Screening Patients on Long Term Non-steroidal Anti-inflammatory Drugs (NSAIDs) for Nephrotoxicity — Why Necessary and How Frequently?

AR Chogle*

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed to patients with conditions as diverse as acute pain episodes, lower back pain, rheumatoid arthritis (RA), and osteoarthritis. Individuals with inflammatory musculoskeletal conditions often need NSAIDs because of the limited activity of non-NSAID analgesics (e.g., acetaminophen) and the unacceptable side effect profile of corticosteroids. NSAIDs are usually prescribed on long-term basis for patients with RA, for providing symptomatic relief and do not alter the course of the disease, nor do they prevent joint destruction.

The treatment of rheumatoid arthritis (RA) is rapidly evolving and guidelines for the management of RA have been formulated and regularly updated. Current recommendations encourage earlier use of disease modifying antirheumatic drugs (DMARD) and combination therapy.\(^1\) While these recommendations are clear, there is a great variability in actual prescribing patterns. In a cohort of patients with RA cared for either by general practitioners or rheumatologist, NSAID was the most commonly prescribed medication, with substantially lower rates of use of DMARD and corticosteroid.

These differences might be explained by patient and physician preference, physician experience with specific drug classes, and physician speciality.\(^2\) Although Indian guidelines on the management of RA have been formulated and published,\(^3\) there is paucity of data on the patterns of drug use in Indian patients suffering from RA seen by generalists, specialists, or both.

In the current issue of the Journal, Pathan et al\(^4\) describe their pattern of drug use in RA patients seen in a tertiary referral centre. It is noteworthy that out of the 99 patients almost all were receiving DMARDs in addition to NSAIDs. DMARD therapy requires more prescribing experience than NSAID therapy. As a result primary care physicians prescribed DMARD less frequently.\(^5\) Pathan et al\(^4\) advocate regular monitoring of serum creatinine levels while the patients are on NSAID therapy. A review of current understanding of the renal effects of NSAID and consideration of the strength and limitations of the Pathan’s study\(^4\) will be necessary to highlight the scope for future research in this area.

Cyclooxygenase (COX), the key enzyme involved in the synthesis of prostaglandins and other eicosanoid mediators, is the main target of NSAID action. Two isoforms, COX1 and COX2, have been identified. They are products of distinct genes and their expression is under different regulatory control. Both COX1 and COX2 are highly expressed in the kidney and both are inhibited by conventional NSAID. The NSAIDs block two very important prostaglandins from the standpoint of renal function: prostaglandin E2 and prostaglandin I2, better known as prostacyclins which are very important for renal homeostasis, maintenance of glomerular filtration rate (GFR), and renal blood flow. In the setting of significant physiologic stress, renal function becomes dependent upon prostaglandin and NSAID use may be associated with acute deterioration of renal function, including development of sodium retention, oedema, hypertension, hyperkalemia, and or papillary necrosis.\(^6\) Accumulating data using recently developed selective COX2 inhibitors suggest that while these agents spare the gastrointestinal tract they have similar renal effects as non-selective NSAIDs.\(^7\) Both cyclooxygenase enzymes are constitutively expressed in the kidney, but at different locations. COX1 is predominantly expressed in the collecting duct, and appears to elaborate a vasopressor compound that promotes angiotensin-induced hypertension, whereas COX2 is primarily localised in the renal medullary interstitial cells and the macula densa/cortical thick ascending limb, and generates a vasodepressor compound that reduces angiotensin-II-induced hypertension. Inhibition of COX2 or knockout of the COX2 gene results in reduction of renal medullary blood flow and urine formation, whereas COX1 inhibitors have no effect.\(^8\) This suggests that inhibition of COX2 accounts for the majority of the renal effects of the non-selective NSAIDs. Therefore, caution should be taken when prescribing selective COX2 inhibitors to patients, especially to patients with predisposed physiologic stress.

Despite the well-characterized acute biologic effects of NSAIDs on the kidney, there are no scientifically acceptable data that documents the safety of this class of drugs on renal function.
structure and function when taken chronically. The hallmark lesion of analgesic-associated nephropathy is renal papillary necrosis, which can lead to progressive renal failure but also may be present with a well-preserved glomerular filtration rate, making ascertainment of cases by renal function studies alone problematic. The frequency of renal papillary necrosis as a primary or contributing cause of end-stage renal disease is unknown because of the infrequent radiographic diagnosis by physicians resulting in misclassification and the insensitivity of renal diagnosis by currently available renal function tests, such as serum creatinine.

In their retrospective study, Pathan et al\(^4\) found a high incidence of abnormal creatinine level (27.7% of cases) in patients of RA on long term NSAID therapy and this rise was asymptomatic in all patients and mostly reversible. The study includes carefully characterised cases of RA, has a reasonable sample size, long duration of follow up with regular and a thorough analysis. It identifies a subgroup of elderly males that is likely to be at a particular risk of long term NSAID-induced renal insufficiency. However this study has several limitations some of these being intrinsic to retrospective studies and some of which are peculiar to Pathan study.\(^4\)

Pathan study\(^4\) suffers from several potential biases.

A) Misclassification of exposure: The observed association between NSAID usage and rise in creatinine levels could have several explanations. The possibility arises as cumulative NSAID intake in their patients could not be calculated as patients have used different NSAIDs at different periods of time.

B) Detection bias: NSAID use may have aggravated preexisting renal disease. Besides antirheumatic drug-induced nephrotoxicity, AA amyloidosis and renal vasculitis are important causes of renal lesions in RA. Although it is generally felt that AA amyloidosis due to RA is quiet uncommon in Indian patients, a recent study from tertiary referral centre showed that abdominal fat amyloid deposits are not uncommon in adult Asian North India patients with RA.\(^5\)

The study design and the results of Pathan study\(^4\) do not support a cause and effect relationship between long term NSAIDs usage and chronic renal disease. The hallmark lesion of analgesic-associated nephropathy - renal papillary necrosis, may also be present with well-preserved glomerular filtration rate, making ascertainment of cases by renal function studies alone problematic.

C) Confounding factors: Pathan et al\(^4\) have concluded that males and elderly may be more susceptible to NSAID nephrotoxicity. The finding of greater risk among older patients who may have compromised renal circulation is consistent with toxicity related to the inhibition of prostaglandin synthesis. However the finding of risk being more in males is similar to the findings of Sandler et al.\(^10\) If future studies confirm that elderly males are more at risk, new questions about pathogenesis will arise.

Analysis of several other possible confounding factors such as hypertension, diabetes, IHD and use of drugs such as diuretics and ACE inhibitors failed to reach statistical significance because of small number of cases in each subgroup.

Important aspect of Pathan study\(^4\) is that their findings are a ground for more intensive research using properly designed controlled studies to assess the renal safety of chronic NSAID therapy (including recently available selective COX2 inhibitors) by themselves or in the presence of known aetiologies of renal disease. Cautious practitioners may want to consider the findings in Pathan study\(^4\) that may help them in deciding whether to routinely monitor renal functions in their patients on long term NSAID therapy. Further epidemiological evidence that NSAIDs do increase the risk of chronic renal disease and the risk differs across the various subgroups will help in formulating guidelines on how frequently renal function monitoring is required in patients on long term NSAID therapy.

REFERENCES


