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EDITORIAL

- 1 Malignant non-steroidal anti-inflammatory drugs: Misunderstanding of their safety profile in patients with renal insufficiency
Rothschild BM

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Maligned non-steroidal anti-inflammatory drugs: Misunderstanding of their safety profile in patients with renal insufficiency

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Abstract

Non-steroidal anti-inflammatory drugs have a fundamental and pivotal position in management of many of the disorders managed by rheumatologists. Promulgation of a false perspective of their toxicity has compromised our ability to advise our patients and participate in the management of their disorders. The literature sources, from which the false perspective derives, do not accurately reflect safety and fail to address the value of appropriate drug use monitoring. We, as rheumatologists, must stand up and proactively address engrained misconceptions-if we are to be able to continue to provide safe, effective care for our patients.

Key words: Non-steroidal anti-inflammatory drugs; Renal function; Safety; Toxicity

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Core tip: Non-steroidal anti-inflammatory drugs are safe when appropriately dosed and renal function monitored. Evaluation for complete blood count, comprehensive metabolic panel and urinalysis within two weeks of initiation, at dose augmentation and with use of interacting or hemodynamically-altering concomitant medications, and again at a month and at three month intervals provides an appropriate monitoring regimen.

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MAIN TEXT

A major tool in the armamentarium of the rheumatologist is the non-steroidal anti-inflammatory (NSAID) group of medications. They have proven relatively safe when

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their effects, both beneficial and potential risks are appropriately monitored^[1-5]. Proactive protection against ulcers is routine, as is monitoring renal function. If the patient and their laboratory profiles are assessed within weeks of initiating NSAID therapy or initiating a concomitant hemodynamic-altering medication, potentially related detrimental effects can be identified and addressed.

The recommended approach is evaluation of blood pressure, complete blood count [specifically hemoglobin, white blood cell (WBC) and platelet count], comprehensive metabolic panel [complete metabolic panel including specifically creatinine, aspartate aminotransferase (referred to as AST or SGOT) and alanine aminotransferase (referred to as ALT or SGPT) and urinalysis (for red blood cells, protein and cellular casts) within two weeks of initiation, at dose augmentation and with use of interacting or hemodynamically-altering concomitant medications, and again at a month and at three month intervals provides an appropriate monitoring regimen. Rise of blood pressure more than 15 mm (on repeated assessment) or above “normal” values is indication for dosage modification. Reduction of WBC by half or below two, hemoglobin reduction by greater than 1.5 g/dL or platelet count by half or less than 100000 are indications for dosage modification.

Some nephrologists seem to have a different perspective, aggressively encouraging patients that they should never take an NSAID-if their renal function is not absolutely normal at baseline of treatment consideration-instead of assuring appropriate monitoring. That nephrology opinion appears to be based on retrospective studies wherein a NSAID may have been used within a period of time before renal alteration was identified^[6-11], without consideration of whether there had been safety monitoring of its use, the condition(s) for which it was used, or concomitant afflictions^[12,13]. Further, the response of nephrologists when queried as to the source of their perspective site seems to base it on that analysis of Medicaid databases^[7] and even the authors^[7] noted the low strength of such observations. However, there is a difference between citation and actual evidence.

Medicaid data bases have been the subject of great controversy, because of “lack of information on many potential confounding factors. They don’t examine medication compliance^[14]. The latter is a major factor in subsequent disease development^[14]. Even more pertinent is failure to consider that those individuals receiving medications may be less healthy than the so-called control group^[14]. These have been referred to as both immortal time and selection biases and Lund *et al*^[15] suggest that they “invalidate estimated treatment effects on safety outcomes.” Healthy individuals, not requiring use of a specific medication, and those who utilize that medication create selection bias, compromised even further by failure to consider the bias created by healthier behaviors and greater compliance^[15,16]. Comparison of vaccination history might be one useful measure to assure similar health attitudes. Failure to consider indication for treatment and lack thereof and a priori valid contraindications to medication use further compromises such comparisons. If exposure and the disorder being attributed share a common etiology, actual relationship is not required for correlation^[17]. Such is a significant source of misinterpretation. Comparing a selected subgroup from a general population introduces the converse of the “healthy worker” bias^[17]. Even worse bias is introduced by extrapolating when medication usage is non-descript (indication and actual consumption). Toxicity assessment is applied to specific indications and without consideration of appropriate monitoring for safety. Focusing on apparent relationships narrows the search image with risk of faulty extrapolations, such that underlying causes are overlooked^[18].

Prospective analyses of impact of NSAIDs on renal function have assessed changes after NSAID initiation, but have not examined whether elimination or reduction of dose ameliorated those changes^[7-11,13], although Schlondorff^[19] and Ejaz *et al*^[20] did document return to baseline values. It is unclear that previously published population studies have considered the effect of such intervention, representing more the art than the science of medicine, although it is exactly the evidence-based approach for which medicine now strives^[21]. Curiously, studies on “renal dysfunction” in rheumatoid arthritis identified advanced age, female gender, hypertension and obesity as correlates, but not NSAIDs^[22]. Appropriate monitoring by rheumatologists appears to prevent permanent damage. Möller *et al*^[23] specifically observed that a 10 year prospective review of effect of baseline renal disease revealed no progression when initially characterized as chronic renal disease stages 1-3. It was only when glomerular filtration rate fell below 30 mL/min that progression of renal disease was noted, and only in those with consistent NSAID usage.

Is unmonitored use of NSAIDs (typically reported in retrospective studies) less bothersome than unmonitored absolute preclusion instruction by some nephrologists. Acting independently without offering an alternative treatment and without discussion with the primary physician places the patient in the middle as to whose advice they should follow. The difficulty of reversing preconceived notions serves to

emphasize the importance of critical review of data supporting those philosophies.

Medical care always requires assessment of risk *vs* benefit. NSAIDs are a major component of our armamentarium as rheumatologists and we have learned to appropriately monitor their use to assure safety. Any nephrologist demanding total NSAID avoidance leaves us with much less safe and/or much more expensive alternatives, if indeed any remain. We, as rheumatologists, must stand up and proactively address engrained misconceptions-if we are to be able to continue to provide safe, effective care for our patients.

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