Journal of Medical Genetics and Clinical Biology
Homepage : https://journal.antispublisher.id/index.php/JMGCB
Email : admin@antispublisher.com

e-ISSN : 3032-1085
JMGCB, Vol. 2, No. 3, March 2025
Page 1-8

Histomorphology of Kidney of Experimental Animals After Meloxicam Administration

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DOI : https://doi.org/10.61796/jmgcb.v2i3.1181

Sections Info

Article history:
Submitted: January 14, 2025
Final Revised: January 14, 2025
Accepted: January 15, 2025
Published: January 15, 2025

Keywords:
Meloxicam
NSAID
Kidney disease

ABSTRACT

Objective: *This study investigates the deleterious effects of nonsteroidal anti-inflammatory drugs (NSAIDs), specifically meloxicam, on renal tissue in albino rats.* ***Methods:*** *Sixteen Sprague Dawley albino rats were divided into two groups: Group A received normal saline, while Group B was administered meloxicam at a dose of 15 mg/kg/day via a feeding tube for 14 days. On day 15, all animals were sacrificed, and their kidneys were extracted, preserved, and sectioned. The kidney samples were stained with silver methenamine, PAS, and H&E, and renal histology was examined under a light microscope to assess changes in the renal tubules.* ***Results:*** *The study found that meloxicam caused significant damage to the distal and proximal convoluted tubules in Group B rats. Notable histological changes included tubule dilatation, epithelial flattening, rupture of the brush border in proximal tubules, and thickening of the basement membrane surrounding the tubular epithelium.* ***Novelty:*** *This research highlights the nephrotoxic effects of meloxicam, a commonly used NSAID, providing new insights into its potential harmful impact on renal health, which has not been widely emphasized in previous studies on its adverse effects.*

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs), recognised as cyclooxygenase inhibitors, are extensively utilised as analgesics, antipyretics, anti-inflammatory agents, and anticancer medications for the treatment of various cancers, chronic pain, postoperative pain, rheumatoid arthritis, osteoarthritis, and muscle spasms [1], [2], [3]. Meloxicam (4-hydroxy-2-methyl-N- (5-methyl-2-thiazolyl) -2H-1, 2-benzothiazine-3 carboxamide-1, 1-dioxide) is a non-steroidal anti-inflammatory medication (NSAID) that is selectively specific for cyclooxygenase-2 (COX-2) [4], [5]. It is utilised globally to manage the manifestations and indicators of inflammation, specifically in musculoskeletal disorders, osteoarthritis, and rheumatoid arthritis [6], [7], Moreover, it is beneficial for postoperative pain management [8].

Meloxicam undergoes extensive metabolism, primarily facilitated by the cytochrome P4502C9 enzyme (CYP2C9), with a negligible contribution from the cytochrome P4503A4 enzyme (CYP3A4). Approximately 60% of the supplied dosage is metabolised into its primary metabolite, 5′-carboxymeloxicam, by the oxidation of liver cytochrome enzymes, resulting in the formation of an intermediate metabolite, 5′-hydroxymethylmeloxicam. Despite the significant therapeutic application of NSAIDs, they can induce detrimental effects on various organs, including gastrointestinal, cerebral, cardiovascular, renal, hepatic, and pulmonary systems, potentially resulting in

organ damage, particularly with prolonged high-dose daily use [1], [2]. Thus, Meloxicam Among the NSAIDs, those that are most accessible, cost-effective, and frequently utilised. Numerous studies have demonstrated their harmful effects in Rats exhibit gastrointestinal ulcers, stomach damage, significant lesions in the liver and cerebrum, hepato-renal impairment, and acute pulmonary toxicity. The objective of this study is to elucidate the hematopathological and histological impacts of Meloxicam on the renal tissues of rats.

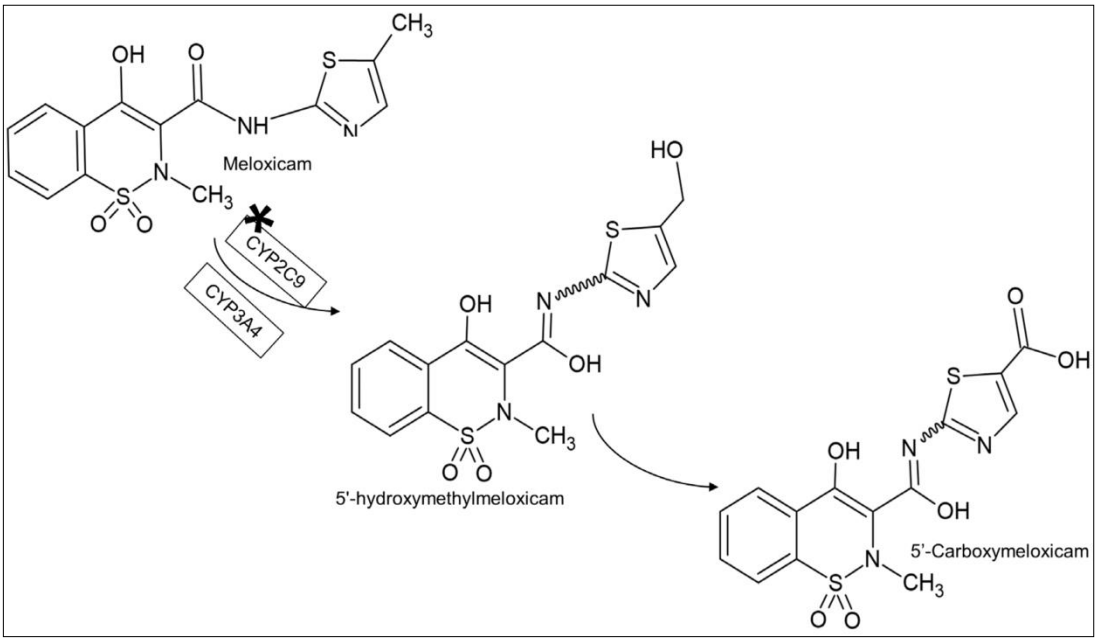

Figure 1. Meloxicam metabolism (* main enzyme responsible for the drug metabolism) [9].

RESEARCH METHOD

The current study will treat 16 albino rats with weights between 200 and 250 g that wereobtained from the University of Tikrit Faculty of Science's animal house. The rats are housed in 42 cm long by 25cm wide by 15 cm high plastic cages with metal coverings that were made especially for them. The rats are kept inthe proper laboratory settings, which include a temperature range of 20 to 25 degrees Celsius, a light/dark cycle of10 to 14, a ventilation rate of 15 to 20 breaths per hour, and a relative humidity range of 30 to 70 percent. Both A and B were the two groups that were formed from them. Each of the groups of animals was housed in a separate cage and its members were given labels. Before beginning the treatment, each animal was given a weight. As a control, the animals in group A were given Normal Saline at a rate of 10 millilitres per kilogramme of body weight orally every day for a period of two weeks. Group B animals were administered Meloxicam at a dosage of 15 mg/kg for two weeks, dissolved in distilled water and delivered orally via a feeding tube once daily. On day 15, the animals were sacrificed using deep ether anaesthesia. The specimens were dissected; their kidneys were excised and weighed using a sensitive balance. Animals will be euthanised following the

conclusion of the experiment. On day 15, a combination of ketamine and xylazine was administered intraperitoneally at a ratio of 90mg/kg to 10mg/kg, use 0.5ml of ketamine and 0.1ml of xylazine per 250g of body weight for the anaesthesia of the animals. allgroups, their kidneys were excised and weighed using a sensitive balance. Saved the kidney in containers contain ten percent formalin [10]. Histological Preparationsall samples should be fixed after dissected from animals in containers contains 10% formalin (38%100mlformalin in 900ml tap water) to be ready for processing them in following steps in [11].

RESULTS AND DISCUSSION

Results

The histological analysis of kidney tissue in the control group revealed glomeruli with a thin glomerular basement membrane, notable cellularity, and an unobstructed capsular space around the proximal and distal convoluted tubules (figure 2, 3). The kidney sections from rats administered Meloxicam at a dosage of 15 mg/kg body weight exhibited glomerular damage, thickening of Bowman's capsule walls, tubular cell degeneration, lymphocytic infiltration, haemorrhage, and fibrosis (figure 4). Demonstrate glomerular injury characterised by thickened renal vein walls, degeneration and desquamation of tubular epithelial cells, and fibrosis (figure 5). And damage tubules with fibroblasts (figure 6, 7). The rats at a dose of 15 mg/kg body weight exhibited detrimental histological alterations, including abnormalities in the renal tubules and glomeruli. Other sections had degeneration and swelling, accompanied by the accumulation of hyaline material in the lumen. The alterations in the glomeruli included dilated Bowman’s space accompanied by congestion of glomerular capillaries, whereas another portion exhibited the absence of Bowman’s space due to the proliferation of mesangial cells. The administration of a larger dose of 15 mg/kg body weight to rats resulted in more detrimental histological alterations in the kidneys, evidenced by the lysis of certain glomeruli. The renal tubules exhibit necrosis of the lining cells, accompanied by sloughing of some cells into the lumen, fibrosis, haemorrhage between the renal tubules, and the presence of hyaline material within the lumen of the renal tubules.

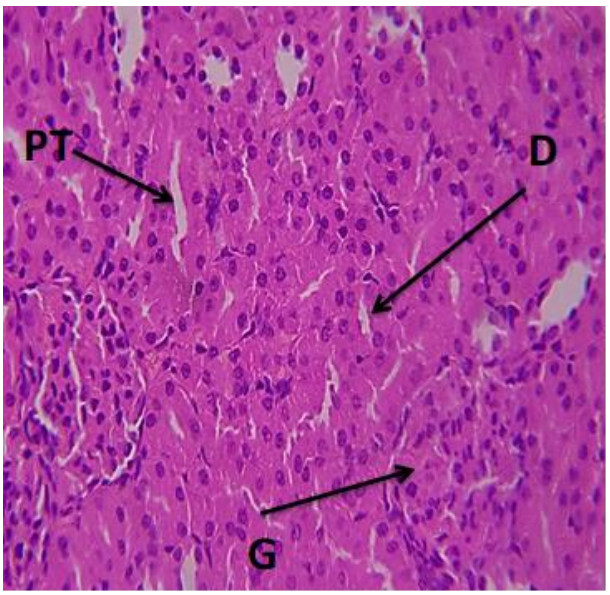

Figure 2. Kidney of control group show normal structure of glomerulus (G), proximal tubules (PT) and distal tubules (DT) H&E X400.

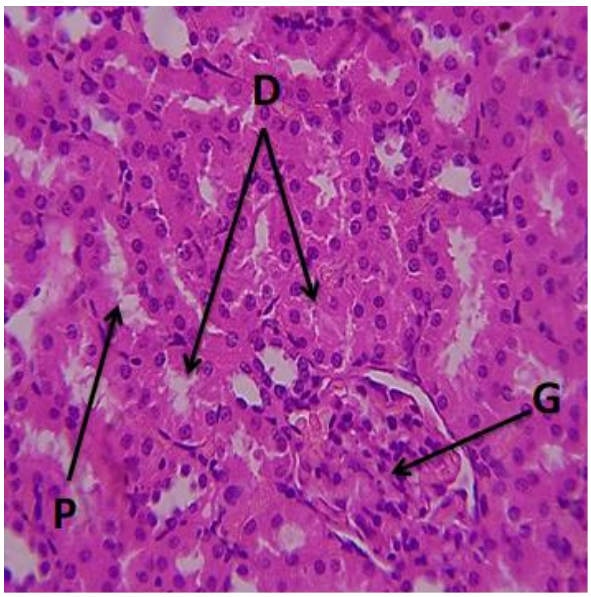

Figure 3. Kidney control group show glomerulus (G), proximal tubules (PT) and distal tubules (DT) H&E X400.

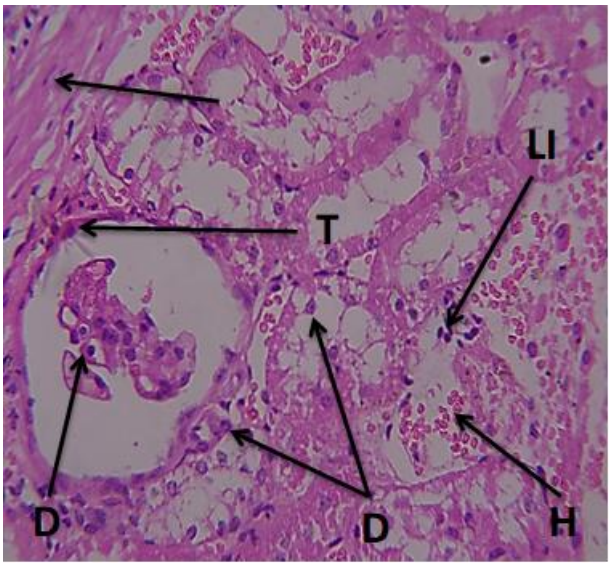

Figure 4. Kidney of drug group show damage glomerulus (DG) with thickening wall (TW) of Bowman's capsules, degeneration (D) cells of tubules, lymphocytes infiltration (LI), hemorrhage (H) and fibrosis (F) H&E X400.

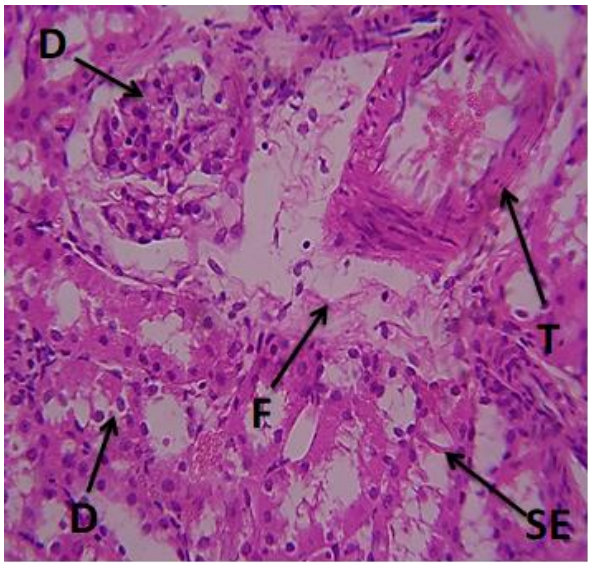

Figure 5. Kidney of drug group show damage glomerulus (DG) with thickening wall (TW) of renal veins, degeneration (D) and slough epithelial cells (SE) of tubules and fibrosis (F) H&E X400.

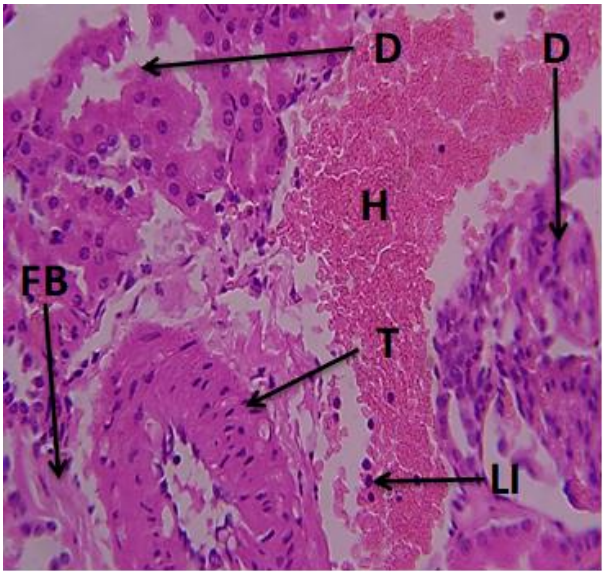

Figure 6. Kidney of drug group show damage glomerulus (DG) and damage tubules (DaT) with thickening wall (TW) of renal veins, lymphocytes infiltration (LI) of tubules, hemorrhage (H) and fibroblast (FB) H&E X400.

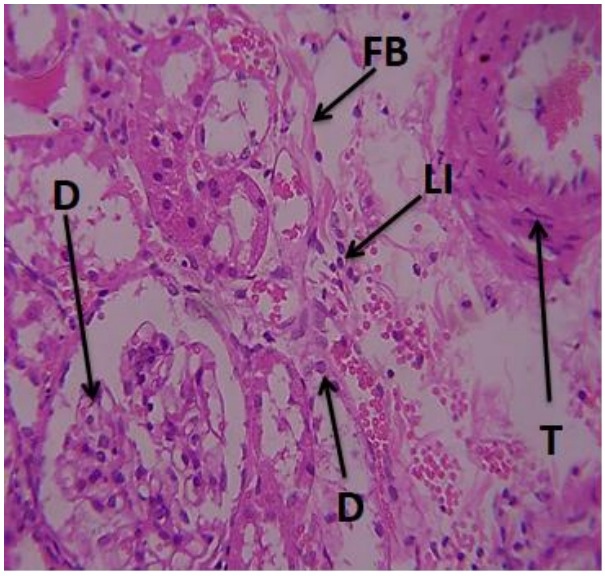

Figure 7. Kidney of drug group show damage glomerulus (DG) and degeneration (D) cells of tubules with thickening wall (TW) of renal veins, lymphocytes infiltration (LI) of tubules and fibroblast (FB) H&E X400.

Discussion

The findings of the current study demonstrated that Meloxicam administration at 15 mg/kg daily for for two weeks had a negative impact on the histologic structure of the rat kidney, and cleardifferences were found when different kidney sections from control and treated rats were examined under a lightmicroscope. Meloxicam-treated groups' kidneys displayed abnormalities and histological alterations, includingsevere amyloid accumulation (degeneration) between proximal convoluted tubules in the cortex section, whichmanifests as extracellular accumulation of homogeneous, eosinophilic, and amorphous material in the interstitial,as well as increased glomerular space and shrinkage. Due to bleeding caused by diapedesis of blood cells andleaking out of blood vessels, which occurs in the renal parenchyma, the renal blood vessels exhibit obvious [12]. Renal prostaglandins (PGI2 and PGE2) not only produce renin secretion, sodium, potassium, and waterreabsorption, but also control glomerular filtration, hemodynamics, and salt and water excretion in the kidneysystem (PGI2 and PGE2). Inhibiting prostaglandin production thus increases risk of weight gain, hypertension,peripheral edema, hyperkalemia, and acute renal damage. renal capsule injury that was visible [13]. Non-steroidal anti-inflammatory drugs (NSAIDs) have a number of renal hazards, including salt retention, peripheral oedema, hypertension, weight gain, congestive heart failure, hyperkalaemia, and acute renal failure [14]. Any NSAID increases the likelihood of a drug-related renal adverse event in patients who are dehydrated. Asystematic review of the safety of NSAIDs was conducted [15]. Meloxicam may impair the diuretic

andantihypertensive effects of diuretics due to its fluid retention properties, requiring a greater diuretic dose. Patientswho develop Meloxicam-induced renal insufficiency may be at risk for catastrophic hyperkalemia if they are onpotassium-sparing diuretics [16]. The existence of considerable increases in the electrolyte levels (K+) anddecreases in the electrolyte levels (Na+) in the treated animals suggested that salt retention was present due to thekidneys' inability to discharge them outside the body [17], [18], [19], which is considered an additional proof that high dosesof Meloxicam induced acute defects and disorders in the kidney structure.

CONCLUSION

Fundamental Finding : Meloxicam administration in rats has demonstrated profound histological changes, particularly in the kidneys. These alterations primarily include toxic damage to the epithelial cells of Bowman's capsule, resulting in poor filtration efficiency and cellular dehydration. Prolonged usage also causes arteriole breakdown, leading to blood flow irregularities visible in histological slides. These findings establish a clear link between Meloxicam toxicity and significant renal impairment. **Implication :** The study underscores the need for cautious use of Meloxicam, especially for long-term applications. Emphasis should be placed on preventing drug misuse by minimizing sedative consumption when not medically necessary and ensuring adequate hydration during treatment. This approach could mitigate some of the adverse effects observed, such as cellular dehydration and impaired renal filtration. **Limitation :** The findings are primarily limited by the study's scope, which focuses exclusively on the histological effects of Meloxicam in rats. Generalizing these results to humans requires caution due to potential species-specific variations in drug metabolism and response. Additionally, the study lacks broader investigation into other organs or long-term systemic effects, leaving gaps for further exploration. **Future Research :** Future studies should investigate the systemic impact of Meloxicam, including effects on other vital organs beyond the kidneys. Expanding research to include varying dosages, durations, and comparative studies in other species, including humans, would provide a more comprehensive understanding of the drug's toxicological profile and safer therapeutic strategies.

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