World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(RESEARCH ARTICLE)

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Mefenamic acid and renal health: Unveiling the risks

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World Journal of Biology Pharmacy and Health Sciences, 2025, 23(01), 323-328

Publication history: Received on 06 June 2025; revised on 13 July 2025; accepted on 15 July 2025

Article DOI: https://doi.org/10.30574/wjbphs.2025.23.1.0679

Abstract

Mefenamic acid is a non-selective non-steroidal anti-inflammatory drug (NSAIDs) used in the management of pain and inflammation. They are non-opioid analgesics. They inhibit the synthesis of prostaglandins in body tissues by inhibiting COX-1 and COX-2. Thus inhibits the synthesis of prostaglandins, reducing blood supply to the kidneys. Hence, there is always a possibility of kidney injury after administration of Mefenamic acid. We hereby present a series of 7 patients where they developed kidney injury while on treatment with Mefenamic acid.

Keywords: Mefenamic Acid; NSAID; Pain and Inflammation; CKD; Acute Kidney Injury; DIKI

1. Introduction

Mefenamic acid comes under the class of NSAIDs widely used in the treatment of pain. Injury to kidney can occur in various forms including AKI (Acute Kidney Injury), electrolyte acid base disorders, acute interstitial necrosis followed by nephrotic syndrome and papillary necrosis [1]. Mefenamic acid and other NSAIDs reversibly inhibit the production of renal prostaglandins via their inhibition of COX-1 and COX-2. Renal prostaglandins cause dilatation of the renal afferent arteriole. This mechanism is important for maintaining GFR when renal blood flow is reduced [2]. In India, approximately 8% of patients who use NSAIDs develop acute kidney injury (AKI). Additionally, the point prevalence of NSAID-induced renal complications-encompassing both acute and chronic kidney issues-is about 27.88%, indicating a significant impact on the broader patient population [3].

2. Case report 1

A 27-year-old male patient with no known comorbid conditions, consumed Tab. Mefenamic acid 500 mg once daily for nearly a week owing to his high fever. A week later the patient presented with right sided lower abdominal pain and nausea and other differential diagnoses were ruled out. There was no guarding, rigidity on examination. His initial creatinine level was 2.47 mg/dL and urea were 24.9mg/dl. Ultrasound of the kidneys showed that Right kidney appears mildly rounded up with minimal hyper echoic parenchyma. The patient maintained a good urine output. The clinical presentation suggested NSAID-induced interstitial nephritis. Urine examination was normal. Blood and urine cultures were sent, and the patient was started on empirical antibiotics parenteral Cefoperazone -Sulbactam combination 3 g twice daily for a suspected urinary tract infection. Both the blood and urine cultures were negative. The patient was started on Inj. Methylprednisolone 125 mg once daily for NSAID-induced interstitial nephritis. After two days, there was significant improvement, and his creatinine levels and urea level were normalized to 1.19 mg/dl and 25.3 mg /dl

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respectively. The dosage of steroids was adjusted and switched to an oral form. The patient became better and was discharged with oral steroid, Tab Prednisolone 40 mg once daily for 5 days, then tapered and stopped.

3. Case report 2

A 68-year-old elderly male with known case of Type 2 Diabetes Mellitus for 2 years on Tab Glipizide 1 mg and Tab Metformin 500 mg once daily came to the Emergency Department with complaints of loose stools 15 - 20 episodes, watery consistency, non-foul smelling and yellow colored associated with history of fever with chills and fatigue since a day. Fever was high grade and insidious in onset. There was no history of food intake from outside. No history of vomiting. Blood investigation was done which showed normal total counts (9270 cells/ microL) with CRP of 11.9 mg/dl and ESR of 16 mm/hour, hemoglobin 15.8 mg/dL, Platelets 1.79 Lakh/microL, serum sodium of 134 mmol/l, serum calcium of 8.61mg/dl (corrected calcium is 9.1 mg/dl) and serum magnesium of 1.04mg/dl. His initial Urea (25.9 mg/dl) and creatinine (0.83mg/dl) were normal. His LFT showed deranged bilirubin (T/D/I: 1.71/0.45/1.26), total protein (8.85g/dl), albumin (3.96g/dl), A:G ratio reversal (0.81) and transaminitis (AST/ALT of 68/64). His aPTT was elevated (T/C: 37.9/27.5). Blood and stool were sent for culture and sensitivity. He was started empirically on Inj. Ceftriaxone 1g twice daily considering the possibility of an infective etiology. Later Inj. Metronidazole 500mg eighth hourly was added. His blood culture and sensitivity showed no growth. Stool routine examination was found to be normal. He had multiple episodes of fever spike. He is allergic to Paracetamol. Hence was treated with tepid sponging and Tablet Mefenamic acid 500 mg thrice daily. On 3rd day of hospital admission,his Urea (62.3mg/dl) and creatinine(1.5mg/dl) was found to be elevated and it worsened the following day as well with urea level at 101.8mg/dl and creatinine at 2.67g/dl. USG Abdomen and Pelvis were taken and showed Hepatomegaly with heterogeneous echotexture and multiple small hyperechoic and hypoechoic foci scattered in both lobes –suggestive of Chronic liver parenchymal disease and few hepatic cysts. It also showed a relatively enlarged left kidney (11.3cm x 5.6cm) with the right kidney appearing normal in size. Presence of hyperechoic intraluminal focus in gallbladder could be a calculus. Nephrology consultation was sought and Tab Mefenamic acid was stopped. Inj. Ceftriaxone dose was hiked to 2g BD and tablet Rifaximin 550 mg twice daily was added. Urea and creatinine showed a declining trend in the following days with the last urea level being 24 mg/dl and creatinine at 0.98mg/dl respectively. At the time of discharge, the patient was symptomatically better and was discharged with Tab. Rifaximin 550 mg twice daily for 5 days.

4. Case report 3

A 4.5-year-old girl went to a local hospital with complaints of fever for 5 days, acute in onset and high grade. She was prescribed Tab. Mefenamic acid 250 mg- 4 doses 6 hours apart, following which they noticed facial edema with periorbital puffiness on the next day morning. They consulted the same hospital and were advised to stop Mefenamic acid. Nonetheless as edema persisted, she was referred to BCMC hospital. They also noticed weight gain of about 1 and 1/2 kg over a period of 10 days. Her mother also gave a history of frothing of urine. No history of abdominal pain, crying on micturition, vomiting or loose stools and no history of travel or contact with fever. On further examination, the child was alert, active, afebrile with mild periorbital puffiness and pedal edema were present. Systemic examination revealed soft, distended and non-tender abdomen with presence of bowel sounds. No organomegaly was noted. Blood investigations showed normal total counts 8000 /microL with inflammatory marker values, ranging CRP less than 3.22 mg/dl. Her urine routine showed albuminuria (3+ albumin). Clinical diagnosis of nephrotic syndrome induced by Mefenamic acid was suspected and she was investigated for the same. Serum albumin (1.51 g/dl) was very low with elevated total cholesterol (401 mg/dl) and LDL values (252 mg/dl). Investigations were also suggestive of the Mefenamic acid induced nephrotic syndrome. Nephrology consultation was sought and they advised to stop Mefenamic acid and start Syrup Prednisolone at 2 mg/kg while holding back antihypertensives and loop diuretics. She was given albumin infusion and daily monitoring of blood pressure, abdominal girth, weight and urine albumin were done. On day 9 of hospital stay, her urine was devoid of albumin, although monitoring was continued for 2 more days. Presently she is in remission with adequate urine output, stable vitals and good oral intake. Hence, she was discharged with the Oral steroid's prescription (Syrup Prednisolone 8.5 ml once a day for 5 weeks and reduce the dose to 6.5 ml alternate days for 6 weeks).

5. Case report 4

A 20-year-old female patient with no comorbidities gives a history of continuous intake of Mefenamic acid 250 mg tablets twice a day for 1 week for her abdominal pain. She came with complaints of unresolved abdominal pain, intermittent hematuria and vomiting. Complete Blood Count and Renal Function tests were sent which showed, normal total counts of 7300/microL and hemoglobin of 9.8 g/dl, deranged creatinine and urea level 1.25 mg/dl and 26.2 mg/dl

respectively. The clinical picture suggested Mefenamic acid induced Acute Kidney Injury. Hence the patient was advised to stop the medication. Later, after about 1 week, the creatinine level was found to be 0.85mg/dl.

6. Case report 5

A 62-year-old female presented with complaints of acute dyspnea, generalized edema, polyarthralgia and paresthesia over the past 5 days. She has a history of Type 2 Diabetes Mellitus for 10 years (not on any regular medications) , Hypertension for 40 years (on Tab.Telmisartan 40 mg once daily). She has dyspnea on exertion for the past 3 years and was on inhalers (MDI Salmeterol + Fluticasone propionate 2 puff twice daily) for Asthma. Breathlessness accentuated over the last 5 days. She was previously evaluated at a nearby hospital for upper back pain and lower limb ulcers. She also has a history of NSAID abuse (Tab Mefenamic acid 500mg) for almost a year for her upper back pain. On arrival, she was tachypneic (respiratory rate was 36/min), generalized edema, elevated JVP and hypoxemia and therefore she was admitted in view of acute respiratory distress. On admission, her initial evaluation showed hypervolemic hyponatremia (125 mmol/l), with potassium level of 5.2 mmol/l, raised creatinine(1.69mg/dl) and anemia (Hemoglobin 10 g/dl). Peripheral smear showed normocytic normochromic picture with relative neutropenia and occasional reactive lymphocytes along with severe iron deficiency. Her Chest Xray showed gross cardiomegaly which was followed up with an ECHO which yielded uneventful results. She was started on IV broad spectrum antibiotics Inj . Ceftriaxone 2g BD for her exacerbation of Asthma, diuretic Inj . Furosemide 40mg twice daily iron supplements and responded well to treatment. Her HRCT showed mild atelectatic changes with cardiomegaly. A nephrology consultation was sought and it was suggested that her AKI could be NSAID induced, hence she was conservatively managed with diuretics, which was increased to twice daily administration. The following day, her edema reduced, electrolytes settled but Serum Creatinine continued to be 2.63 mg/dl, subsequently reduced to 1.79 mg/dl over a couple of iand LDL cholesterol 183 mg/ dl and had vitamin D deficiency. Her anti-hypertensive drug (Telmisartan) was changed to Nifedipine 10mg twice daily and she was started on Aspirin, Atorvastatin and Vitamin D3. On discharge, her Creatinine improved to 1.2mg/dl along with electrolytes, Sodium (132 mmol/l), Potassium (4.79 mmol/l). She was also diagnosed with diabetic peripheral neuropathy and possible entrapment median neuropathy for which Tab. Pregabalin 75 mg and Tab.Duloxetine 20 mg once daily were started.

7. Case report 6

A 69-year-old male patient with a known history of Diabetes Mellitus for 18 years (on Biphasic Isophane Insulin,Tab Metformin 500 mg and Tab Glimepiride 2 mg twice daily), BPH (on Tab Silodosin 8 mg at bedtime) and early CKD owing to long standing diabetes came for review on 8th February 2024. The creatinine value on the last review was 1.11 mg/dl . On 5th February 2024, he took Mefenamic acid oral and Intramuscular injection from a local hospital for lower back ache. Vitals were found to be stable. But his creatinine level and urea were found to be 1.29 mg/dl and 40 mg/ dl . The aggravation in kidney Injury was suspected probably due to the added effect of Mefenamic acid. Hence the patient was informed to stop taking Mefenamic acid and was provided with Tab.Tramadol and Acetaminophen combination for pain. No further worsening of creatinine level was found.

8. Case report 7

A 48-year-old male patient with a history of Hypertension for 4 years (on Tablet Telmisartan 40 mg once daily) presented with complaints of right sided loin pain for 3 days, nausea and occasional hematuria for a few days and was admitted for further evaluation. He gives the history of intake of Tab. Mefenamic acid 500 mg once daily for 2 days while at home.

His initial blood investigations showed deranged RFT, with creatinine level 7.41mg/dl, and urea was found to be 124.7 mg/dl and elevated levels of inflammatory marker CRP 44 mg/l. The clinical picture coupled with the absence of other causative factors suggest Acute kidney Injury by Mefenamic acid use. CT KUB was taken to assess any underlying pathology and it showed right lower ureteric calculus causing mild hydroureteronephrosis with perinephric and periureteral fat stranding. Urology opinion was sought and he was posted for double J stenting, post procedure he was stable. He was then started on IV Antibiotics – Cefoperazone -Sulbactam combination 3g for 5 days after sending urine samples for culture and sensitivity testing. The urine culture showed no growth. He had hyponatremia (116 mmol/l) for which IV correction was given. He was symptomatically better, clinically stable with serum creatinine 2.76mg/dl (lowering from Creatinine - 7.41 mg/dl) and urea level 47.4mg/dl respectively at the time of discharge. He was discharged with Cefixime 200 mg tablets for 2 more days.

9. Discussion

Patients consume a variety of medications, including both prescribed and over-the-counter types. Regretfully, medications continue to be a frequent source of both acute and chronic kidney damage. A number of factors, such as the inherent nephrotoxicity of medications, underlying patient traits that raise the risk of kidney damage, and the way the kidneys metabolize and excrete various substances, increase the risk of drug-induced nephrotoxicity. Mefenamic acid and similar NSAIDS are one of the most common over-the-counter medications used globally. Approximately 1%–5% of patients exposed to nonsteroidal anti-inflammatory drugs (NSAIDs) develop diverse nephrotoxic syndromes warranting potential physician intervention[4]. Although they have lower predisposition of damaging kidneys, the extensive use profile of these agents implies that many people are at risk[5] .

NSAIDS act via inhibition of the COX pathway, inhibiting the Prostaglandins and causing anti-inflammatory, analgesic, antipyretic and anti-inflammatory effects. NSAIDs have produced a variety of distinct renal syndromes which include acute ischemic renal insufficiency and acute interstitial nephritis caused by hemodynamic effect, which is a direct result of COX inhibition. The mechanism suggested is the involvement of prostaglandin I_2 and Prostaglandins E_2 which are synthesized by both the glomerular and medullary interstitial cells. Prostaglandins will diminish vascular resistance, dilate renal vascular areas and promote organ perfusion. This will lead to redistribution of blood flow from the renal cortex to nephrons in the juxtamedullary region [6]. NSAIDs including Mefenamic Acid inhibit prostaglandin synthesis, decreasing the blood supply to the nephrons causing acute ischemic renal insufficiency. They also impair salt and water excretion, leading to edema and hypertension. Electrolyte imbalances like hyperkalemia, hyponatremia, could also accelerate kidney disease progression.

Mefenamic acid has greater propensity to damage the kidneys. The mechanism of damage caused in the aforesaid cases is similar to other studies conducted on both animals and humans. Mefenamic acid when given to mice at a dose 100 or 200 mg /kg single dose or as a 50 or 100 mg/kg single daily dose for 14 days induced alteration of kidney histology leading to mild glomerular and tubular atrophy. Chronic doses lead to a dose dependent glomerular necrosis, massive degeneration, inflammation and tubular atrophy.[8] Gonzalez et al explains the role of Intrarenal Prostaglandins in the maintenance of renal perfusion and thus Glomerular Filtration Rate when the autoregulatory RAAS system is activated, which is inhibited by the use of NSAIDs.[9] Similar results were echoed in meta-analysis conducted by the University of Dundee involving 1,609,163 participants [12] and the study by Yu Zhu et al including 23,073 patients[13]which elucidates the risk of NSAIDs induced Kidney Damage.

According to our study, Kidney Injury could be triggered even with limited use of Mefenamic acid such as two days to a week. All the reactions were Type A reactions,because they were dose dependent and predictable. The de-challenge of the medication was necessary to decrease or stop the severity of kidney damage which emphasizes that it is reversible. In this case, the causality was found to be “PROBABLE” according to World Health Organization-Uppsala Monitoring Centre (WHO-UMC) assessment scale and Naranjo Assessment Scale (the score was found to be 5-6). Among the various adverse effects of Mefenamic Acid, renal and urinary disorders account for only about 2% of cases, with a total of 487 reports documented till date. These include Acute Kidney Injury (160), Renal Impairment (105), Tubulointerstitial Nephritis (66), and Renal Failure (17)[21]. Outcome? Severity?

Applying the Modified Hartwig and Siegel Severity Assessment Scale,our study typically falls into the moderate category (Levels 3 to 4b). and All the Above clinical series have a recovering outcome.

From the case series,it was clearly established that patients with or without comorbidities can develop Kidney Injury. However, the worsening of kidney injury was seen more in patients with comorbid diseases like underlying anemia, pre-existing Diabetic Kidney Disease or in the presence of concomitant medications like Diuretics, ACE inhibitors or even Angiotensin Receptor Blockers like Telmisartan. Both males and females are equally susceptible to Mefenamic acid induced Kidney Injury, although there was a higher precedence in the elderly age group.

The cornerstone of conservative management involves the immediate cessation of NSAID therapy, which often results in the improvement of renal function within 2 to 7 days. In addition to discontinuing the offending agent, fluid therapy plays a pivotal role in restoring intravascular volume and enhancing renal perfusion which facilitates shorter hospital stay and earlier discharges. [11]The use of Steroid therapy in Drug Induced Kidney Injury is controversial. [9] Some studies have reported a more rapid and complete recovery of baseline renal function in patients treated with steroids[10,] . After discontinuation of Mefenamic Acid, we found that the majority of our patients who received Steroid treatment have had a faster recovery compared to the patients who didn't receive Steroids at all.

10. Conclusion

Pain being a distressing symptom, many patients self-medicate with NSAIDs. Mefenamic acid is found to be a widely used NSAID. Hence, the physicians should be alert and need to keep track of the patient's own use as well as in-house prescribing of Mefenamic acid. In conclusion, management of the Kidney Injury induced by Mefenamic Acid includes, eliciting a prompt history of Mefenamic Acid use along with concomitant medication history, ensuring 'lowest effective dose' of NSAID use for the 'shortest possible time', immediate withdrawal of drug in the event of adverse reaction, regular monitoring of the creatinine and urea level to help analyse the progression of renal injury, screening via ultrasonography to confirm and estimate the extent of kidney damage, maintaining fluid and electrolyte balance which may be vital for the body's proper functioning and addition of steroids when necessary to protect the kidneys from further damage.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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