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Influence of chronic use of diclofenac sodium and meloxicam in liver and kidney of sheep model: Histopathological evaluation

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Abstract

Background: Non-steroidal anti-inflammatory medicines (NSAIs) are the most often prescribed medications nowadays. The fact that conventional NSAIs have been shown to produce hepatic and renal damage has limited the intake of these medicines for treatment of pain and inflammatory conditions. Objectives: to study the histopathological changes of liver and kidney induced by chronic use of diclofenac sodium and meloxicam on in sheep model, Material and method: Fifteen mature healthy male sheep were assimilated in the reserch. Sheep were divided at random into 3 groups: Group 1(5 animals): not administered by any drugs. Group 2 (5 animals): administered diclofenac sodium (1mg/kg/day). Group 3 (5 animals): administered meloxicam (0.5 mg/kg/day). On day 125, animals undertook sacrifice, liver and kidneys organs were washed with saline, and fixed with 10% neutral buffered formalin for histopathological inspection. Results: The Microscopic examination of kidney and liver specimens from normal group express normal usual tissue architectural details, while histopathological analysis of kidney and liver from diclofenac and meloxicam treated animals show renal and hepatic tissues destruction. These alterations were observed systemically and reflected to be a side effects related with these medications. Conclusion: possibilities of amplified hepatic and renal destruction due to an elongated interval use of diclofenac sodium and meloxicam. Although its effective in pain management their damaging effects must be well thought-out during the continual medication.

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Introduction

Non-steroidal anti-inflammatory medications (NSAIDs) suppress components of the inflammatory response and are frequently prescribed in veterinary medicine as a supplement to antibiotic therapy (1,2). The use of NSAIDs in ruminants has been linked to the management of pain, and inflammatory diseases (3). Not impartial in humans, but similarly in animals, non-steroidal anti-inflammatory drugs (NSAIDs) were using for pain, arthritis, and gout. By in-activation of cyclo-oxygenase 2, it reduces the production of PG from arachidonic acid. However, gastrointestinal tract-related symptoms, skin-related symptoms, renal and liver damage, as well as nonspecific symptoms like overall weakness, have all been reported as side effects of these medicines (4,5). Diclofenac undergoes extensive hepatic metabolism before being eliminated as conjugated metabolites (glucuroconjugated and sulfate metabolites), which are then excreted via the kidneys. In light of these metabolic differences. (6)

The majority of side effects related to diclofenac sodium were found in the renal, hepatic, and GI-systems in nonclinical investigations in diverse species. In mice, for example, hepato-biliary and gastrointestinal toxicity was observed after 28 days of repeated oral treatment (7). In rats, the administration of diclofenac sodium for 2–24 weeks in dose of 0.25−40 mg/kg/day caused in gastrointestinal injuriousness, hypertrophy and hyperplasia of lymph node,

anemia and also alterations in hepatic or renal function (8). Diclofenac sodium has also been shown to have hematological consequences overdose lead to in gastrointestinal toxicity, lymphadenitis and extramedullary hematopoiesis (9).

Meloxicam is an NSAID that belongs to the linoleic acid family. It decreases, selectively, cyclooxygenase2, which is activated by stimulation of inflammatory signals in pathophysiological situations. Meloxicam is degraded widely in the liver into inactive acid metabolite, 5′-hydroxymethyl alcohol metabolite, and those produced by cleavage of side chain (10,11). Healing features of Meloxicam surpass those of other NSAIDs, and it has a strong intrinsic properties paired with a minimum ulcerogenic possibility. Meloxicam's kinetic characteristics, such as excellent absorption, a prolonged half-life, and great bioavailability, give it the opportunity to be an appropriate analgesic for usage in animals (12,13).

The goal of this study was to see how prolonged diclofenac sodium and meloxicam usage affected the liver and renal tissues in an ovine model, concentrating on histological alterations.

Materials and methods

Ethical approval

The College of Veterinary Medicine at the University of Mosul provided ethical approval for the research project UM.VET.05 on February 27, 2024.

Experiment

Groups of 15- mature male sheep (10-12 months) with a bodyweight of (25±2kg), were kept in a normal housing condition. Animals divided randomly into 3 main groups (5 animals): Group 1: not treated by the drugs (control). Group 2: received I/M injection of diclofenac sodium (1mg/kg/day). Group 3: received I/M injection of meloxicam (0.5 mg/kg/day). On day 125, all animals in all groups underwent sacrifice and tissues specimens from the liver and kidneys were rinsed with physiological saline and subsequently fixed through 10% neutral buffered formalin for morphological and histopathological analysis. All specimens were implanted in paraffin and sectioned (5 µm) by using microtome, consequently stained using routine (H&E) and Masson's Trichrome technique (14). These organ sections were subsequently microscopically analysis for to assessing the outcome of long-lasting using of diclofenac sodium and meloxicam on liver and kidney, concentrating on histopathological alterations. Histological changes by 2 blind pathologists.

Results

Microscopic inspection of renal specimens takings from untreated animals group show normally architectural of glomerular and renal tubules, while histopathological exploration of renal tissue from diclofenac treated animals demonstrated pathological alteration in the renal tubules and glomeruli including degeneration and necrosis of renal tubules epithelia cells, which was marked by swelling of epithelial cells causing stenosis and obstruction of tubular lumen. While other renal tubules lumens filled with Calcium deposition. As for the glomeruli showed shrinkage of glomerular tuff leading to expansion of bowman's space. Additional sections showed minor infiltration of chronic MNCs in the paranchymatous tissue, along with congestion of peritubular blood vessels. On the other hand, specimens of kidneys taking from Meloxicam treated animals showed obvious histological changes in renal tubules, glomeruli, blood vessels, and interstitial tissue which characterized by histological lesions include acute epithelial renal tubules necrosis, decreased in the number of glomeruli with degeneration, lobulation of the glomerular tissue, as well as there is focal hemorrhage in the interstitial tissue. Other sections revealed basement membrane thickening of the renal tubules. Thickening of blood vessels wall due to deposition of collagen fiber within and around the tunica adventitia of peri-tubular an interlobular blood vessel. Granulomatous reaction is also seen in the interstitial tissue characterizing by deposition of chronic type (mononuclear) inflammatory cells surrounding by fibrous capsule. Other section showed focal segmental sclerosis of mesangial cells, also glomerulus appeared with segmental necrosis and small cellular debris (Figure 1).

liver specimens of animals treated with diclofenac, revealing histopathological alteration characterized by degenerative and necrotic hepatocytes, minor central veins congestion and sinusoids dilatation as well as small accumulation of chronic types inflammatory cells at peri-portal area. As for the histological examination of liver specimens collected from animals treated with Meloxicam showed histopathological changes characterized by severe degeneration and necrosis of hepatocytes, shrinkage and atrophy of other hepatocytes leading to dilatation of the sinusoids. Additional sections discovered fibrous tissue replacement the hepatocytes with infiltration by lymphocytes and plasma cells, as well as extreme infiltration of chronic types inflammatory cells in the portal area. Additionally, dense deposition of fibrous tissue at the bile duct wall and hyperplasia of epithelial cells lining the bile duct (Figure 2).

Discussion

Analgesic drugs named as non-steroidal anti-inflammatory medication that blocks production of prostaglandins by inhibiting cyclooxygenases (15). They were created for use in veterinary medicine to treat inflammatory and rheumatic disorders as of their analgesic, antipyretic, and anti-inflammatory characteristic. Foot rot,

mastitis, lameness, vaginal prolapse, castration, vasectomy, and laparoscopy are among the painful and inflammatory diseases that NSAIDs are used for in sheep (16).

The administration of diclofenac and meloxicam intramuscularly for 125 days resulted in renal and hepatic tissue damage in this research. We studied reactions in the livers and kidneys of sheep following repeated diclofenac therapy in order to establish mechanisms of Reno-hepatotoxicity. Nephrotoxicity, the third most frequent cause of acute kidney disease (AKD), has gotten worse lately as a result of the increased use of nephrotoxic medications (17,18). Diclofenac and Meloxicam causing mmunological response, which might explain the detections of the existing study. Our data support the overall theory of diclofenac hepatotoxicity, according to which liver damage is caused by reactive metabolites and immune-mediated pathways. (19).

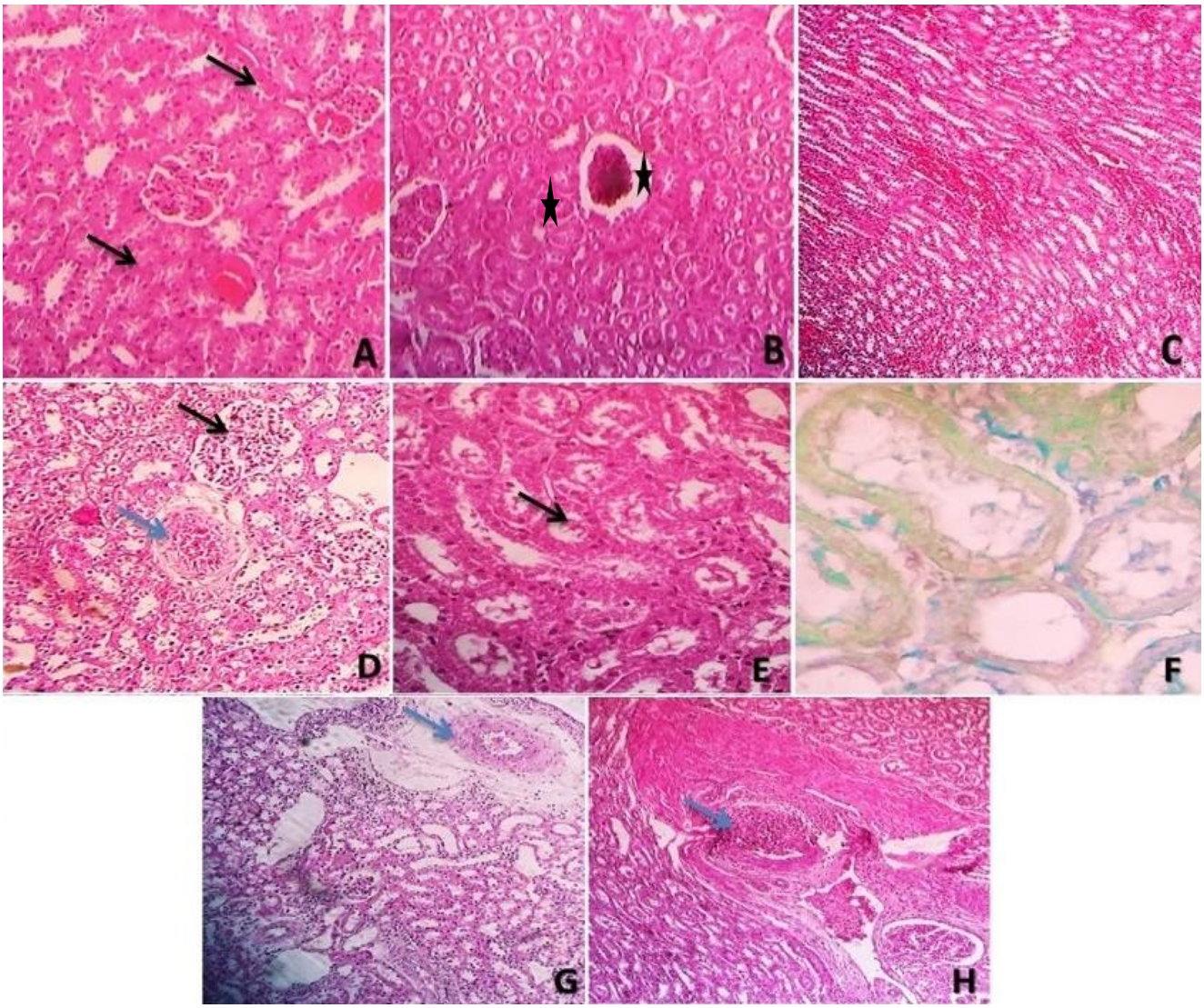

Figure 1: Micrograph of sheep Kidney, treated with Diclofenac and Meloxicam(A) degeneration and necrosis of renal tubules epithelia cells, which was marked by swelling of epithelial cells causing stenosis and obstruction of tubular lumen (Black Arrow) (H&E 10x). (B) shrinkage of glomerular tuft leading to spreading out of bowman's space (star) (H&E 10x). (C) slight aggregation of MNCs in the parenchymal tissue, along with congestion of the peritubular blood vessels. (H&E10x). (D & E) acute epithelial renal tubules necrosis, degeneration, lobulation of the glomerular tuft (Black Arrow) and Thickening of blood vessels wall (Blue Arrow) (H&E 40x). (F) thickening of the basement membrane of the renal tubules Masson's Trichrome stain(40x). (G) Thickening of blood vessels wall due to deposition of collagen fiber (Arrow) (H&E 10x). (H) Granulomatous reaction detected in the interstitial tissue illustrated by chronic types of mononuclear inflammatory cells accumulation bordered by fibrinous capsule (Arrow) (H&E 10x).

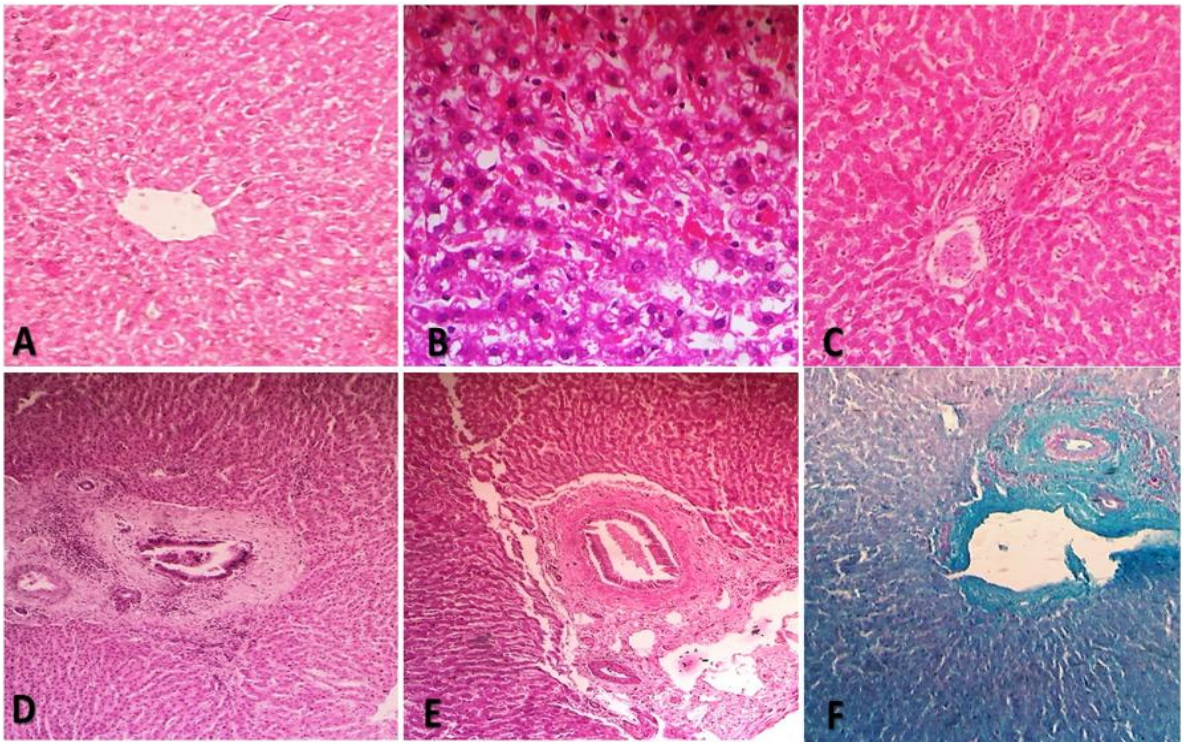

Figure 2: Micrograph of sheep liver, treated with Diclofenac and Meloxicam (A & B) degeneration and necrosis of hepatocytes, with minor congestion of central veins and sinusoids (H&E 10x & 40x). (C) slight collection of chronic typed of inflammatory cells at periportal area (H&E 10x). (D) necrotic hepatocytes replacement by fibrous tissue and penetrate with lymphocytes and plasma cells (H&E 10x). (E & F) dense deposition of fibrous tissue at the bile duct wall and hyperplasia of epithelial cells lining the bile duct (H&E 10x), Masson's Trichrome stain.

Following both single and multiple diclofenac and meloxicam administration, the research identified many master regulators, four of them including Lepr Ghr, Ptpn2, and Socs3, interact with Stat3 in direct manner to impact the gene networks that are built. As previously stated, numerous growth factors and cytokines, like IL-6, EGF family members, and HGF, quickly activate Stat3 as an immune and inflammatory reactions (20). These findings support a diclofenac-induced liver damage mechanism including both acute phase responses and pro-inflammatory cytokine. A biochemical mechanism leading to an imbalance of pro- and anti-inflammatory activity is postulated as a source of what is thought to be an idiosyncratic liver damage (21).

Meloxicam is targets cyclooxygenase-2. It has been utilized widely in humans and in several domestic animal species (22). Meloxicam pharmacokinetics have not been studied in sheep, even though it presents as a promising non-steroidal anti-inflammatory drug (NSAID) for application in small ruminants. This evidence is critical for reasonable therapeutic use of the medication in these species (23). By blocking cyclooxygenase, NSAIDs prevent the creation of prostaglandins (24), This enzyme has two homologs: COX1 and COX2(25). The release of salts and water is controlled by COX2, while the glomerular filtration rate (GFR) and renal hemodynamics are regulated by COX1(25). COX-1 and COX-2 inhibitors, according to (26), also cause intestinal damage.

By using invitro tests, the synthesis of thromboxane A2 (TXB2) by platelets, which is the end product of the COX1-dependent pathway, was selectively measured and compared with the production of PGE2 by monocytes, which is dependent on COX2 (27). Diclofenac was shown to inhibit the COX2 enzyme more effectively than the COX1 enzyme (28).

Nonselective prostaglandin inhibitors, nitric oxide generation, and myeloperoxidase enzymatic activity were found to cause this harm. Some research also back up these findings (29). In a research by (30,31), it was discovered that meloxicam, among other anti-inflammatory medicines, is one of the pharmaceuticals that produces the most ulcerations, despite the fact that it is a prescribed anti-inflammatory treatment. (32) discovered that only meloxicam and piroxicam were effective in rats in a research employing meloxicam and piroxicam. A research was conducted to see how three NSAIDs (flunixin meglumin, ketoprofn, and phenylbutzone) affected the brain, kidneys, and liver when given intravenously to clinically normal Iranian fat-tailed sheep (33). They concluded that while

considering the consumption of these medications in clinical instances, the risk of adverse effects and noxious potential, as well as the efficacy of the chemical for the disease being treated, should be taken into account (34). They discovered that all drug-treated groups had renal and hepatic abnormalities (35).

The NLRP3 inflammasome is a multiprotein complex that is activated by cellular stress or infection. By assisting in the priming process, ROS promotes the activation of the NLRP3 inflammasome (36), which triggers the release of proinflammatory cytokines such interleukin1 (IL1) and IL18, as well as pyroptosis, an inflammatory type of cell death. Drug-damaged kidney cells and hepatocytes can release damage-associated molecular patterns (DAMPs) that, in the absence of infectious microbes, can trigger innate immunity and cause sterile inflammation (37,38). The NLRP3 inflammasome is created by NLRP3 in reaction to pathogen-associated molecular patterns (PAMPs) or DAMPs. The apoptosis-associated speck-like protein with a caspase recruitment domain (ASC) is how this big molecule complex connects to caspase1. The release of pro-inflammatory cytokines and caspase1-dependent pyroptosis is initiated by this macromolecular complex (39,40).

Conclusion

Intramuscular administration of Diclofenac sodium and Meloxicam daily resulted in Harmful effects on the histologic characteristics of liver and kidney. These alterations were seen systemically and reflected to be a side effects connected with these drugs. NSAIDs exist described as active in managing pain, but their adverse toxic rejoinders is essential to be taken into consideration.

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Conflict of interest

The investigator announces there is no conflict of interest.

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تأثير الاستخدام المزمن للديكلوفيناك الصوديوم والميلوكسيكام في كبد وكلى نموذج الأغنام: التقييم النسيجي المرضي

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الخلاصة

تُعدّ الأدوية المضادة للالتهابات غير الستيرويدية (NSAIs) أكثر الأدوية الموصوفة شيوعًا في الوقت الحاضر، ان مضادات الالتهاب غير الستيرويدية التقليدية تُسبب تلفًا في الكبد والكلى مما حد من تناول هذه الأدوية لعلاج الألم والحالات الالتهابية. الأهداف: دراسة التغيرات النسيجية المرضية في الكبد والكلى الناتجة عن الاستخدام المزمن لديكلوفيناك الصوديوم وميلوكسيكام في نموذج الأغنام. المواد والطريقة: تم استخادم خمسة عشر خروفًا ذكرًا ناضجًا وصحيًا في البحث، قُسّمت عشوائيًا إلى ثلاث مجموعات: المجموعة ١ (٥ حيوانات): لم تُعطَ أي أدوية. المجموعة ٢ (٥ حيوانات): أعطيت ديكلوفيناك الصوديوم (١ ملغ/كغ/يوم). المجموعة ٣ (٥ حيوانات): أعطيت ميلوكسيكام (٠,٥ ملغ/كغ/يوم). في اليوم ١٢٥، خضعت جميع الحيوانات في جميع المجموعات للتضحية وتم غسل أنسجة الكبد والكليتين بمحلول ملحي فسيولوجي، وتم تثبيتها بنسبة ١٠% من الفورمالين المحايد للفحص النسيجي النتائج: أظهر الفحص المجهري لعينات الكلى والكبد من المجموعة السليمة تفاصيل معمارية طبيعية للأنسجة، بينما أظهر التحليل النسيجي المرضي للكلى والكبد من الحيوانات المعالجة بديكلوفيناك وميلوكسيكام تلفًا في أنسجة الكلى والكبد. لوحظت هذه التغيرات جهازيًا، وتبين أنها من الآثار الجانبية المرتبطة بهذه الأدوية. الاستنتاج: احتمالية تفاقم تلف الكبد والكلى نتيجةً لاستخدام ديكلوفيناك الصوديوم وميلوكسيكام لفترات طويلة وعلى الرغم من فعاليته في تسكين الألم، إلا أنه يجب دراسة آثاره الضارة جيدًا أثناء العلاج المستمر.