**INTERNATIONAL JOURNAL OF HEALTH & MEDICAL RESEARCH**

ISSN(print): 2833-213X, ISSN(online): 2833-2148

Volume 05 Issue 01 January 2026

DOI : 10.58806/ijhmr.2026.v5i1n16

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# Renal Tissue Damage and Urea Level Due to of Mefenamic Acid (500 Mg) In Laboratory Rats (*Rattus Norvigicus*)

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**ABSTRACT:** Non-steroidal anti-inflammatory drugs (NSAIDs) represent a class of chemically diverse agents with analgesic, antipyretic, and anti-inflammatory effects. The cyclooxygenase enzymes catalyzing the first step in prostanoid biosynthesis are predominantly inhibited by them. Differences in NSAID efficacy and safety might be explained via relative selectivity for the COX-2 or COX-1 enzyme. This results in reduced prostaglandin synthesis, which has both undesirable and good effects. COX-1 is present in the kidneys, stomach, platelets, and intestines by default, but COX-2 is inducible through inflammation in the brain, vascular endothelium, joints, kidneys, and reproductive tract. This research was done to evaluate the effect of mefenamic acid (500 mg) on male rats' kidneys. 12 males wistar rats 8- week aged, (190 ± 20 gm) body weight was used, divided into two groups, treatment group and control group, former were dosed daily for a week at dose of (643± 10µ) of mefenamic acid syrup, which approximately equivalent to the dose of adult (500 mg / 70 kg), the results showed histopathological changes in kidney like, bleeding, vacuolation, glomerulosclerosis, renal tubules damage.

**KEYWORDS:** Mefenamic acid, rats, kidney, urea.

## INTRODUCTION

NSAIDs are a class of chemically diverse agents with analgesic, antipyretic, as well as anti-inflammatory effects. The cyclooxygenase enzymes catalyzing the first step in prostanoid biosynthesis are predominantly inhibited by them. Differences in NSAID efficacy and safety might be explained through relative selectivity for COX-2 or COX-1 enzyme, which has both good and unfavorable effects (Whalen et al., 2019). The NSAID's activity is attributed to their inhibition of COX activity, and consequently of PG synthesis. In addition, COX comes in two isoforms, each of which can be expressed constitutively (that is, they are often generated) in a small number of tissues. COX-1 is present in the kidneys, stomach, intestines, and platelets by default, but COX-2 is activated by inflammation in the brain, joints, vascular endothelium, kidney, and reproductive tract (Greene et al., 2008). COX-1 activation causes the synthesis of autacoids in the vascular endothelium and gastric mucosa, as well as thromboxane (TXA2) in the platelets and PGE2 in the kidney. COX-2 plays a role in central pain modulation, fever, and the start of fetal expulsions and uterine contractions during childbirth, although its physiological functions are unknown. Even though COX-2 appears around human gastric ulcers and might play a function in ulcer healing in animals, the clinical importance of this is unidentified. COX-2 is primarily induced via cytokines and other pro-inflammatory stimuli which create a localized inflammatory response, such as in joints. COX-2 varies from COX-1 only in the active site, where isoleucine is replaced with valine. This results in a bigger NSAID binding site, which is why COX-2 inhibitors were developed in the first place (Greene et al., 2008). Clinical trials with numerous COX-2 non-selective and selective NSAIDs lasting up to 3 years had demonstrated an elevated risk of major cardiovascular (CV) thrombotic events, stroke, and myocardial infarctions, all of which could be fatal, according to the FDA (FDA, 2008). NSAIDs, especially Mefenamic acid, might worsen preexisting hypertension or cause new hypertension, both of which might contribute to an elevated risk of cardiovascular events (FDA, 2008).

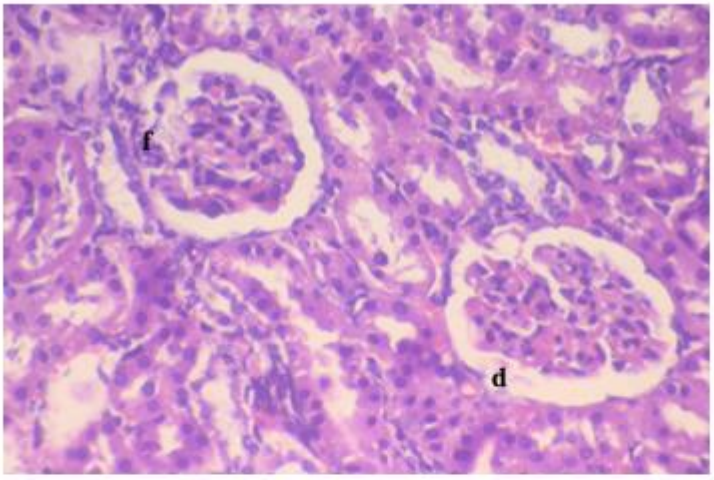
## MATERIALS AND METHODS

This study included twelve mature male rats (*Rattus norvegicus*) weighted (190± 20 gm), their age was 8 weeks. Animals were placed in individual plastic cages and by six rats per cage, the animals left for one week to acclimatization prior to the start of the experimentation. Under standard lab conditions of (12h light: 12h dark photoperiod cycle (LD) (20 ± 2C°) and relative humidity (45-

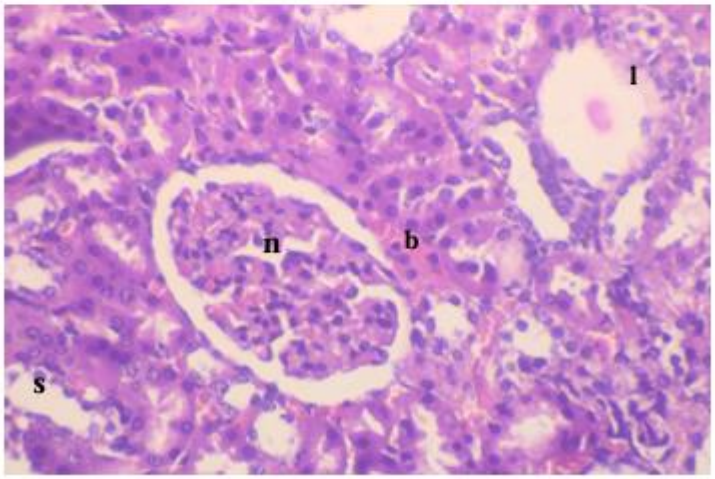
55) %. The animals were divided into two groups, treatment group and control group. The group included six males and was dosed daily for a week at a dose of (643 ± 10 µ) of mefenamic acid syrup, which approximately equivalent to the dose of adult (500 mg / 70 kg). Rats were used for kidney abnormalities detection according to the method of (Luna, 1968). Colorimetric and enzymatic approach depending on urease's particular action in hydrolyzing urea to produce carbon dioxide and ammonium ions. After that, ammonium ions form a blue-green complex with salicylate and chloride. At 600 nm, this coloration is related to the amount of urea in the specimen (Searcy et al., 1967). Statistical Analysis System V9.1 (SAS) has been utilized in order to do statistical analyses of the data. The difference between two groups was determined using an independent t test. Statistical significance has been characterized as a P value of $< 0.05$.

**RESULTS**

The microscopic examinations of kidney's sections of treatment group showed some histopathological changes like, bleeding, vacuolation, glomerulosclerosis, renal tubules damage, loss of brush border in some renal tubules, destruction of endothelial layer of some renal tubules and, fragmentation of nucleus (figure 1 & 2). The results indicated non-significant effects at ($p \leq 0.05$) of mefenamic acid in this dose for one week on urea in the treatment group (mean = 39.16±1.24) compared to control group (mean = 40.00±2.54) (table 1) and (chart 1).




**(Fig. 1): C.S. shows the kidney of the treatment group, fragmentation of Nucleus (f), destruction of endothelial layer (d). (H&E), 400X.**




**(Fig. 2): C.S. shows the kidney of the treatment group, Loss of brush border (l), bleeding (b), glomerulosclerosis (n), Destruction of renal tubules (s). (H&E), 400X.**

| | Groups | N | Mean | P-value |
|---|---|---|---|---|
| Urea | Control | 5 | 40.00±2.54 | 0.76 |
| | Treated | 6 | 39.16±1.24 | |

**Table (1): effect of mefenamic acid on urea in treatment group compared to control.**

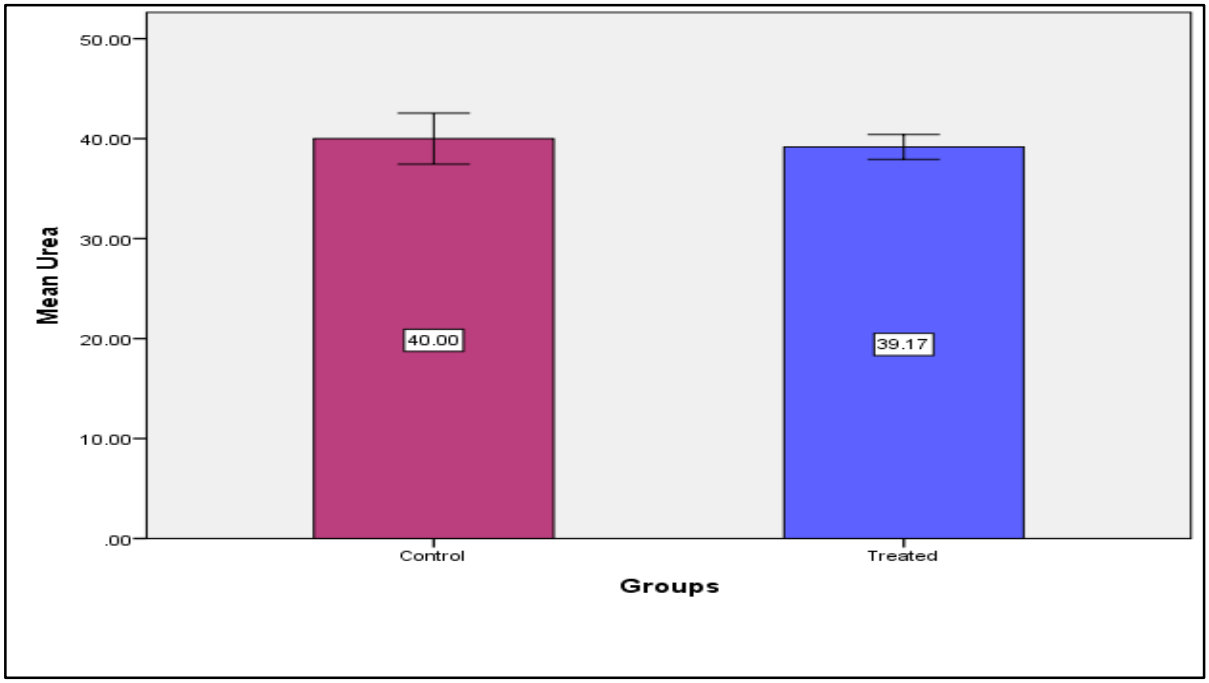



**Chart (1): effects of mefenamic acid on urea in treatment group compared to control.**

**DISCUSSION**

Our results show that there are histopathological effects of mefenamic acid (500 mg) on kidneys tissue, this may be due to the renal toxicity that induced by this drug. Mefenamic acid at doses of 50–200 mg kg_1 was shown to produce renal toxicity in rats. This has been validated by evaluating levels of renal enzyme markers that have indicated glomerular damage (Somchit *etal*., 2014). Various NSAIDs have been linked to renal toxicity, however in several circumstances, patients are unable to avoid such drugs (Prince and Simon, 2016). The short dosage time could have resulted in no considerable impacts of mefenamic acid (500 mg) on urea in the treated rats. With longer use and higher daily doses, the risk of negative effects increases. Mefenamic acid toxicity to the central nervous system has only been mentioned infrequently in the literature. Its neurotoxicity was defined in an animal study as a stimulant effect at high doses and a depressive effect at low dosages (Dogan et al., 2018). Renal toxicity was observed in patients who have a compensatory role for renal prostaglandins in maintaining renal perfusion. A dose-dependent reduction in the prostaglandin synthesis and, subsequently, renal blood flow might occur after administration of a non-steroidal anti-inflammatory drug, potentially precipitating overt renal decompensation in such patients. Furthermore, patients with poor renal function, liver dysfunction, heart failure, diuretics, and ACE inhibitors, as well as the elderly, are at the highest risk of this reaction. After stopping NSAID therapy, most people return to their pre-treatment state (FDA, 2008).

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