Can NSAIDs be used safely for analgesia in patients with CKD?: CON

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Non-steroidal anti-inflammatory drugs (NSAIDs) reversibly inhibit cyclooxygenase (COX) and therefore alter prostaglandin synthesis in many tissues with a range of effects beyond their intended one. NSAIDs have a number of well-known adverse effects on the kidney, gastrointestinal tract, and cardiovascular system. Adverse effect profiles vary by drug, in part depending on relative selectivity for the COX-1 and COX-2 isozymes, with more COX-2 selective inhibitors having lower risk of gastrointestinal (GI) bleeding but higher risks of cardiovascular disease. All NSAIDs therefore have potentially serious adverse effects, and NSAIDs are a common cause of drug-related emergency hospital admission and drug-related death, from gastrointestinal bleeding, acute kidney injury, and serious cardiovascular events.1,2

International consensus guidelines recommend avoiding NSAIDs in people with eGFR<30ml/min/1.73m², and to avoid prolonged use in those with eGFR 30-59ml/min/1.73m².3 Despite this, NSAIDs are commonly prescribed to people with chronic kidney disease (CKD). One in ten people with CKD in the Chronic Renal Insufficiency Cohort Study were prescribed an NSAID annually, with 24% exposed at some point during eight years of follow-up. Exposure was common in all subgroups examined but was somewhat less likely in people with more severe CKD and those seeing nephrologists.4 A systematic review of NSAID use in people with CKD in seven cross-sectional studies found that 8-21% were currently taking NSAIDs.5 One likely reason for liberal prescribing is that NSAID prescribing has rapidly observable benefits on pain, whereas harms are merely theoretical risks at the point of prescribing. In addition, the prescriber will often not observe the harmful outcome because the patient presents with adverse effects elsewhere in the healthcare system.

Randomized controlled trials examining NSAID effectiveness routinely exclude people with CKD, and often do not evaluate renal outcomes or other potential harms.6 Most of our evidence for NSAID harms in people with CKD therefore comes from observational studies. Although this means that causality cannot always be proved, there is no doubt that NSAID prescribing in people with CKD has a number of important adverse effects on the kidney and on other body systems.

Renal adverse effects

Prostaglandins play an important role in maintaining or increasing renal blood flow in the face of extracellular volume depletion or reduced filtration, and have effects on renal handling of sodium, potassium and water. NSAID inhibition of renal prostaglandin synthesis can therefore cause abnormalities of serum sodium and potassium, fluid retention, and acute kidney injury in the face of dehydration and intercurrent illness.
There is consistent evidence from observational studies that NSAIDs are associated with increased risk of acute kidney injury. A systematic review estimated pooled odds ratio (OR) of 1.63 (95% CI 1.22 to 2.19) for acute kidney injury (AKI) for current NSAID exposure in people with CKD. This relative risk is similar to that observed in the general population, but baseline risk of AKI is higher in people with CKD meaning that absolute risk of NSAID exposure is higher. A population study in Canada published since the review, found OR 1.41 for AKI and 1.50 for hyperkalaemia for new NSAID use in older adults irrespective of renal function. Estimated OR were similar in those with and without CKD, but baseline risk and therefore absolute risk of AKI associated with NSAID exposure was higher in people with CKD. People with CKD are commonly prescribed diuretics and/or renin-angiotensin system inhibitors (RASI) (table 1), which is a further risk factor for AKI. The risk of NSAID exposure for AKI in people taking renin-angiotensin system inhibitors (RASI) and/or diuretics is somewhat larger in people with CKD (OR 2.51) compared to those without (OR 1.60). However, the absolute risk of AKI is four times greater in people with CKD because their baseline risk of AKI is higher.

Table 1: Prevalence of selected prescribing and comorbidities in people with CKD (reanalysis of existing dataset)

<table>
<thead>
<tr>
<th></th>
<th>Aged&lt;65 years N=5,159</th>
<th>Aged ≥65 years N=28,412</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current diuretic b</td>
<td>38.5%</td>
<td>57.8%</td>
</tr>
<tr>
<td>Current RASI b</td>
<td>52.6%</td>
<td>57.3%</td>
</tr>
<tr>
<td>Current diuretic and RASI b</td>
<td>26.8%</td>
<td>37.0%</td>
</tr>
<tr>
<td>Current antiplatelet b</td>
<td>32.7%</td>
<td>52.6%</td>
</tr>
<tr>
<td>Current oral anticoagulation b</td>
<td>3.8%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Cardiovascular disease c</td>
<td>24.7%</td>
<td>50.6%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>6.0%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Any of the above</td>
<td>73.8%</td>
<td>90.8%</td>
</tr>
<tr>
<td>Two or more of the above</td>
<td>48.0%</td>
<td>73.7%</td>
</tr>
</tbody>
</table>

a. Reanalysis of data for 33,571 people recorded as having CKD in primary care medical records in Scotland
b. Current prescribing = prescription issued in last 84 days. RASI = renin-angiotensin system inhibitor (either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker)
c. Coronary heart disease, stroke, transient ischemic attack or peripheral vascular disease

In contrast, the evidence that NSAID exposure is associated with progression of CKD is more mixed. Some studies show a dose-related increased risk of incident CKD in people with hypertension. However, a systematic review of seven studies found no association with progression of CKD for regular-dose NSAID use, although a significantly increased risk of progression from high-dose use (pooled OR 1.26, 95% CI 1.06–1.50).
**Gastrointestinal and cardiovascular adverse effects**

There are many other reasons to be concerned about NSAID exposure in people with CKD, because NSAIDs cause gastrointestinal (GI) bleeding, cardiovascular disease, and worsening of heart failure. People with CKD are at higher risk of GI bleeding. Compared to people with eGFR ≥60 ml/min/1.73 m² and after adjustment for age, sex, comorbidity and coprescribing, risk of hospitalization with GI bleeding is 50% higher in people with CKD stage 3, and seven times higher people with CKD stage 4 or 5. NSAIDs can cause gastrointestinal bleeding in anyone, but their risks are therefore potentiated in people with CKD because of higher baseline risk, and further potentiated by the frequent co-prescribing in people with CKD of other drugs which increase bleeding risk (table 1).

Many but not all NSAIDs are also associated with increased risk of major vascular events, particularly Cox-2 inhibitors and diclofenac where risk is increased by a third. Ibuprofen is associated with some increased cardiovascular risk in high doses, but has lower risk of GI bleeding. In contrast, naproxen appears safe from a cardiovascular perspective but is associated with higher rates of GI bleeding. NSAIDs are associated with a doubling of risk of heart failure hospitalization in randomized clinical trials, with evidence of increased mortality associated with NSAID prescription in people with established heart failure, particularly in higher doses. People with CKD have higher cardiovascular risk, and commonly have established CVD and/or heart failure (table 1), meaning that absolute risk of harm from NSAID exposure will be larger than in the general population.

**Summary**

NSAIDs have a number of adverse renal effects in people with CKD, and in particular are associated with clinically significant increased risks of AKI. People with CKD (and particularly older people with CKD) are very commonly prescribed other nephrotoxic or drugs which increase bleeding risk, very commonly have established cardiovascular disease, and fairly commonly have heart failure (table 1). More than three-quarters have at least one additional reason to avoid NSAIDs, and more than half have two or more additional reasons. In addition to renal risks, there will therefore often be good reasons to avoid NSAIDs in people with CKD. Although it is possible to mitigate NSAID risks by choosing NSAIDs which are safer for one outcome (such as naproxen for cardiovascular risks, or Cox-2 inhibitors for GI bleeding risks) there is no NSAID which is consistently safer across all outcomes. Similarly, although co-prescribing of gastro-protective drugs can mitigate (but not abolish) GI bleeding risks, there is growing evidence that proton pump inhibitors are themselves associated with both incident CKD, and with AKI in established CKD.

There is therefore no safe way to prescribe NSAIDS in CKD. NSAID use in people with CKD always carries some risk, and that risk accrues across multiple domains (AKI, electrolyte disturbance, GI
bleeding, cardiovascular disease, fluid retention and exacerbation of heart failure) which are all more common in people with CKD than the general population. NSAIDs can therefore never be considered safe in CKD. However, they are sometimes indicated when baseline risk of all adverse effects is low, and the indication is sufficiently strong that expected benefit outweighs all expected risk. In this context, untreated pain is clearly suboptimal. Other analgesics are not always effective and opioids in particular have significant problems of their own. If you must prescribe NSAIDs, then consider and aim to mitigate all potential adverse effects of NSAIDs in an individual. Gastroprotection with proton pump inhibitors should be used where indicated, interacting drugs should be stopped where possible, and patients should be instructed to stop NSAIDs and other nephrotoxic drugs should they develop diarrhea or vomiting or febrile illnesses with reduced fluid intake. NSAIDs cannot be used safely in people with CKD because they are always risky. However, risk of NSAID use varies between individuals. NSAID use is therefore not always wrong because clinical practice not infrequently requires choosing the least bad option in situations where every option is problematic.
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Author Contribution
B Guthrie: Project administration; Writing - review and editing
References