Kidney360

Renal Safety of Nonsteroidal Anti-Inflammatory Drugs and Opioids in Hospitalized Patients on Renin-Angiotensin System Inhibitors

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KIDNEY360 1: 586–587, 2020. doi: https://doi.org/10.34067/KID.0003682020

Nonsteroidal anti-inflammatory drug (NSAID) prescriptions for analgesia during hospitalization are increasing as health systems implement opioid-minimization initiatives (1). This trend can lead to an increase in the use of alternative agents, including NSAIDs, which are known to cause or increase susceptibility to hemodynamically mediated AKI among other renal adverse events. The risk for these outcomes may be particularly high among patients with multiple comorbidities and who are acutely ill (2). This may be especially true when NSAIDs are prescribed concurrently with renin-angiotensin-aldosterone inhibition (RAASi), which may reduce the threshold for hemodynamically mediated AKI, especially among those with actual or effective volume depletion or with decreased systemic vascular resistance. The higher risk with this drug-drug interaction is known and well documented in the outpatient setting (2,3); however, this study is the first to evaluate the potential and the magnitude for synergistic nephrotoxicity of NSAIDs and RAASi agents in patients who are hospitalized.

In this study, the authors conducted a large-scale pharmacoepidemiologic study in 25,571 hospitalized patients admitted to four hospitals in Pennsylvania to evaluate the risk of AKI in patients that are prescribed NSAIDs concurrently with RAASi therapy. They used advanced and rigorous methods to control for confounders. One of these approaches is the use of an active comparator (drugs with similar clinical indication), which allows to control for confounding by indication (4). For NSAIDs, the active comparator was oxycodone and that for RAASi was amlodipine. A highlight of their design is the use of two active comparators (like a 2×2 factorial design), which allows for the estimation of the incidence rates, risk differences, attributable risk, and to test for interactions between the different drug exposure groups.

Patients on RAASi are essentially different than those in amlodipine because these drugs have indications that go beyond BP control (*e.g.*, CKD, heart failure, and diabetes). As such, the authors used propensity score matching and innovative machine learning methods such as generalized boosted models coupled with multiregression decision trees to minimize covariate imbalance across all treatment groups (5) as well as inverse probability of treatment-weighted Poisson regression to further control for confounders (6). The analysis was then restricted to the subset of patients with overlapping multinomial propensity scores so that the authors could compare patients that have a similar probability of being treated with a given drug choice. These restrictions balanced baseline covariates, paralleling the standard table 1 found in randomized control trials. However, in observational designs, unmeasured confounders always remain because there is no randomization. Additionally, this study included covariates for conditions known to be associated with increased risk for AKI with combinations of these drugs, namely, heart failure, liver disease (cirrhosis), solid organ transplant (calcineurin inhibitor prescription), CKD, and nephrotic syndrome. To summarize, the authors applied innovative and rigorous methods used in real-world evidence studies (7,8), attending to questions that would be unfeasible for a randomized controlled trial to address.

The overall incidence rate of AKI was 23.6 episodes for 1000 days, which is lower than previous findings, and most of the episodes of AKI were mild (*i.e.*, 80% were stage 1) (9). When analyzed without the interaction term, NSAIDs alone significantly increased the risk of AKI in the hospitalized patients by 24% to 28%. RAASi increased the risk of AKI by 25% in the sensitivity analysis. These findings highlight the importance of considering the risk factors for NSAID- and RAASi-induced, hemodynamically mediated AKI in patients who are hospitalized.

In the interaction analysis (the main analysis for this study), the authors found 5.9 excess AKI episodes in 1000 days among patients taking NSAIDs (versus oxycodone) concurrently with RAASi compared with 4.1 excess AKI episodes in 1000 days among patients taking NSAIDs (versus oxycodone) concurrently with amlopidine, for an overall risk difference estimate of 1.8 excess AKI episodes in 1000 days for the interaction.

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This risk difference was not statistically significant. However, when this analysis was restricted to the patients on diuretics, the overall risk difference of AKI was much higher: 9.9 AKI episodes per 1000 days of hospitalization. For this subset of patients, NSAIDs carry a higher risk of AKI and hence, in our opinion, should be avoided.

Additionally, in a rate ratio analysis, the authors found a significant increase in risk for AKI for NSAIDs versus oxycodone among RAASi users: 1.26 (95% CI, 1.09 to 1.45). There was a small but nonsignificant increase in risk for AKI with the concurrent use of NSAIDs versus oxycodone on RAASi versus the concurrent use of NSAIDs versus oxycodone and amlodipine: 1.04 (95% CI, 0.74 to 1.45). These findings further suggest that NSAIDs increase the risk of AKI but again support that this risk was not magnified in RAASi users.

The reason for the lack of interaction between NSAIDs and RAASi in this study may be related to multiple factors: limited power, the short-term administration of NSAIDs (with the median duration being 2 days of analgesia in all study groups), and the patient population characteristics. For example, only 10% of the patients had CKD in cohort B, two thirds were surgical patients, and only 7% were patients in the intensive care unit (ICU), which makes these results not generalizable to patients with CKD or in ICU. Also, this cohort may have been less sick than the usual hospitalized patient cohort, as reflected by the low AKI incidence rate of stage 2 and 3 AKI cases.

Overall, opioids carry significant consequences, including the potential for abuse and adverse drug events (10,11). Significant national efforts have ensued to achieve pain management with alternative drugs and methods, including the use of NSAIDs in the hospital setting. This study suggests that the choice of short-term administration of NSAIDs for acute analgesia (*i.e.*, no longer than 2 days) may be safe in hospitalized patients on RAASi, and not all patients on RAASi need to be committed to opioids. However, we should use caution when interpreting this study because these results are applicable only to patients with a very specific comorbidity profile, without CKD, not in ICU, not on diuretics or volume depleted, *etc.*, and the decision for use needs to be made on a case-by-case basis. This study also highlights a gap in knowledge and an area of need for developing support systems for risk prediction for AKI induced by the NSAIDs that are made widely available in the healthcare system.

Acknowledgments

We thank Allyson Dickson for proofreading the manuscript.

Author Contributions

A. Hung and C. Chung wrote the original draft and provide critical revisions.

Disclosures

All authors have nothing to disclose.

Funding

This work was supported by US Department of Veterans Affairs grant CSR&D Merit I01CX001897 (to A. Hung) and National Institutes of Health grant R01AR073764 and US Department of Veterans Affairs grant CSR&D Merit I01CX001741 (to C. Chung).

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Received: June 5, 2020 **Accepted:** June 23, 2020

See related article, "Effect of Renin-Angiotensin System Inhibitors on the Comparative Nephrotoxicity of NSAIDs and Opioids during Hospitalization" on pages 604–613.