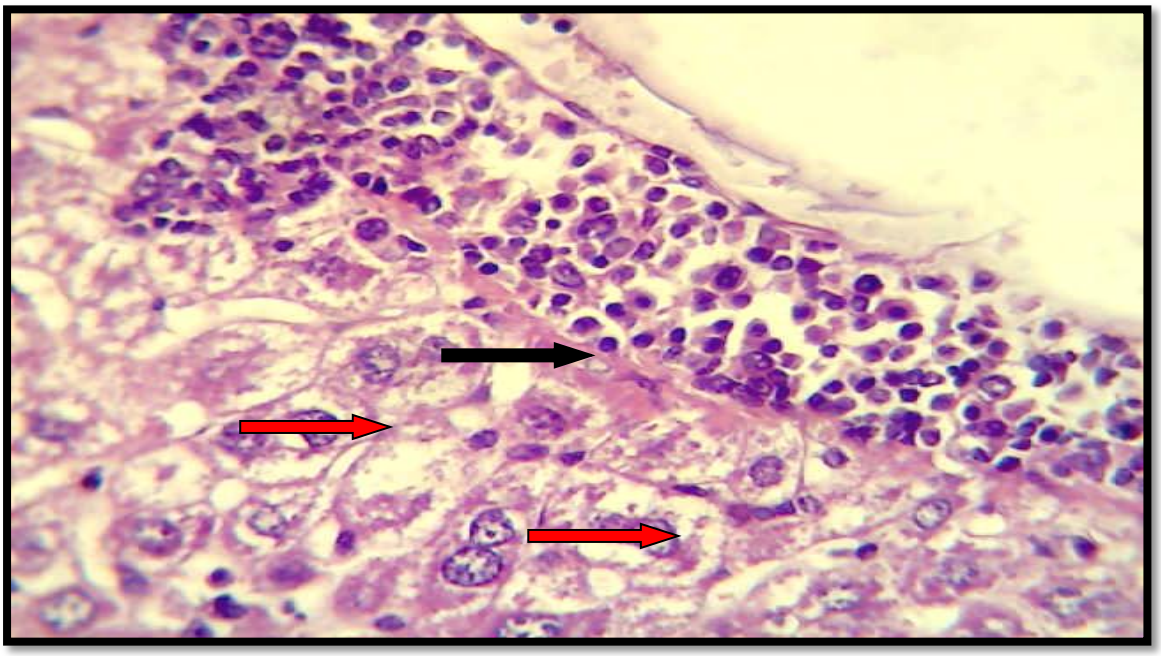

Figure 7- Section in the liver of animal dosed with (0.15ml) of Duprost, shows degenerated hepatocytes (red arrows) and inflammatory cells aggregation close to the wall of the blood vessels (black arrow).(H&E stain 400X).

b) Effect of 0.05 ml dose of Duprost:

The section of liver obtained from mice dosed with (0.05 ml) of duprost after 30 days, showed mixed inflammatory cells infiltrate (mononuclear and polymorphs) in liver parenchyma (Figure- 8)

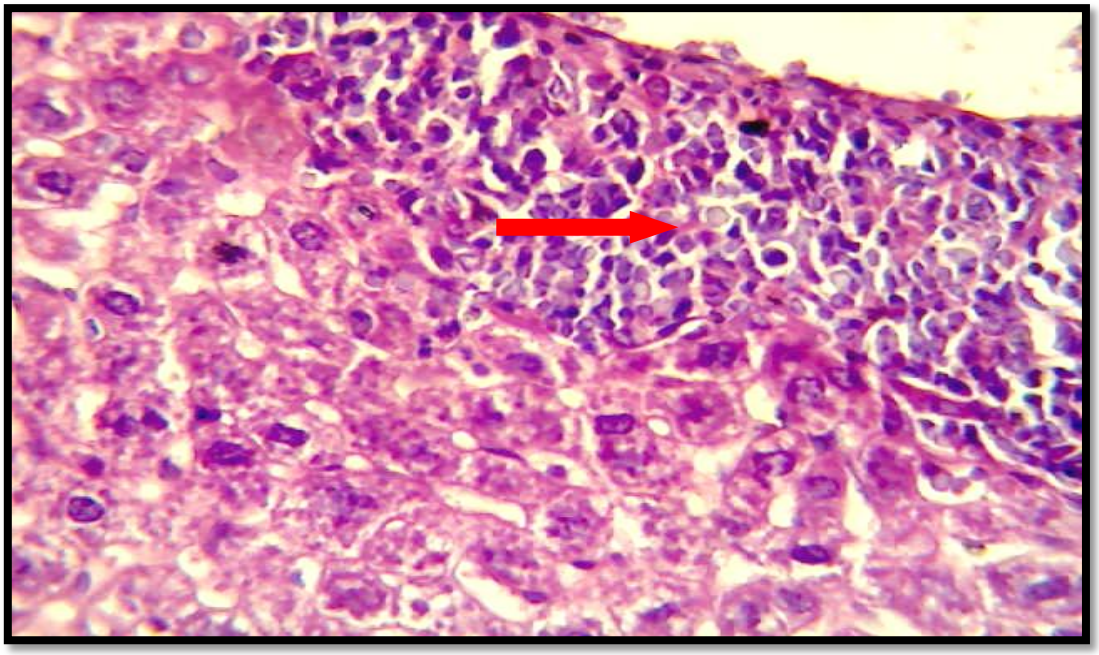

Figure 8-Section in the liver of animal dosed with(0.05 ml) of Duprost, shows mixed inflammatory cell infiltrates (mononuclear and polymorphs) into hepatic parenchyma (red arrow) (H&E stain 400X)

As well, results showed areas of coagulative necrosis of hepatocytes mixed inflammatory cell infiltrates (mononuclear and polymorphs) and inflammatory cells around bile duct Figures- (9, 10& 11).

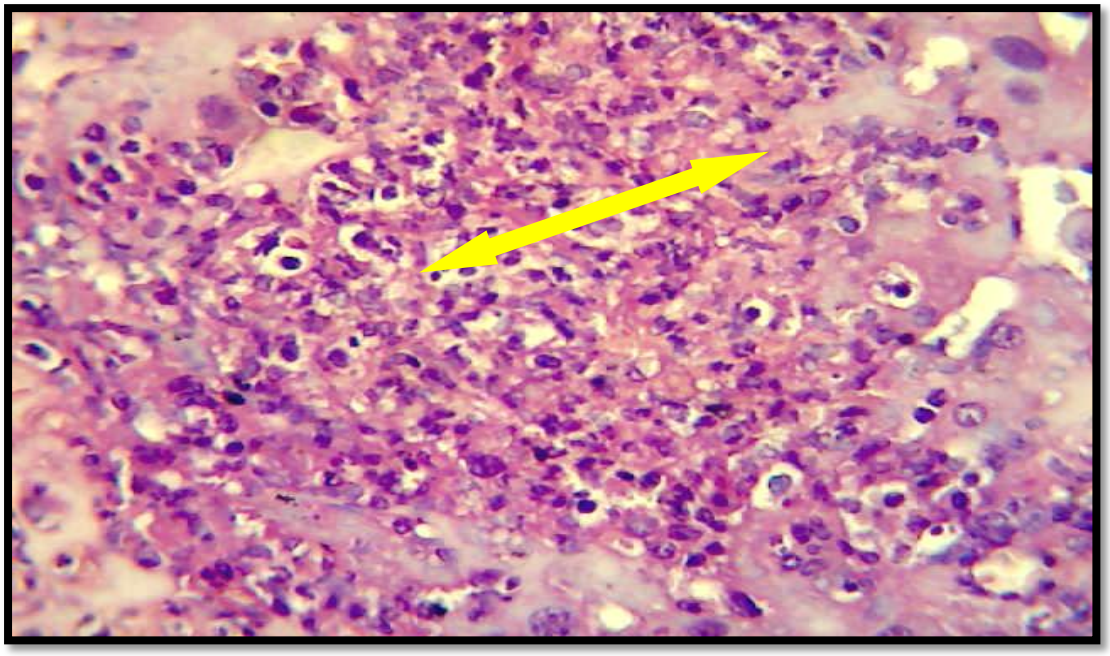

Figure 9- Section in the liver of animal dosed with(0.05 ml) of Duprost, shows mixed inflammatory cell infiltrates (mononuclear and polymorphs) with focal necrosis of hepatocytes (yellow arrow) (H&E stain 400X).

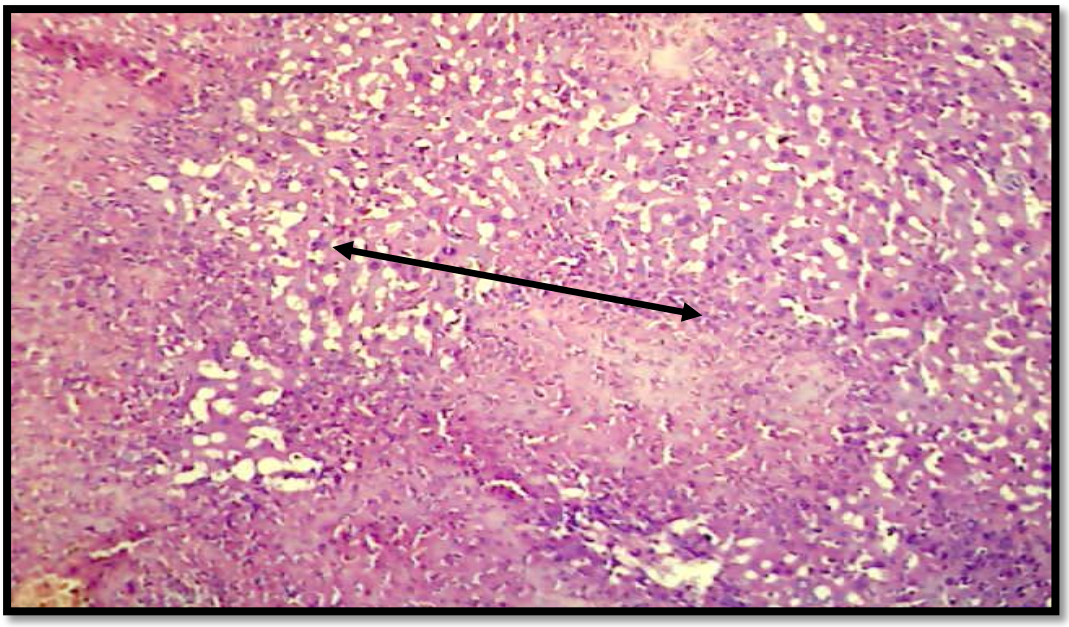

Figure10-Section in the liver of animal dosed with(0.05ml) of Duprost, necrosis and inflammation are prominent (black arrow) (H&E stain 400X).

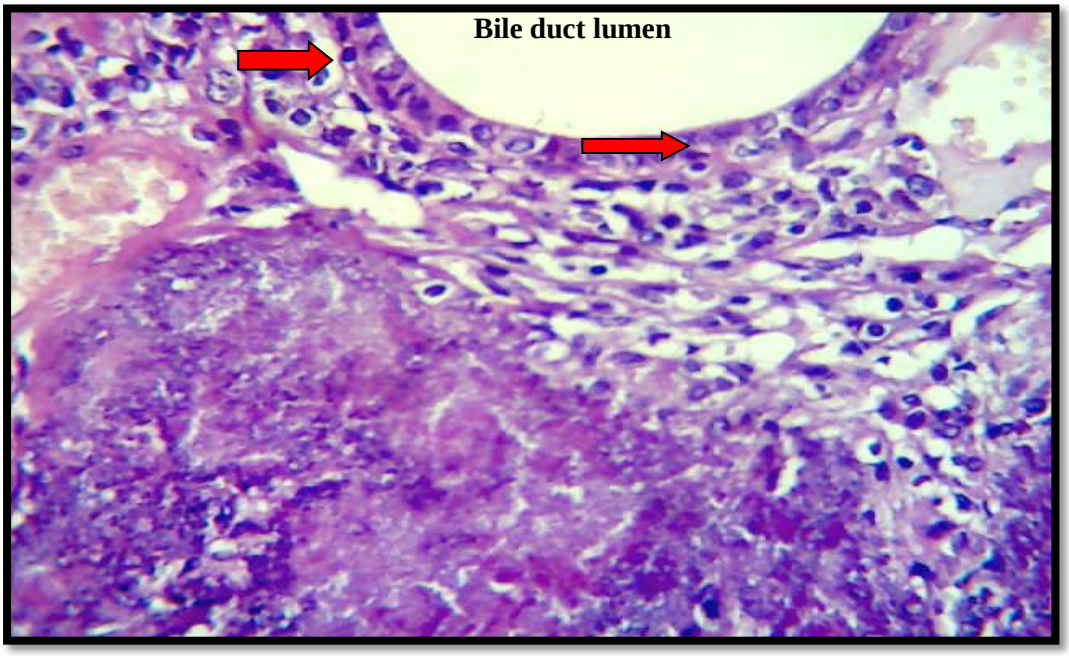

Figure11- Section in the liver of animal dosed with (0.05ml) of Duprost shows inflammatory cells (red arrow) around bile duct (H&E stain 400X).

Discussion

Benign prostatic hyperplasia is the fourth most commonly diagnosed medical condition in the elderly. Selective 5α-reductase inhibitors have an important role in the medical treatment of symptomatic BPH [12].

It provides rapid symptom relief that is maintained in the long term [13].

Safety and efficacy of Dutasteride have been widely studied in recent trials, but side effects on liver had not been studied yet [12, 14].

It has been reported that in a 1-year comparative trial in men who received dutasteride (n = 813), the incidence of impotence (7%), decreased libido (5%), ejaculation disorders (1%), gynecomastia (1%), headache (1%), and fatigue (1%) [9].

Other finding by *Perrotti et al*., 2012, who found in their pilot study that treatment with dutasteride resulted in a significant decrease in serum prostate specific antigen (PSA) in men with serologic relapse following radical treatment for adenocarcinoma of the prostate.

The current study was designed to evaluate the toxic effects of different doses of a new brand; Duprost, given for one month on the liver and blood of adult male mice. Our results showed that this brand caused appetite & weight loss, as well as aggressive behavior in treated mice compared to the controls. While blood results showed significant decrease in Hb level, WBC's and platelets' count among acute subgroups in comparison with chronic subgroups which showed significant increase in WBC and platelets' count, but a significant decrease in Hb levels. These results may belong to androgens which in general influence hematopoiesis [15].

As well, the histological findings of the treated liver illustrated hepatotoxicity manifested by formation of granulomatous lesions in the liver parenchyma, inflammatory cells in dilated sinusoids, as well as inflammatory cells aggregation close to the wall of the blood vessels.

These results may due to anticancer properties of active ingradient dutasteride [16, 17], that is, it is well known that the anticancer drug kills cancer cells and, at the same time can kill normal cells causing some unpleasant side effects.

Conclusion

Our results may provide histological evidence of hepatotoxicity caused by Duprost. This can be used to consider administration of the lowest possible dose of this drug in order to improve its' hepatotoxic effects.

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