Aceclofenac and Analgesic Nephropathy : A Transcendent Adverse Effect of Concern

Dr.Amee D. Pandya*, Dr. Sapna Gupta , Dr. Jaldipsinh N. Gohil***,**
Dr. Supriya D. Malhotra** , Dr. Pankaj Patel*****
*1st Year Resident, ****Professor and Head, Department of Pharmacology. **Assistant Professor,
2nd Year Resident, Department of Emergency Medicine,** Dean, Smt.NHL Municipal Medical College,
Ahmedabad, Gujarat, India-380006

Abstract: To eliminate the preventable deaths due to Acute Kidney Failure(ARF), especially due to chronic usage of over the counter non-steroidal anti-inflammatory drugs (NSAID) medications should be a pre-defined healthcare goal. Ever after the discovery of selective cyclooxygenase-2 (COX-2) inhibitors, nephrotoxicity still remains a concern. Here we are highlighting a case of Aceclofenac induced Acute on chronic renal disease exemplifying unregulated use of NSAIDs is an under recognized and potentially dangerous problem and that constant pharmacovigilance is the key to detect such events. This case was notified and uploaded to Vigiflow with I'd 2018-58102. Even after the availability of diversity of NSAIDs, a renal safe NSAID is yet to be discovered. [Pandya A Natl J Integr Res Med, 2019; 10(1):51-53]

Key Words: Aceclofenac, Acute renal failure, Analgesic nephropathy, Pharmacovigilance

Author for correspondence: Dr. Sapna Gupta, Assistant Professor, Department of Emergency Medicine, Smt.NHL Municipal Medical College,Ahmedabad-380006,Gujarat, India.,
Email: sapna_gupta76@yahoo.com. M:9898244423

Introduction: Nephropathy associated with non-steroidal anti-inflammatory drugs (NSAIDs) is a pre-eminent and common adverse drug event in medical literature, yet they are over prescribed by the medical practitioners and also consumed without restraint by the patients for fever and pain. Also, due to the convenient over-the-counter availability of these drugs, majority of the population follows the proposition of self-treatment with these analgesics. Most of the consumers are unaware of the serious adverse effects of these painkillers and ultimately end up with life-threatening consequences like upper gastrointestinal bleeding and acute kidney injury.[1]

Case Report: A 50 year old male patient was admitted to our hospital with chief complaints of reduced urine output and vomiting since 3 days. He was having generalized weakness since a month. Also he was a known case of Rheumatoid Arthritis since past 12 years but not taking medications regularly for the same. The patient was taking T. Aceclofenac 100mg almost every day once daily since last 4 years for severe pain mitigation and had restricted activity since then. On examination patient was in altered sensorium but following verbal commands. Patient was malnourished and had multiple joint deformities. His heart rate was 110/min, BP was 110/70mmHg and respiratory rate around 30/min. His Arterial Blood Gas Analysis (ABG) showed mild metabolic acidosis. His Per abdominal examination showed suprapubic distension due to urine retention. On gross examination the urine was turbid. Patient was diagnosed with Acute on Chronic Kidney Disease(CKD) associated with co-morbidities urinary tract infection(UTI), cardiomyopathy and hypotension. He was intubated and mechanically ventilated and was started on vasopressor therapy along with other symptomatic treatment. His investigations showed Hb: 11.6gm/dl, TLC: 33,060/mm^3, Serum creatinine : 2.20gm/dl(raised), Serum Urea: 62mg/dl(raised), Serum K+: 3.3mmol/L, Serum Calcium: 3.9mg/dl and Serum Uric acid : 14.5mg/dl(raised). His 2D Echo showed Dilated cardiomyopathy. USG KUB showed bilateral enhanced echogenicity with loss of CMD (Corticomedullary differentiation). Patient also had multiple rashes on both lower limbs and dorsum of feet and was also diagnosed with Progressive pigmented purpuric dermatosis by the Dermatologist and was prescribed T. Levocetirizine for the same. In the course of admission patient rapidly deteriorated with worsening of renal parameters and hypokalaemia and death was encountered on the second day due to refractory hypotension.

Discussion: A number of guidelines and literature reviews relating to the management of chronic pain in the elderly exist, but non-steroidal anti-inflammatory drugs (NSAIDs) still remain the first-line management option.[2] Although NSAIDs are widely considered safe, considering their frequent and accepted usage, in reality, even therapeutic doses carry a risk of loss of renal function. Acute Kidney Injury(AKI) following NSAIDs usage is more likely to occur in hypovolaemic states which can be further

precipitated by co-morbidities like pre-existing chronic kidney disease (CKD), hypertension, use of the 'triple whammy' (ACE inhibitor or ARB plus diuretic plus NSAID) and various drug interactions that increase plasma level of NSAIDs and worsens the condition which highlights that hydration particularly in post-operative period as well as assessment of co-morbid conditions are crucial before administration of NSAIDs to prevent acute renal failure.[3]

Aceclofenac is indicated for the relief of pain and inflammation particularly in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. The importance of prostaglandins in maintaining renal blood flow should be taken into account in patents with impaired cardiac or renal function, with diuretic treatment, liver dysfunction or recovering from major surgery. Adverse renal events occur in approximately 1 to 5 percent of all patients using NSAIDs. Despite their efficacy, NSAIDs are best avoided in the elderly, and if they are required to be used then, they should be given in the lowest possible doses for the shortest period as NSAID administration might induce a dose dependent reduction in prostaglandin formation and can precipitate renal failure.[3]

Analgesic nephropathy(AN) is a condition of slowly progressive renal failure, decreased concentrating capacity of the renal tubule, and sterile pyuria. Risk factors are the chronic use of high doses of combinations of NSAIDs and frequent urinary tract infections. If recognized early, discontinuation of NSAIDs may permit recovery of renal function.[3]The nephrotoxicity of NSAIDs is mediated via nonspecific blocking of cyclooxygenase, subsequent inhibition of prostaglandin synthesis leading to vasoconstriction, and reversible renal impairment in volume-contracted states. This may lead to acute tubular necrosis and acute renal failure.[3]Also, PG-induced inhibition of reabsorption of Cl^- and the action of antidiuretic hormone might be impaired by NSAIDs, resulting in the retention of salt and water. Inhibition of COX-2–derived PGs that contribute to the regulation of renal medullary blood flow may lead to a rise in blood pressure, increasing the risk of cardiovascular thrombotic events and heart failure. NSAIDs promote reabsorption of K+ as a result of decreased availability of Na+ at distal tubular sites and suppression of the PG-induced secretion of renin. [4]

AKI can occur with any class of traditional, nonselective NSAID or cyclooxygenase-2 (COX-2)-specific NSAIDs. NSAIDs can induce several different forms of kidney injury including hemodynamically mediated acute kidney injury (AKI); electrolyte and acid-base disorders and acute interstitial nephritis (AIN) associated with papillary necrosis.[5,6]Renal functions might deteriorate in patients with mild to moderate renal impairment with chronic usage of NSAIDs, so they should always be kept under surveillance. Researches have also found that there is a 4-fold increase in risk of AKI associated with NSAID use which was dose dependent during the first month of chronic usage of NSAIDs.[7,8]Thus administration of NSAIDs should be explored meticulously in hospitalized patients with unexplained renal failure also.

Henceforth the association between nonphenacetin-containing combined analgesics and renal disease is a topic of concern and has been debated for several years. Yet there is insufficient evidence to claim that combined analgesics in the absence of phenacetin, are causally associated with nephropathy and that a new epidemiological study is needed to address this question to prevent further morbidity and mortality. [9,10]

Conclusion: Regular use of NSAIDs may increase the risk for chronic kidney disease especially in some high-risk groups. Due to over-the-counter availability and also increasing popularity of NSAIDs, the possibility of an increased risk for acute on chronic renal disease associated with their long term use may require further perusal. Thus awareness of the dangers following use of NSAIDs could reduce the episodes of nephrotoxicity.

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