Original Article

Individual non-steroidal anti-inflammatory drugs and risk of acute kidney injury: A systematic review and meta-analysis of observational studies

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Abstract

Background: The association between acute kidney injury (AKI) and use of non-steroidal anti-inflammatory drugs (NSAIDs) is well established. However, little is known about the comparative risk of individual NSAIDs, including specific COX-2 inhibitors.

Methods: We conducted a systematic review and meta-analysis of cohort studies that reported relative risk, hazard ratio or standardized incidence ratio with 95% confidence interval comparing AKI risk in NSAID users versus non-users. Pooled risk ratios and 95% confidence intervals for individual NSAIDs were calculated using random-effect, generic inverse variance methods.

Results: Five studies were identified and included in our data analysis. Pooled risk ratios were calculated for seven traditional NSAIDs and two specific COX-2 inhibitors, including indomethacin, piroxicam, ibuprofen, naproxen, sulindac, diclofenac, meloxicam, rofecoxib and celecoxib that were evaluated in at least two studies. The pooled risk ratios were fairly consistent among individual traditional NSAIDs, ranging from 1.58 to 2.11. Differences between pooled risk ratios did not reach statistical significance (p ≥ 0.19 for each comparison). Elevated AKI risk was also observed in diclofenac, meloxicam, rofecoxib and celecoxib users, although did not achieve a statistical significance.

Conclusion: A statistically significant elevated AKI risk among traditional NSAID users has been demonstrated in this meta-analysis. The pooled risk ratios among individual traditional NSAIDs were not significantly different. The pooled risk ratios of specific COX-2 inhibitors and the two traditional NSAIDs with the most COX-2 selectivity (diclofenac and meloxicam) were also comparable with other traditional NSAIDs even though they did not achieve a statistical significance.

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1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used classes of medications in the United States [1] despite their several notorious adverse effects, particularly gastrointestinal (GI) bleeding and renal dysfunction [2,3]. NSAIDs work by inhibiting the cyclooxygenase (COX) enzyme which has two isoforms, COX-1 and COX-2. Traditional NSAIDs inhibit both isoforms while the newer specific COX-2 inhibitors have a substantially higher specificity for the COX-2 isoform, thus preserving the anti-inflammatory property of COX-2 inhibition while theoretically reducing the adverse effect related to inhibition to the COX-1 isoform [2]. A superior GI safety profile of specific COX-2 inhibitors has been demonstrated in several randomized controlled trials and epidemiological studies [4–7] though this benefit is offset by the increased risk of serious cardiovascular events [8,9].

Acute kidney injury (AKI) associated with the use of NSAIDs has been well-documented by several population-based studies as well, with the relative risks compared with non-user ranging from 1.6 to 2.2 [10–12]. However, little is known about the risk of individual NSAIDs, including specific COX-2 inhibitors. Further data are needed to quantify the risk of AKI associated with individual NSAIDs to help physicians in selecting the most appropriate treatment for individual patients. Thus, we conducted this systematic review and meta-analysis of observational studies that compared the risk of AKI in NSAID users versus non-users to provide pooled risk ratios for AKI associated with use of each NSAID.

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2. Methods

2.1. Search strategy

Two investigators (P.U. and W.C.) independently searched published studies indexed in Medline, EMBASE and Cochrane databases from inception to September 2014. The search terms were compiled from the terms for AKI, the names of individual drugs, the therapeutic class and the mode of action in conjunction with the terms for observational studies that were suggested by Furlan et al. [13]. The detailed search strategy is provided as Supplementary material 1. A manual search of references of selected retrieved articles was also performed.

2.2. Inclusion criteria

The inclusion criteria were as follows: (1) Studies had to be observational study (case–control or cohort study), (2) relative risk (RR), odds ratio (OR), hazard ratio (HR), standardized incidence ratio (SIR) or standardized prevalence ratio (SPR) with 95% confidence intervals (CI) or raw data necessary to calculate these ratios and their CIs for individual NSAIDs were provided, and (3) non-users of NSAIDs were used as a reference group for cohort study while participants without AKI were used as control for case–control studies. Study eligibility was independently determined by each investigator noted above. Quality of the included studies was also independently appraised by the two investigators using the Newcastle-Ottawa quality assessment scale which assessed each study in three areas including (1) the selection of the study groups, (2) the comparability of the groups and (3) the ascertainment of the exposure or outcome of interest for case–control or cohort studies, respectively [14]. Any differing decisions were resolved by consensus with the third investigator (C.T.).

2.3. Data extraction

A standardized data collection form was used to extract the following information: title of the article, first author’s last name, authors’ affiliation, publication year, country where the study was conducted, study size, study population, names of NSAIDs that were studied, definition and diagnosis of AKI, average duration of follow-up, number of cases, number of controls, percentage of female, potential founders that were adjusted and adjusted pooled effect estimates with 95% CI. This data extraction was independently performed by the two investigators. Any differences in data extraction were resolved by consensus.

2.4. Statistical analysis

Data analysis was performed using Review Manager 5.3 software from the Cochrane Collaboration. Adjusted point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird for individual NSAIDs [15]. We reported the pooled effect estimate of AKI risk using the combination of the data from case–control and cohort studies to increase the precision of our estimates. As the outcome of interest was relatively uncommon, OR of case–control study was used as an estimate of the RR to pool this data with the RR or HR of cohort studies. We used a random-effect model rather than a fixed-effect model in light of the high likelihood of between study variance. The statistical heterogeneity was assessed by Cochrane’s Q test. This test was complemented with the I² statistic, which quantifies the proportion of the total variation across studies that is due to heterogeneity rather than chance. A value of I² of 0 to 25% indicates insignificant heterogeneity, 26% to 50% low heterogeneity, 51% to 75% moderate heterogeneity, and 76% to 100% high heterogeneity [16]. Comparisons of pooled risk ratios between 2 different NSAIDs were performed using indirect comparison methods (i.e., two-sample t-tests of the log-transformed pooled risk ratios with pooled standard error estimates) [17].

3. Results

Our search strategy yielded 2201 potentially relevant studies (495 studies from Medline, 1706 studies from EMBASE and none from Cochrane library), including 301 duplicates. 1810 studies were excluded based on the review of titles and abstracts, leaving ninety studies for full-length article review. Fifty-two studies were excluded since they were not observational studies while twenty were excluded as they were descriptive studies without a control group. Eight studies reported the overall risk of AKI among NSAID users but did not report the risks for individual NSAIDs while the other four studies reported risk of chronic kidney disease associated with NSAID use but did not report risk of AKI. These twelve studies were, thus, excluded from this meta-analysis. Six studies (five case–control studies [18–22] and one retrospective cohort study [23]) met our eligibility criteria. However, two studies utilized the same database [18,23]. Thus, to avoid potential patient duplication, we excluded the study by Gutthann et al. [18] as the data from the study by Guess et al. [23] was more comprehensive, leaving five studies with 28,992 patients with AKI for the data analyses. Fig. 1 outlines our literature search methodology and review process. The detailed characteristics and Newcastle-Ottawa quality assessment scale of all included studies are described in Table 1.

Pooled risk ratios were calculated for seven traditional NSAIDs and two specific COX-2 inhibitors, including indomethacin, piroxicam, ibuprofen, naproxen, sulindac, diclofenac, meloxicam, rofecoxib and celecoxib that were evaluated in at least two studies. There was a statistically significant elevated AKI risk for each of the traditional NSAIDs except for diclofenac and meloxicam. The pooled risk ratios were fairly consistent among individual traditional NSAIDs, ranging from 1.58 to 2.11. We tested for differences between pooled risk ratios and did not find any statistically significant differences between any two individual NSAIDs (p ≥ 0.19 for each comparison). Statistical heterogeneities were low to moderate in all analyses.

In contrast to the traditional NSAIDs, a statistically significant elevated AKI risk was not found in rofecoxib and celecoxib users, the two specific COX-2 inhibitors included in this study. The pooled risk ratios of rofecoxib and celecoxib were 1.50 (95% CI, 0.63–3.58) and 1.25 (95% CI, 0.79–1.97), respectively. Fig. 2A to C demonstrates the forest plots and I² values for each NSAID. Fig. 3 demonstrates the pooled risk ratios and 95% CIs for all NSAIDs included in this meta-analysis.

3.1. Sensitivity analysis

We perform a sensitivity analysis by excluding the only study with a retrospective cohort design [23]. In fact, it was also the only study with a quality concern as its Newcastle-Ottawa score was comparatively low and its effect estimates were not adjusted for any potential confounders. Nevertheless, exclusion of this study did not significantly alter the result of this meta-analysis. Forest plots of this sensitivity analysis are available as online Supplementary material 2.

3.2. Evaluation for publication bias

An evaluation for publication bias was not performed as only five primary studies were included in this meta-analysis.

4. Discussion

To the best of our knowledge, this is the first meta-analysis of observational studies that compares the risk of AKI among individual NSAIDs. We were able to estimate the risk for most of the commonly used NSAIDs in the USA.
Our study was able to demonstrate a statistically significant elevated AKI risk among most of the included traditional NSAIDs. The highest risk ratio was observed among indomethacin users while the lowest risk was found in subjects who used sulindac. However, as mentioned above, the differences between pooled risk ratios did not reach statistical significance.

NSAIDs can induce two different forms of acute kidney injury, including hemodynamically-mediated and acute interstitial nephritis. Inhibition of COX-1 enzymes with a subsequent reduction in prostaglandin (PG) synthesis is the cornerstone of the pathogenesis of hemodynamically-mediated AKI [24]. In healthy individuals, PGs do not have a significant role in renal hemodynamics. However, in the setting of prolonged renal vasoconstriction, such as patients with intravascular volume depletion or chronic kidney disease, PG-mediated afferent arteriole vasodilation plays a very crucial role in preserving renal blood flow and glomerular filtration rate by decreasing preglomerular resistance [25,26]. Thus, inhibition of COX-1, the major enzyme for PG synthesis, could jeopardize this compensatory mechanism, leading to acute renal dysfunction.

Based on this pathogenesis, theoretically, hemodynamically-mediated NSAID renal adverse effects are primarily associated with COX-1 inhibition. Our meta-analysis might support this hypothesis as the pooled risk ratios of rofecoxib and celecoxib, the two specific COX-2 inhibitors included in this study, were lower than traditional NSAIDs, although the risk differences did not reach a statistical significance. Our findings are in line with a recent meta-analysis of randomized controlled trials (RCTs) that also failed to demonstrate a statistically significant increased risk for composite renal endpoints, including renal dysfunction, hypertension and peripheral edema for most of their investigated specific COX-2 inhibitors (except for rofecoxib) [27]. Moreover, the pooled risk ratios of diclofenac and meloxicam, the two traditional NSAIDs with the most COX-2 selectivity [28,29], did not achieve a statistical significance as well, even though this might be simply related to a smaller sample size. It should also be noted that
Table 1
Main characteristics of the studies included in this meta-analysis.

<table>
<thead>
<tr>
<th>Country</th>
<th>Study design</th>
<th>Year</th>
<th>Cases</th>
<th>Controls</th>
<th>Definition of NSAID exposure</th>
<th>Diagnosis of AKI</th>
<th>Follow up NSAIDs included in the study</th>
<th>Number of cases</th>
<th>Number of control Confounder adjusted</th>
<th>Quality assessment (Newcastle--Ottawa scale)</th>
</tr>
</thead>
</table>
| Canada  | Retrospective cohort | 1987 | Any residents of Saskatchewan who filled prescription for NSAIDs in 1983. Cases were identified by using Saskatchewan prescription drug plan which covered more than 95% of all provincial residences. | Subjects without NSAID who were randomly selected from same database.    | Filled one or more prescription for NSAIDs in 1983. Information of NSAID prescription was obtained from the same database. | Admission Cr level of ≥2 mg/dL and either a ≥20% increase in Cr from baseline value or a ≥20% decline in Cr during hospitalization. | Piroxicam 29,616 Ibuprofen 27,792 Naproxen 23,051 Indomethacin 22,977 Sulindac 8333 Diclofenac 5615 | 1799           | 833,000                              | Selection: 3 stars Comparability: 0 star Outcome: 3 stars | 4228

SIR represents standardized incidence ratio; NA, not available; CXR, chest X-ray.

the I² of meloxicam, rofecoxib and celecoxib studies were also high (69%, 92% and 68%, respectively) which could jeopardize the validity of the pooled results. Furthermore, several cases of AKI associated with the use of specific COX-2 inhibitors have been reported in the medical literature and adverse effect surveillance program [30]. Thus, we could not dismiss the relationship between uses of specific COX-2 inhibitor and AKI.

Early anecdotal evidence had suggested that sulindac might have a relatively safer renal profile owing to the rapid renal oxidation of its active metabolic that may spare renal COX enzyme and thus PG synthesis [31]. Our meta-analysis does not support this assumption, as the pooled RR for sulindac was significantly elevated (pooled risk ratio of 1.58; 95% CI, 1.16–2.16) and overlapped with other traditional NSAIDs.

Even though most of the included studies are of high quality, there are some limitations and, thus, our results should be interpreted with caution.

First, most of the included studies were conducted using medical registry-based databases, raising a concern of coding inaccuracy and incompleteness. Second, exposure to NSAIDs was defined by prescription in all of the included studies. Therefore, over-the-counter use of NSAIDs was not recorded. Third, as mentioned above, we could not perform an evaluation for publication bias. Thus, publication bias in favor of a positive or negative study might have been presented, which could potentially jeopardize the validity of our results. Fourth, this is a meta-analysis of observational study which, by study design, is at risk of several types of bias [32]. For example, exposure to NSAIDs might have caused the patients to undergo more medical examination and laboratory testing, resulting in detection bias. Patients with increased baseline risk for renal dysfunction might have been preferentially exposed to certain NSAIDs, leading to confounding by indication [33].

Moreover, our study did report only the risk of AKI associated with NSAID use. We did not evaluate the risk of chronic kidney disease (CKD). Thus, one could not assume that specific COX-2 inhibitor is not associated with risk of CKD or CKD progression. In fact, the association between both traditional NSAIDs and specific COX-2 inhibitor has been previously demonstrated [34].

Fig. 2. A–C: Forest plots for pooled risk ratios for acute kidney injury for several individual nonsteroidal anti-inflammatory drugs.
5. Conclusion

In conclusion, a statistically significant elevated AKI risk among traditional NSAID users has been demonstrated in this meta-analysis. The pooled risk ratios were fairly consistent among individual traditional NSAIDs, ranging from 1.58 to 2.11. These pooled risk ratios were not significantly different from each other. The pooled risk ratios of specific COX-2 inhibitor and the two traditional NSAIDs with the most COX-2 selectivity (diclofenac and meloxicam) were comparable to other traditional NSAIDs, even though they did not achieve a statistical significance which were possibly related to a smaller sample size. Clinicians must weigh the possible risks of AKI and other NSAID related adverse events, including chronic kidney injury, hypertension and gastrointestinal bleeding against their potential benefit. Where possible, strategies using the minimum amount of drug for the shortest duration possible are preferred over long term treatment.

Conflicts of interest

The authors have declared no conflicts of interest. The results presented in this paper have not been published previously in whole or part.

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Patompong Ungprasert: study design, data search and collection, statistical analysis, and writing the manuscript.
Wisit Cheungpasitporn: data search and collection and writing the manuscript.
Cynthia S. Crowson: statistical analysis and revising the manuscript.
Eric L. Matteson: study design and revising the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ejim.2015.03.008.

References


