Can NSAIDs be used safely for analgesia in patients with CKD?
Moderator Commentary

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The debate in this issue of *Kidney360* addresses the quandary that exists regarding the safety of non-steroidal anti-inflammatory drug (NSAID) use in patients with chronic kidney disease (CKD). This is an important issue as pain syndromes are common in patients with CKD. While NSAIDs are a widely employed and effective analgesic, they can be associated with several adverse “clinical kidney syndromes” (*Table 1*), particularly in patients with underlying CKD (1,2). Clinicians struggle to achieve adequate analgesia while also avoiding toxicity in this group. However, is avoiding NSAIDs in patients with CKD too restrictive and unnecessary? Our two expert debaters Erin Baretto and Bruce Guthrie tackle the conundrum of whether NSAIDs can be safely used in patients with non-dialysis CKD. They will present the PRO and CON sides of the debate. We provide background on NSAID therapy in patients with CKD to set the stage for the debate.

Pain management in patients with CKD is limited by a number of analgesic drug-related adverse effects (3). Reduced glomerular filtration rate (GFR) and impaired tubular secretion put patients with acute kidney injury (AKI) or CKD at increased risk for drug-related nephrotoxicity due to increased accumulation of parent drugs and their metabolites from impaired metabolism and excretion (4). A significant number of drugs with potential toxicity are concomitantly prescribed to patients with advanced CKD(5). As such, NSAIDs are considered a class of drugs that should be avoided in patients with CKD, particularly those with advanced CKD (6,7). This approach has led to increased opioid administration and use of adjuvant therapies to manage pain (8,9). Importantly, opioid use poses many risks, and data regarding the safety of even commonly used agents in patients with CKD are markedly limited (8). In fact, a recent publication noted that NSAIDs were safer than opioids in this group of patients (10). In light of this, a more nuanced approach encompassing CKD stage and other risk-enhancing comorbidities should be employed given the difficulty in managing pain in this population. Let’s see what our two expert faculty debaters have to say about this issue.

Dr. Barreto on the PRO side of the debate provides perspective regarding the relative risk of NSAID use compared to the use of alternative analgesics. Her article cites multiple studies demonstrating non-inferiority of NSAIDs in comparison to opioids in causing worsening kidney disease and hospitalization, and the higher risk of death with use of opioids compared to NSAIDs in CKD patients. Multiple studies cited for this side of the debate offer evidence that NSAID use
is not associated with a greater risk of AKI or worsening kidney disease in CKD patients, and Dr. Barreto argues that the idea that non-NSAID analgesics are consistently safer for patients with CKD is not supported by data. Dr. Barreto concludes that the appropriateness of NSAID use in patients with CKD should be based on an individualized evaluation encompassing type of pain, expected dose and duration, patient risk profile including stage of CKD, suitability of alternative therapies, and goals of care.

On the CON side of the debate, Dr. Guthrie highlights the physiologic underpinnings of NSAID-related adverse effects and how the “CKD kidney” may be more susceptible to these processes. He highlights that the risk of development of adverse clinical kidney syndromes with use of these agents is made higher in the setting of certain risk factors, such as dehydration and illness. Selected observational studies which he outlines demonstrate the increased risk of AKI with NSAID use in the general population, and that while there is a similar absolute increased risk of AKI with NSAID use in patients with CKD, their baseline risk of developing AKI from any cause is greater due to many factors. His article suggests that between the combined risks of gastrointestinal, kidney, and cardiovascular adverse events and the high burden of comorbid risk factors in the CKD population, NSAID use is almost never safe in this population, though he acknowledges that in real clinical practice, we are frequently faced with the decision to choose between options which are all unsafe in some respect.

So what should clinicians caring for patients with CKD suffering with pain take away from this debate? Both debaters make strong arguments for their respective sides, and as they both point out, the strength of the current data available on this subject in the literature is fairly weak because of the observational nature of the vast majority of the studies. In our view, in patients with CKD stages 1-3 in whom predisposing nephrotoxic risk factors are adequately addressed, short-acting NSAIDs used for up to 5-7 days is a reasonable pain management strategy with an acceptably low risk of significant nephrotoxicity. In this setting, routine labs and follow-up within 2 to 3 weeks should be undertaken to monitor for adverse effects. Long-term therapy may be employed in patients cognizant of those conditions (vomiting, diarrhea, volume depletion, etc.) that should prompt immediate NSAID discontinuation. Patients must also be willing to participate in close medical follow-up. NSAIDs should likely be avoided in those with prostaglandin-dependent states, including states of uncorrected volume depletion, advanced
cirrhosis, decompensated heart failure, or nephrotic syndrome (11). In addition, NSAID therapy should be used cautiously in CKD patients who are prescribed RAAS inhibitors, diuretics, and other hyperkalemia-promoting drugs.

In contrast to patients with early stage CKD, the risk of nephrotoxicity has not been adequately studied in patients with stage 4 and 5 CKD. As such, stage 4 CKD patients require a more judicious approach to NSAID therapy since these patients often struggle with increased AKI events, electrolyte and acid-base abnormalities, hypertension, and hypervolemia in the absence of NSAID therapy. NSAID use will exacerbate these complications, especially in patients with underlying heart failure, nephrosis, cirrhosis, hypertension, and type-4 renal tubular acidosis. Furthermore, concomitantly prescribed medications noted above will enhance risk for these complications. When stable stage 4 CKD patients necessitate therapy with NSAIDs, low doses of short half-life preparations for ≤5 days and with close monitoring is required. In patients with non-dialysis dependent stage 5 CKD, these drugs should be avoided due to the significant risk for potentially severe complications. However, if palliation and patient comfort are the primary goals, then NSAIDs can be used judiciously recognizing the potential risk for adverse outcomes.

NSAIDs are clearly associated with adverse kidney outcomes. As such, the benefit of improved pain control must be weighed against toxicity. The most judicious approach is one that is highly individualized based on CKD stage, age, comorbidities, and concomitant medication use. Ultimately, cautious use of NSAIDs in CKD patients is reasonable with the major focus on avoiding iatrogenic life-threatening NSAID-related complications such as severe AKI, hyperkalemia, and hypervolemia. While NSAIDs are generally avoided in patients with kidney disease, their use in this population after appropriate patient selection is reasonable, especially after weighing the risks posed by currently available alternative therapies.
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References


Table 1. Clinical kidney syndromes of NSAIDs

- Acute kidney injury (reduced renal prostaglandins)
  - Hemodynamic kidney failure
  - Ischemic acute tubular injury
- Hyperkalemia +/- non-anion gap metabolic acidosis
- Hyponatremia
- Hypervolemia and sodium avidity
  - Edema, congestive heart failure
  - Diuretic resistance
- Increased blood pressure
- Exacerbation of underlying hypertension
- Acute tubulointerstitial nephritis (idiosyncratic reaction)
- Nephrotic syndrome
  - Membranous nephropathy
  - Minimal change disease
- Acute or chronic papillary necrosis
- Progression of chronic kidney disease