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Evaluation of Hematological and Biochemical Alterations Induced by Non-selective Cyclooxygenase Inhibitors (Piroxicam) in Rabbits

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تقييم التغيرات الدموية والكيمائية الحيوية الناجمة عن المثبطات الغير انتقائية لأنزيم الاكسدة الحلقية (بيروكسيكام) في الأرانب

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Abstract
Piroxicam is a nonsteroidal anti-inflammatory drug (NSAID) recommended for various medical conditions. Conversely, piroxicam's hemato-biochemical and hepato-renal-induced toxic effects have been reported. Therefore, the present study aimed to evaluate the impact of piroxicam on some hematological and biochemical parameters in rabbits and examine the histological changes in the kidney and liver. Eighteen adult male New Zealand rabbits weighing (1800-2000 grams) were used in this study and randomly distributed into three groups (n=6). Group 1 is considered as a control. The second and third groups were intramuscularly treated for five consecutive days with concentrations (1, 2) mg/kg of piroxicam respectively. After 5 days blood samples were collected and used for hematological and biochemical analysis. Then, animals were sacrificed; their kidneys and livers were removed and processed for histological examination. High-dose piroxicam significantly ($P \leq 0.05$) decreased red blood cell count, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and White blood cells compared to the control group. Additionally, Piroxicam high dose significantly ($P \leq 0.05$) elevated the serum levels of AST, ALT, urea, creatinine, and uric acid, while decreased levels of triglycerides, and glucose significantly ($P \leq 0.05$) compared to the control. Histopathological examination revealed a dose-dependent piroxicam-induced renal damage, including, cortical blood vessel dilatation, tubular necrosis, glomerular tuft swelling, and interstitial inflammation. Similar dose-dependent effects were observed in liver tissues exhibiting hydropic and ballooning hepatocyte degeneration. The present study demonstrated that piroxicam induced significant hematological, biochemical, and hepato-renal histological alterations in rabbits.

Keywords: Piroxicam, Biochemical Parameters, Blood Indices, Histopathology, Rabbit**s.**

الملخص

البيروكسيكام هو دواء مضاد للالتهاب غير ستيرويدي (مضاد التهاب غير كورتيكوستيرويدي) موصي به لعلاج العديد من الحالات الطبية. ومع ذلك، فقد تم تسجيل آثار سامة للبيروكسيكام على المقاييس الدموية والكيميائية الحيوية والنسيجية للكبد والكلى. لذلك، هدفت هذه الدراسة إلى تقييم تأثير البيروكسيكام على بعض المقاييس الدموية والكيميائية الحيوية في الأرانب وفحص التغيرات النسيجية في الكلى والكبد. في هذه الدراسة تم استخدام ثمانية عشر أرنبًا ذكرًا بالغًا من نوع نيوزيلندا يزنون (1800-2000 جرام) وتم توزيعهم عشوائيًا على ثلاث مجموعات (n = 6) . اعتبرت المجموعة الأولى مجموعة تحكم وتم معالجة المجموعتين الثانية والثالثة عن طريق الحقن العضلي لمدة خمسة أيام متتالية بتركيز (1، 2) ملغم / كجم من بيروكسيكام على التوالي. بعد 5 أيام، تم جمع عينات الدم واستخدامها للتحاليل الدموية والكيميائي الحيوية. ثم تم ذبح الحيوانات وإزالة الكلي والأكباد وتجهيزها للفحص النسيجي. أدت الجرعة العالية من بيروكسيكام إلى انخفاض معنوي ($P \leq 0.05$) في عدد خلايا الدم الحمراء والهيموجلوبين وحجم كرات الدم الحمر المكدسة ومتوسط الهيموجلوبين الجسيمي ومتوسط تركيز الهيموجلوبين الجسيمي والخلايا البيضاء مقارنة بمجموعة التحكم. بالإضافة إلى ذلك، رفعت الجرعة العالية من بيروكسيكام بشكل معنوي ($P \leq 0.05$)مستويات AST و ALT واليوريا والكرياتينين وحمض اليوريك في الدم، بينما خفضت مستويات الدهون الثلاثية والجلوكوز بشكل معنوي ($P \leq 0.05$)مقارنة بالتحكم. كشف الفحص النسيجي عن حدوث تلف كلوي يعتمد على جرعة البيروكسيكام، بما في ذلك توسع الأوعية الدموية القشرية وتنخر الأنابيب وتورم الكبيبات والالتهاب بين الأنسجة. لوحظت تأثيرات مماثلة تعتمد على الجرعة في أنسجة الكبد التي أظهرت تنكس مائي وتنفخ في الخلايا الكبدية. أظهرت الدراسة الحالية أن بيروكسيكام أحدث تغييرات كبيرة في المقاييس الدموية والكيمياء الحيوية والنسيجية الكبدية والكلوية في الأرانب.

الكلمات المفتاحية: بيروكسيكام، معايير كيميائية حيوية، مؤشرات دموية، علم الأنسجة المرضي، أرانب.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in human and veterinary medicine. This family depicts central and peripheral activities and has analgesic, antipyretic, and antithrombotic properties [1]. They are indispensable for alleviating pain and inflammatory conditions. Regarding treatment of pain associated with acute and chronic illnesses such as musculoskeletal and visceral pain, NSAIDs are extensively prescribed [2], [3].

Piroxicam (PM), a nonselective NSAID from the oxicam group, demonstrates relatively sustained action and is used to manage inflammation-associated illnesses such as rheumatoid arthritis, osteoarthritis, and postoperative pain [4]. Recent investigations have suggested that it affects the biological systems and has abilities to act as an anticancer agent [5]. Piroxicam inhibits the activity of both cyclooxygenase (COX) isoenzymes COX-1 and COX-2 [6]. COX-1 is involved in several physiological functions such as organs' internal microenvironments, intestinal cytoprotection, and inhibition of platelet aggregation, while COX-2 is responsible for producing prostaglandin molecules involved in several pathological and inflammatory conditions, and is found in the renal and vascular endothelial tissues [7], [8].

The non-selectivity of piroxicam is effective in decreasing inflammation and relieving pain due to the inhibition of COX-2. However, it also blocks Cox-1, thereby disrupting the production of prostaglandin E2 and prostacyclins, which are physiological mediators with cytoprotective effects involving the reduction of gastric mucosal ulceration through reduced gastric acid secretion [9],[10]. Furthermore, these prostanoids stimulate the production of thick goblet mucus, which provides a protective layer against the formation of gastric ulcers. COX-1 not only plays an essential role in protecting the gastrointestinal mucosa, it also regulates erythropoiesis and platelet function, so its inhibition could cause such side effects as gastrointestinal ulceration, bleeding, and changes in hematologic picture reflected by anemia, malfunctioning platelets [11], [12].

Recently, the hepatotoxic and nephrotoxic effects induced by piroxicam, are a cause for growing concern due to the essential role of the liver and kidneys in the metabolism and detoxification of piroxicam. Significant results have shown a piroxicam-induced increase in hepatic enzymes (AST, ALT) and renal function markers (creatinine, urea). Moreover, the risk of nephrotoxicity is increased as a result of the drug's interference with prostaglandin-mediated renal hemodynamic balance [13] [14]. The adverse effect of piroxicam on the biochemical level can also be attributed to its high plasma protein binding ability that resulted in the sustained COX inhibition of the drug [15].

There is increasing evidence that piroxicam-induced gastric and hepato-renal toxicity is due to the imbalance between reactive oxygen species (ROS) formation and nuterlization by antioxidant enzymes. Oxidative disturbances caused by piroxicam involve lipid peroxidation, protein damage, free radical formation, mitochondrial dysfunction, DNA oxidation, and apoptosis [16].

Monitoring piroxicam-induced adverse effects might help in avoiding complications and improve patient outcomes. The present study aimed to evaluate the impact of piroxicam on some hematological and biochemical parameters in rabbits and examine the histological changes in the kidney and liver. By evaluating these impacts, we can develop our knowledge about proxicam safety profiles and risk assessment.

Material and methods

Preparation of drugs

Piroxicam was obtained from Outpatient Pharmacy as a preparation Feldene® (Pfizer, USA) which is an intramuscular therapy for inflammatory conditions in man, formulated as 1 mL ampoules equivalent to 20 mg piroxicam. The doses of piroxicam were converted to rabbit ones at 1.5 mg/Kg body weight [17]. All necessary dilutions were made using sterile normal saline.

Animals and Study Design

Eighteen adult male New Zealand white rabbits weighing (1800-2000 grams) purchased from a local farm in Tripoli, Libya were used in this study. The Animal Ethics Committee of Veterinary Medicine, Tripoli University, approved the experimental protocol. The guide for the care and use of laboratory animals was followed. The rabbits were housed in well-aerated cages under hygienic conditions and were provided a commercial diet and water ad libitum for two weeks for adaptation, and housed in a temperature-controlled room (25°C) with constant humidity, and a 12h/12h light/dark cycle. After the adaptation period, the rabbits were divided into three groups (n = 6 in each group). Group 1 was considered as a control and injected intramuscularly with sterile normal saline. Group 2 served as the low piroxicam group and received a small dose (1 mg/Kg) of piroxicam intramuscularly for five consecutive days, while group 3 was treated with high-dose piroxicam (2 mg/Kg) via the same route and for the same period.

Collection of blood

At the end of the experimental period, animals were fasted overnight but allowed free access to water. Blood samples were collected from the ear and jugular veins in heparinized vacuum tubes. Blood was used either directly for hematological examination or subjected to centrifugation at 3000 r.p.m for 10 minutes to separate plasma which was used for biochemical analysis.

Hematological analysis

After blood collection, the following hematological parameters were automatically evaluated by Mindray CBC autohematology analyzer (Shenzhen, China); Hemoglobin concentration HGB, total erythrocytic count RBCs, hematocrit HCT, total leukocytic count WBCs, platelets' count PLTs, mean corpuscular hemoglobin MCH, mean corpuscular hemoglobin concentration MCHC and, mean corpuscular volume MCV.

Biochemical analysis

Biochemical parameters Triacylglycerols (TAGs), Total proteins (TP), urea, creatinine, Plasma Alanine Transaminase (ALT), Aspartate Transaminase (AST), Uric acid, Glucose (GLU), Albumin (ALB), and globulins (GLB) were measured from serum samples. Triacylglycerols (TAGs) were determined using a kit supplied by Biomaghreb® (Ariana, Tunisia). Total proteins (TP), GLB, Glucose, Uric acid, and creatinine were determined using a kit supplied by DIALAB® (Neudorf, Austria). Plasma ALT, AST, and Albumin were quantitatively determined using a kit supplied by AMS® (Hove, UK). Urea was determined using a kit supplied by Analyticon Biotechnologies AG® (Lichtenfels, Germany).

Histopathological examination

Animals from the control and treated groups were sacrificed and dissected. The two kidneys and liver were taken from slaughtered rabbits and preserved in a formalin solution of 10% for 24 hours. The histological examination was performed according to [18]. briefly for fixation, the tissue samples were submerged in 10% neutral buffered formalin for 24 h, then embedded in the paraffin wax (Automatic tissue processor, TP 1050, Leica, Germany). Then, wax blocks were prepared. Next, the tissues were cut into 4 ~ 6 µm sections using a rotative microtome (Leica, Germany). These tissue section slides were stained with Harris hematoxylin and eosin for 10 minutes and then washed with running water for 15 minutes. After that, the samples were dehydrated by different concentrations of alcohol and then immersed in xylol for clearances and covered by DPX. The obtained slides were subjected to routine microscopical examination using a compound light microscope (40X, 80X) and photography was done.

Statistical analysis

Data were expressed as mean ± S.E.M. statistical package SPSS 11.5 (SPSS, IBM, Inc, USA) was used to calculate and compare means of the obtained data using Analysis of Variance (ANOVA) followed by LSD post-hoc test to express the differences between treated groups and control ones and differences were considered to be significant at ($P \leq 0.05$).

Results

Effects of piroxicam on hematological parameters in rabbits

A significant ($P \leq 0.05$) decrease was observed in red blood cell (RBC) count, hemoglobin (HGB) concentration, hematocrit (HCT), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) in group 3 compared to the control group. However, rabbits treated with low doses of piroxcam (1mg/kg) showed no significant differences in the former mentioned erythrocyte parameters in comparison to the control group (Table 1).

White blood cells (WBC) count was significantly ($P \leq 0.05$) decreased in the high-dose group compared to the control group. No significant difference was found between the WBC count in the low-dose and control groups. In addition, the mean corpuscular volume (MCV) and platelets (PLTs) count showed no significant changes among the three groups (Table 1).

Table 1: Effects of low and high doses of Piroxicam on hematological parameters of experimental groups (means ± SE)

Parameters	Group 1 (Control)	Group 2 (Low dose)	Group 3 (High dose)
RBC (1012/L)	4.91± 0.16	4.73 ± 0.12	3.55 ± 0.15*
WBCs	9.88 ± 0.62	9.26 ± 0.45	7.15 ± 0.89*
HGB (g/dL)	15.0 ± 0.44	14.4 ± 0.37	10.1 ± 0.20*
HCT (%)	45.2 ± 1.36	43.3 ± 1.25	33.1 ± 1.07*
MCV (fL)	91.9 ± 0.28	92.6 ± 1.71	95.2 ± 0.80
MCH (pg)	30.4 ± 0.13	30.4 ± 0.19	28.2 ± 0.86*
MCHC (g/dL)	33.1 ± 0.05	33.2 ± 0.64	30.5 ± 0.45*
PLTs	236 ± 9.32	232 ± 17.3	226 ± 22.3

Significant increase or decrease compared with the control group (*$P \leq 0.05$).

Effects of piroxicam on biochemical parameters in rabbits

Administration high dose of piroxicam (2 mg/kg) resulted in a significant ($P \leq 0.05$) increase in the levels of AST, and ALT while, levels of triglycerides (TAGs), and glucose(GLU) were decreased significantly ($P \leq 0.05$). Moreover, renal function biomarkers revealed a significant ($P \leq 0.05$) increase in urea, creatinine, and uric acid in both the high and low proxicam groups compared to the control (Table 2). However, no significant changes were observed in the levels of total proteins, albumins, and globulins in both low and high-dose groups compared to the control group. (Table 2).

Table 2: Effects of low and high doses of Piroxicam on biochemical parameters of experimental groups (means ± SE)

Parameters	Group 1 (Control)	Group 2 (Low dose)	Group 3 (High dose)
AST(IU/L)	33.9± 2.45	35.7± 3.44	55.2± 3.61*
ALT (IU/L)	24.5± 2.24	27.1± 3.44	43.8± 3.64*
UREA (*mg/dl*)	39.0 ± 0.4	48.6± 2.65*	63.6± 2.15*
CREATININE (Mg/dL)	1.63± 0.07	1.93± 0.49*	2.03± 0.05*
URIC ACID (mg/dl)	1.65± 0.18	2.18± 0.20*	3.86± 0.44*
TP (g/dl)	6.44 ± 0.24	6.39 ± 0.29	6.10± 0.06
ALB (g/dl)	2.85 ± 0.25	2.83 ± 0.14	2.81 ± 0.04
GLB (g/dl)	3.50 ± 0.29	3.40 ± 0.29	3.25 ± 0.07
TAG (mg/dl)	134 ± 11.4	117± 13.82	102± 20.4*
GLU (mg/dl)	111 ± 6.14	102 ± 7.4	92 ± 7.05*

Significant increase or decrease compared with the control group (*$P \leq 0.05$).

Effects of piroxicam on histological structure of the liver and kidney of rabbits

The histological examination of the liver from the control group displayed a normal appearance, characterized by the intact structure of the central vein and surrounding hepatocytes (Figure 1, A). Low-dose piroxicam admiration resulted in hydropic degeneration of hepatocytes and central vein dilatation (Figure 1, B). However, the liver of rabbits from the high-dose group showed ballooning degeneration of hepatocytes and mild portal inflammatory cell infiltration (Figure 1, C, D).

Tissues from the kidneys of control animals showed normal histological architecture with intact glomeruli and tubules in both cortical and medullary regions (Fig. 2, A). There was a marked cortical blood vessel dilatation, homogenous eosinophilic casts in tubular lumens, and glomerular tuft swelling with endothelial vacuolization in the kidneys of rabbits treated with low doses of the piroxicam group (Fig. 2, B). Animals treated with high-dose piroxicam exhibited focal interstitial inflammation with tubular degeneration, glomerular endothelial proliferation, and congestion together with medullary tubular casts (Fig. 2, C, D).

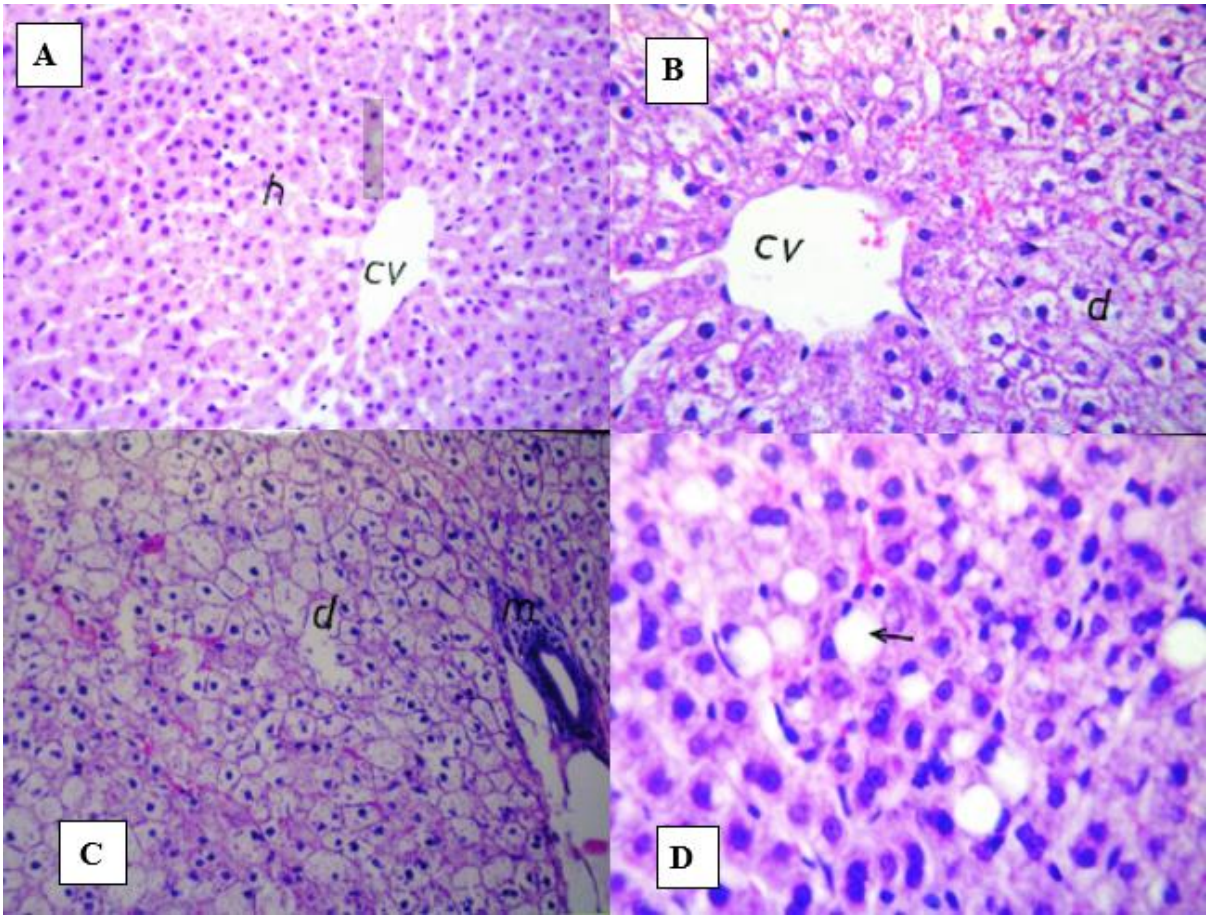

Figure 1. Light micrograph of liver sections. (A) liver of rabbit showing a normal histological structure of the central vein (CV) and surrounding hepatocytes in the hepatic parenchyma(h) (H & E) (× 40) : (B) liver section showing dilated central vein (cv) with hydropic degeneration in the hepatocytes (d) (H & E) (× 40) : (C) liver of rabbit showing ballooning degeneration in the hepatocytes (d) with few inflammatory cells infiltration in the portal area (m) (H & E) (× 40) (D)Hepatic section showing fatty change (arrow) in some of hepatocytes (H & E) (× 80)

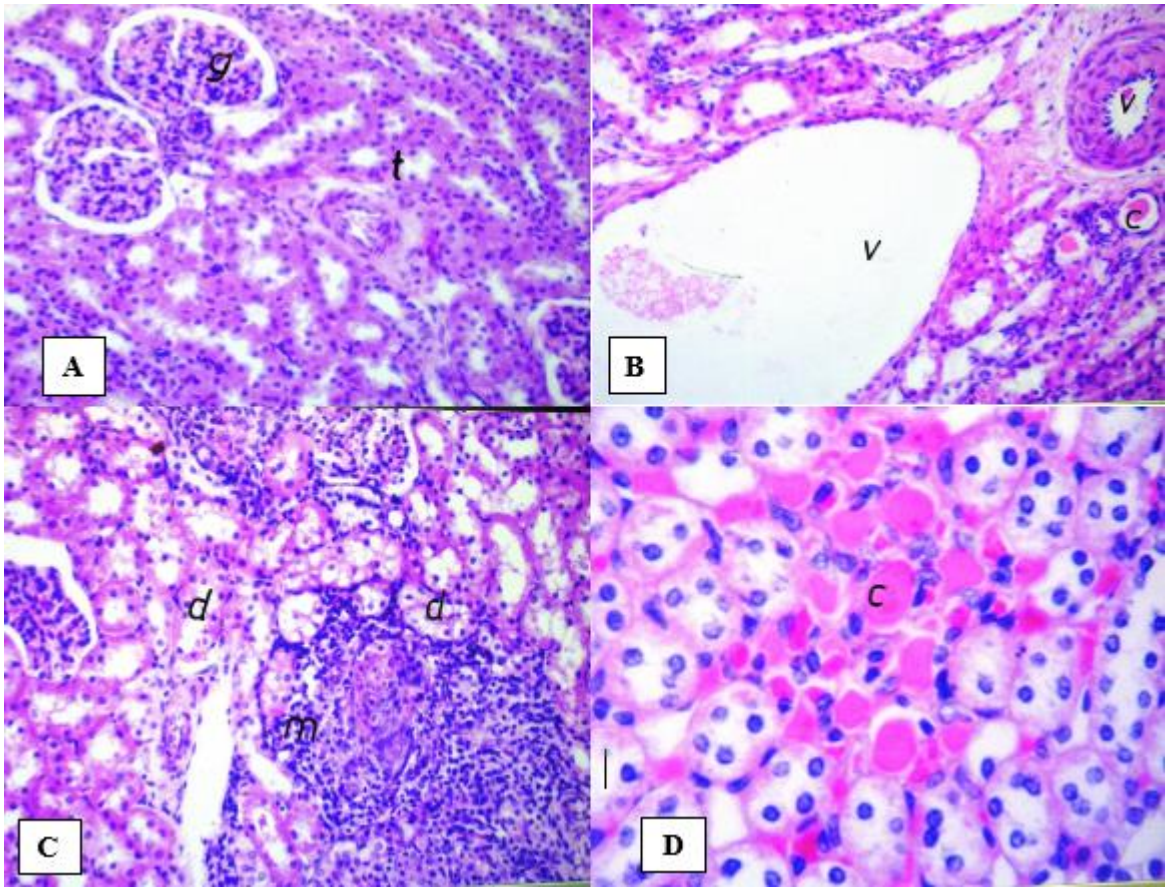

Figure 2. Light micrograph of kidneys sections.: (A) sections of Kidney from control group showing normal histological structure of the glomeruli (g) and tubules (t) of cortex: (B) kidney of rabbit showing sever dilatation in blood vessels (v) with homogenous eosinophilic casts (c) in tubules lumen: (C) kidney sections appeared with homogenous eosinophilic casts in the lumen of degenerated tubules at medullary portion : (D) kidney of rabbit showing focal inflammatory cells infiltration (m) in between the degenerated tubules (d) (H & E) (× 80).

Discussion

Piroxicam is a NSAID within the oxicam class. It is widely prescribed as it has anti-inflammatory, analgesic, antipyretic, antirheumatic, and anticancer effects [4]. Yet, its clinical benefits are limited by growing evidence that has shown piroxicam's induced adverse effects on the blood indices, biochemical parameters, and liver, and kidney functions [11] [13]. Consequently, this study aimed to evaluate the impact of piroxicam on some hematological and biochemical parameters and examine the histological changes in the kidney and liver of rabbits.

Treatment with high-dose piroxicam (2 mg/kg) resulted in significant ($P \leq 0.05$) reductions in red blood cell (RBC) count, hemoglobin (HGB) concentration, hematocrit (HCT), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC). These findings are in agreement with previous study suggesting that piroxicam can adversely affect erythropoiesis and is capable of causing anemia [19]. Anemia caused by piroxicam may have resulted from gastrointestinal ulcer and bleeding induced by piroxicam which inhibits the synthesis of prostaglandins through suppressing the action of COX1. Additionally, piroxicam may induced gastric mucosal injury through a process called lipid peroxidation. This process is likely related to an excess in the levels of damaging reactive oxygen molecules and a reduction in the protective antioxidants such as glutathione GSH and catalyze enzymes (CAT) which play a crucial role in protecting cells from oxidative stress [16].

In addition, results obtained by other researchers showed piroxicam inhibitory effects on prostaglandins and bone marrow function [19] [20]. Prostaglandins are well known mediators for the generation of red blood cells. They regulate bone marrow functions including, stem cell differentiation, cell proliferation, and production of red blood cells. NSAIDs suppress the synthesis of prostaglandin and this might associate with decreasing the physiological process of red blood cell production thus, resulting in anemia. Moreover, the cytotoxic effect of piroxicam was also documented in earlier report that can also participate in NSAID-induced anemia [21]. Conversely, the administration of a low dose of piroxicam (1 mg/kg) did not result in significant alterations in erythrocyte parameters compared to controls. This finding implies that a lower dose of piroxicam might not

produce substantial hematological changes. This supports the idea of customizing the dose to lessen the adverse [22] [23]

Our research also found a marked reduction ($P \leq 0.05$) in white blood cell (WBC) count in the high-dose group compared to controls. This finding agrees with previous literature linking high doses of NSAIDs to the reduction in immune function, bone marrow inhibition, and increased WBC destruction [21] [24]. In general, an inflammatory process is associated with the participation of several inflammatory cells of WBCs. Therefore, as an anti-inflammatory drug, piroxicam is expected to decrease total leukocyte count. On another hand, the insignificant changes in leukocyte level count at the low dose reinforce the notion that lower doses have a less pronounced effect on WBCs [23].

Interestingly, there was no significant change in platelets (PLT) counts among experimental groups. This result might indicate that the possible piroxicam's impact on the hematological parameters might be more specific to particular blood components and molecules rather than affecting all blood elements. It has been shown that piroxicam suppresses platelets aggregation rather than their counts, primarily in response to collagen and epinephrine [25]. Additionally, NSAIDs inhibit platelets aggregation mainly through the inhibitory effect on the activity of thromboxane B2 (TXB2) generation which is an essential biological molecule in the process of platelet activation [12].

In this study, the influence of piroxicam on biochemical markers in rabbits was examined. Our results showed that the high dose of Piroxicam resulted in a significant increase ($P \leq 0.05$) in the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), compared with the control group. This outcome supports the established association between NSAID and liver injury, which is manifested by the abnormal increase in the levels of hepatic enzymes. In addition, there was a significant ($P \leq 0.05$) dose-dependent increase in the levels of urea, creatinine, and uric acid after administration of both low and high doses of piroxicam. This could be due to the impairment of renal excretion capacity induced by piroxicam [25] [26]. The hepatotoxic effect of piroxicam duo to lipid peroxidation in the liver tissue has been linked to the increase in the permeability of the hepatocyte membrane which may result in the release of transaminases (AST and ALT) into the circulating blood, leading to a pronounced elevation in the serum levels of these hepatic enzymes. Moreover, Piroxicam-induced lipid peroxidation exhibits its toxic effect on renal epithelia and results in the damage of the brush border corresponding with increased serum levels of creatinine and urea that indicate the presence of renal insufficiency [16]. On the contrary, glucose (GLU) and triglycerides (TAG) levels showed a significant decrease ($P \leq 0.05$) in comparison with control after treatment with a high dose of piroxicam. A previous study suggested the ability of piroxicam to change the lipid and glucose metabolic parameters. Those effects might be explained based on the increased insulin levels caused by the piroxicam high dose [27] [28].

After piroxicam treatment for five consecutive days, the histopathological examination of the liver and kidney tissues showed mild to moderate degenerative changes. The severity of the recorded changes was parallel to the dose administration. The most pronounced hepatic changes include hydropic and ballooning degeneration of hepatocytes, central vein dilatation, and mild portal inflammatory cell infiltration. [29] and [30] obtained the same observations, which represent substantial hepatocytotoxicity. Hydropic degeneration is attributed to lipid metabolism disturbance during pathological processes. In addition, intracellular accumulation of harmful metabolites and molecules can disrupt the cells' normal function leading to water retention and cellular swelling that is evident in the observed hydropic degeneration. Dilation of the central vein might result from blood congestion due to inflammatory processes in the hepatic tissues [31].

In our study, Kidney tissues demonstrated the following histological changes; severe dilation in cortical blood vessels, eosinophilic casts in tubular lumens, glomerular tuft swelling with endothelial vacuolization, focal interstitial inflammation, and tubular degeneration. This corresponds with findings from other studies that documented extensive renal damage and inflammatory responses due to piroxicam treatment [29]. Signs of inflammatory reaction and vacuolization can result from the same causes behind the similar pathological changes observed in the hepatic tissues i.e. disturbances in the lipid metabolism and intracellular accumulation of waste products. The glomerular swelling induced by piroxicam treatment may have resulted from the proliferation of mesangial cells. When mesangial cells proliferate, they produce more matrix, which can lead to the thickening of the glomerular basement membrane that can reduce blood flow via glomeruli and impair renal function [31].

Conclusion

The present study demonstrated that piroxicam induced significant hematological, biochemical, and hepatio-renal histological alterations in rabbits. These findings suggest that piroxicam has the potential to induce adverse effects on the physiology multiple organ systems. More studies are needed to explain the underlying mechanisms and to evaluate the clinical implications of these findings.

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