Can NSAIDs Be Used Safely for Analgesia in Patients with CKD?: CON

Bruce Guthrie

Nonsteroidal anti-inflammatory drugs (NSAIDs) reversibly inhibit cyclooxygenase (COX) and therefore alter PG 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 (GI) 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 GI bleeding but higher risk of cardiovascular disease. Therefore, all NSAIDs have potentially serious adverse effects, and NSAIDs are a common cause of drug-related emergency hospital admission and drug-related death, from GI bleeding, AKI, and serious cardiovascular events (1,2).

International consensus guidelines recommend avoiding NSAIDs in people with eGFR <30 ml/min per 1.73 m², and to avoid prolonged use in those with eGFR 30–59 ml/min per 1.73 m² (3). Despite this, NSAIDs are commonly prescribed to people with 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 8 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 health care 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

PGs 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 PG synthesis can therefore cause abnormalities of serum sodium and potassium, fluid retention, and AKI in the face of dehydration and intercurrent illness.

There is consistent evidence from observational studies that NSAIDs are associated with increased risk of AKI. A systematic review estimated a pooled odds ratio (OR) of 1.63 (95% confidence interval [95% CI], 1.22 to 2.19) for AKI for current NSAID exposure in people with CKD (6). 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 (6). A population study in Canada published since the review found ORs of 1.41 (95% CI, 1.20 to 1.65) and 1.50 (95% CI, 1.20 to 1.89) for AKI and hyperkalemia, respectively, for new NSAID use in older adults irrespective of renal function. Estimated ORs 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 (7). People with CKD are commonly prescribed diuretics and/or renin-angiotensin system inhibitors (Table 1), which is a further risk factor for AKI. The risk of NSAID exposure for AKI in people taking renin-angiotensin system inhibitors and/or diuretics is somewhat larger in people with CKD (OR 2.51 [95% CI, 1.09 to 5.78]) compared with those without (OR 1.60 [95% CI, 1.31 to 1.95]). However, the absolute risk of AKI is four times greater in people with CKD because their baseline risk of AKI is higher (8).

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 (9). 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 to 1.50) (10).

University of Edinburgh, Edinburgh, United Kingdom

Correspondence: Bruce Guthrie, Centre for Population Health Sciences, Usher Institute, Doorway 3, Old Medical School, Teviot Place, Edinburgh EH8 9AG, UK. Email: bruce.guthrie@ed.ac.uk
risk of harm from NSAID exposure will be larger than in the CVD and/or heart failure (Table 1), meaning that absolute higher cardiovascular risk, and commonly have established particularly at higher doses (13). People with CKD have NSAID prescription in people with established heart failure, (2), with evidence of increased mortality associated with of heart failure hospitalization in randomized clinical trials (11). NSAIDs are associated with a doubling of risk vascular perspective but is associated with higher rates of GI bleeding. In contrast, naproxen appears safe from a cardiovascular risk in high doses, but has lower risk of GI bleeding. Compared with people with eGFR ≥60 ml/min per 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 (11). NSAIDs can cause GI bleeding in anyone, but their risks are therefore potentiated in people with CKD because of higher baseline risk, and further potentiated by the frequent coprescribing in people with CKD of other drugs that increase bleeding risk (Table 1) (12).

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 one third (2). 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 (2). NSAIDs are associated with a doubling of risk of heart failure hospitalization in randomized clinical trials (2), with evidence of increased mortality associated with NSAID prescription in people with established heart failure, particularly at higher doses (13). 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, because NSAIDs cause GI bleeding, cardiovascular disease, and worsening of heart failure (2). People with CKD are at higher risk of GI bleeding. Compared with people with eGFR ≥60 ml/min per 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 (11). NSAIDs can cause GI bleeding in anyone, but their risks are therefore potentiated in people with CKD because of higher baseline risk, and further potentiated by the frequent coprescribing in people with CKD of other drugs that increase bleeding risk (Table 1) (12). 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 people with CKD. However, they are sometimes indicated when baseline risk of all adverse effects is low and the indication is sufficiently strong that the 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 (3). 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.
Disclosures
The author has nothing to disclose.

Funding
None.

Acknowledgments
The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or Kidney360. Responsibility for the information and views expressed herein lies entirely with the author(s).

Author Contribution
B. Guthrie was responsible for project administration, and review and editing the manuscript.

References
1. Howard RL, Avery AJ, Slavenburg S, Royal S, Pipe G, Lucassen P, Pirmohamed M: Which drugs cause preventable admissions to hospital? A systematic review. *Br J Clin Pharmacol* 63: 136–147, 2007. Available at: https://doi.org/10.1111/j.1365-2125.2006.02698.x
2. Bhala N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA, Bombardier C, Cannon C, Chaix AM, Commerford MP, Cooper ME, D The Lancet, Shanghai, China 1: 85–90, 2007. Available at: https://doi.org/10.1016/S0140-6736(07)60900-9
3. Kidney Disease: Improving Global Outcomes (KDIGO): KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Available at: https://www.kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf. Accessed January 1, 2020
4. Zhan M, St Peter WL, Doerfler RM, Woods CM, Blumenthal JB, Oates J, Patrono C, Schnitzer TJ, Solomon S, Tugwell P, Wilson K, Wittes J, Baigent C: Cooxib and traditional NSAID Trailists’ (CNT) Collaboration: Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: Meta-analyses of individual participant data from randomised trials. *Lancet* 382: 769–779, 2013. Available at: https://doi.org/10.1016/S0140-6736(13)60900-9
5. Zhang X, Donnan PT, Bell S, Guthrie B: Non-steroidal anti-inflammatory drug induced acute kidney injury in the community dwelling general population and people with chronic kidney disease: Systematic review and meta-analysis. *BMC Nephrol* 18: 256, 2017. Available at: https://doi.org/10.1186/s12882-017-0673-8
6. Nderitu P, Doos L, Jones PW, Davies SJ, Kadam UT: Non-steroidal anti-inflammatory drugs and risk of chronic kidney disease in subjects with hypertension: Nationwide longitudinal cohort study. *Hypertension* 66: 524–533, 2015. Available at: https://doi.org/10.1161/HYPERTENSIONAHA.114.05105
7. Ishigami J, Grams ME, Naik RP, Coresh J, Matsushita K: Chronic kidney disease and risk for gastrointestinal bleeding in the community: The Atherosclerosis Risk in Communities (ARIC) study. *Clin J Am Soc Nephrol* 11: 1735–1743, 2016. Available at: https://doi.org/10.2215/CJN.02170216
8. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B: Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. *Lancet* 380: 37–43, 2012. Available at: https://doi.org/10.1016/S0140-6736(12)60240-2
9. Gislason GH, Rasmussen JN, Abildstrom SZ, Schramm TK, Hansen ML, Fosbol EL, Sørensen R, Folke F, Buch P, Gadsbøll N, Rasmussen S, Poulsen HE, Køber L, Madsen M, Torp-Hansen ML, Fosbøl EL, Sørensen R, Folke F, Buch P, Gadsbøll N, Rasmussen S, Poulsen HE, Køber L, Madsen M, Torp-Pedersen C: Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs in chronic heart failure. *Arch Intern Med* 169: 141–149, 2009. Available at: https://doi.org/10.1001/archinternmed.2008.525
10. Hart E, Dunn TE, Feuerstein S, Jacobs DM: Proton pump inhibitors and risk of acute and chronic kidney disease: A retrospective cohort study. *Pharmacotherapy* 39: 443–453, 2019. Available at: https://doi.org/10.1002/phar.2235

Received: August 24, 2020 Accepted: September 22, 2020

See related debate, “Can NSAIDs Be Used Safely for Analgesia in Patients with CKD?: PRO” and commentary, “Can NSAIDs Be Used Safely for Analgesia in Patients with CKD?: COMMENTARY” on pages 1184–1188 and 1192–1194, respectively.