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Risk of Nephrotic Syndrome for Non-Steroidal Anti-Inflammatory Drug Users

Mohammad Bakhriansyah,[1,2] Patrick C. Souverein,[1] Martijn W.F. van den Hoogen,[3] Anthonius de Boer,[1] and Olaf H. Klungel[1]

Abstract

Background and objectives Nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with AKI. Their association with nephrotic syndrome has not been systematically studied. This study aimed to assess the risk of nephrotic syndrome associated with NSAID use.

Design, setting, participants, & measurements A matched case-control study was performed in the UK primary care database. Cases were patients with a first diagnosis of nephrotic syndrome and controls were those without nephrotic syndrome. NSAID exposure (grouped either based on cyclooxygenase enzyme selectivity and chemical groups) was classified as either current use at the nephrotic syndrome diagnosis date and corresponding date in the control group), recent, or past use. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated using unconditional logistic regression analysis.

Results We included 2620 cases and 10,454 controls. Compared with non-use, current use of 15–28 days and >28 days of conventional NSAIDs was associated with a higher relative risk of nephrotic syndrome: adjusted OR, 1.34; 95% CI, 1.06 to 1.70, and OR, 1.42; 95% CI, 0.79 to 2.55, respectively. Also, recent use (discontinuation 1–2 months before nephrotic syndrome diagnosis date; OR, 1.55; 95% CI, 1.11 to 2.15) and past use (discontinuation 2 months-2 years; OR, 1.24; 95% CI, 1.07 to 1.43), but not current use of <15 days (OR, 0.78; 95% CI, 0.46 to 1.31) nor past use (discontinuation >2 years; OR, 0.96; 95% CI, 0.85 to 1.09) were associated with a higher relative risk of nephrotic syndrome as well as past use of selective COX-2 inhibitors (discontinuation 2–24 months; OR, 1.24; 95% CI, 0.98 to 1.58). Categorization based on chemical groups showed that acetic acid and propionic acid derivatives were associated with a higher risk of nephrotic syndrome.

Conclusions The use of conventional NSAIDs was associated with a higher risk of nephrotic syndrome starting from at least 2 weeks of exposure, as well as for recent and past exposure up to 2 years before the diagnosis of nephrotic syndrome. This higher risk appeared mainly attributable to acetic acid and propionic acid derivatives.

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[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands; [2]Medical Faculty, Department of Pharmacology, Lambung Mangkurat University, Banjarmasin, Indonesia; and [3]Department of Internal Medicine, Erasmus MC University Medical Centre Rotterdam, Rotterdam, The Netherlands

Correspondence: Dr. Olaf H. Klungel, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Room 3.76, David de Wied Building, Universiteitweg 99, 3584 CG Utrecht, The Netherlands. Email: O.H.Klungel@uu.nl

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) can induce kidney lesions (1). Several studies demonstrated that conventional NSAIDs were associated with a higher risk of AKI and GN and decreased kidney hemodynamic functions, including sodium excretion. However, these adverse effects were not consistently seen for selective cyclooxygenase (COX)-2 inhibitors (2–8). These side effects occurred at a rate as low as 1%–5% for NSAID users (9). However, because NSAIDs are one of the most prescribed drugs and some of them are available over the counter, these small increased risks may translate into high absolute numbers of patients being affected, especially in those with preexisting impaired kidney function (10).

Several case reports indicate a potential causal relation between specific conventional NSAIDs or selective COX-2 inhibitors and nephrotic syndrome (11–17). The exact mechanism by which NSAIDs might cause nephrotic syndrome is largely unknown. Inhibition of COX enzymes by NSAIDs that increases arachidonic cascade products, such as leukotrienes, which may play a pathophysiologic role in inflammatory processes in kidneys, in conjunction with aldosterone are thought to contribute (18,19). In contrast, in another case study, celecoxib was safely administered in a patient developing nephrotic syndrome due to conventional NSAIDs (20). A few case studies showed that indomethacin and ibuprofen improve proteinuria and edema in patients with nephrotic syndrome (21–23).

Since a potential higher nephrotic syndrome risk for NSAID users is uncertain, we performed a systematic observational study to asses and quantify this risk for NSAID users according to both COX enzyme selectivity and chemical groups. The effect of duration of NSAID use on this association was also studied.

Materials and Methods

Study Design and Data Source

We carried out a matched case-control study using data from the Clinical Practice Research Datalink. This general practitioner database is the UK National Health Service observational data and interventional research service that has been established since 1987. The database provides detailed information on demographics, drug prescriptions, clinical events, specialist referrals, and hospital admissions (24). At the time of data extraction, information on more than 15 million patients from 720 general practitioner practices had been registered. Medical diagnoses are recorded on the basis of Read codes, and the drugs are recorded on the basis of British National Formulary and product codes. The independent scientific advisory committee of the Medicines and Healthcare Product Regulatory Agency database research approved this study (protocol number: 17_268).

Case and Control Definition

Cases were patients with a first diagnosis of nephrotic syndrome during valid data collection from October 1989 until November 2017. Nephrotic syndrome diagnoses are entered into the database in various manners. Most of them are entered as nephrotic syndrome only. A few nephrotic syndrome diagnoses are entered with information on either comorbidities or kidney biopsy (Supplemental Table 1). The date of this diagnosis was the index date. Controls were patients without nephrotic syndrome before and at the index date. Up to five controls were matched to each case by age, sex, general practitioner practice, and index date. Participants were included if they were 18 years or older and had at least one year of history in the database before the index date. Participants who were <18 years old were excluded because the causes of nephrotic syndrome in children are different from adults like congenital disorders, genetic mutations, and certain diseases such as infections that damage kidneys (25,26).

Exposure Definition

NSAID exposure was determined according to the prescription information before the index date and was categorized as either current, recent, or past use of NSAIDs. NSAIDs were further classified by their COX selectivity or chemical groups. Current users were patients who received the last NSAID prescription within 28 days before the index date. Current use was further categorized according to the duration of use by calculating the number of days of continuous NSAID exposure before the index date, using a permissible gap of 28 days between prescriptions to determine whether the current use period was continuous or not. The duration was classified as either 1–14 days, 15–28 days, or >28 days. Those who had received the last NSAID prescription within 29–56 days and 57 days or more before the index date were categorized as recent and past users, respectively. Past users were then divided according to the length of discontinuation before the index date, *i.e.*, between >2 months to 2 years and >2 years. Because of limited sample size, only current use of conventional NSAIDs was categorized according to the duration of use. Patients who switched between conventional NSAIDs and selective COX-2 inhibitors were classified to the subgroup that was closest to the index date. Those who did not receive any prescriptions of NSAIDs before and at the index date were defined as nonusers. Chemical groups of NSAIDs were determined according to the Anatomic Therapeutic Chemical Classification systems, including acetic acid derivatives, propionic acid derivatives, fenamates, oxicams, coxibs (selective COX-2 inhibitors), and other NSAIDs, *i.e.*, NSAIDs that are not classified elsewhere (Supplemental Table 2). Butylpyrazolidines were excluded because this chemical group has not been longer approved for human use in the UK. Fenamates, oxicams, and other NSAIDs were then grouped as "other conventional NSAIDs" because their sample size was too low to study them separately.

Potential Confounders

We considered comorbidities associated with nephrotic syndrome (diabetes mellitus, SLE, rheumatoid arthritis, amyloidosis, and leukemia). Several factors associated with kidney toxicity were also collected including comorbidities (hypertension, CKD, heart failure, and chronic liver disease), comedications (cardiovascular drugs [angiotensin-converting enzymes inhibitors, angiotensin II antagonists, β-blockers, diuretics, calcium channel blockers, and statins], systemic corticosteroids, antibiotics [aminoglycosides, sulfamethoxazole and trimethoprim, vancomycin, and ciprofloxacin], and chemotherapeutic agents), and lifestyle factors (body mass index, smoking, and alcohol abuse). Comorbidities were assessed as ever before the index date, and comedications were evaluated during 6 months before the index date. Body mass index and lifestyle factors were defined according to the latest information, with a maximum of 1 year allowed between the latest assessment and the index date.

Data Analyses

Demographic and medical data of cases and controls were compared using *t* test or chi-squared, whichever applicable. We performed conditional logistic regression analyses to calculate odds ratios (ORs), 95% confidence intervals (95% CIs), and to adjust for confounding factors. Because the risk of nephrotic syndrome for conventional NSAIDs was assessed separately, the matching was lost. We therefore also performed unconditional logistic regression analyses to calculate ORs, 95% CIs, and to adjust for all confounding factors including matching variables (age, sex, the general practitioner practices, and index date). The ORs for current users of conventional NSAIDs were stratified by the duration of use. We stratified our analyses by either age or sex to assess whether the estimated risks for NSAIDs were different within these subgroups. ORs were presented if there were at least five patients exposed to NSAIDs in case or control groups. We applied multiple imputations with fully conditional specification, using a total of five datasets to address missing values for body mass index and smoking status. All other variables in the model were used as predictors in this iterative method. All statistical analyses were performed using statistical software SPSS version 24 (IBM), and $P<0.05$ was considered statistically significant.

Sensitivity Analyses

We performed several sensitivity analyses. First, we assessed the risk for NSAID users by including only nephrotic syndrome diagnoses that were entered with information on kidney biopsy cases. Small sample size prevented us from assessing the ORs for current users on the basis of duration of use. Second, to anticipate on the delay in establishing the diagnosis of nephrotic syndrome from the first complaints, we considered four different time windows, *i.e.*, assuming that the index date was 3, 6, 9, or 12 months before the index date we have chosen in our study. Third, we excluded cases and controls with comorbidities that are well known causes of nephrotic syndrome, including diabetes mellitus, SLE, rheumatoid arthritis, amyloidosis, and leukemia. Finally, we tested the applicability of our findings for hospitalized patients with nephrotic syndrome in which the data were collected from the Hospital Episode Statistics Admitted Patient Care. It includes inpatients and outpatients, and accidental and emergency admissions to the National Health Services hospitals in England. About 98%–99% of private or charitable hospitals are funded by the National Health Service (27,28). Cases were hospitalized patients with a first discharge diagnosis of nephrotic syndrome on the basis of the International Statistic Classification of Diseases and Related Health Problems 10th Revision (code N04). Because of the limited sample size, we presented the ORs only for conventional NSAID use.

Results

Characteristics

A total of 2620 nephrotic syndrome cases and 10,454 matched controls were identified from more than 27 years of data collection. The mean age (±SD) of cases and controls was 58±17 and 57±17 years, respectively, and 55% were women. Compared with controls, cases had a higher prevalence of comorbidities associated with either nephrotic syndrome or kidney toxicity and comedications associated with kidney toxicity. Most cases and controls had normal weight to obese, had no alcohol abuse (95% versus 96%, respectively), and were smokers (57% versus 52%, respectively). Controls had a higher proportion of missing values on body mass index (12% versus 8%) and smoking status (5% versus 3%) than cases, respectively (Table 1).

Of 2620 cases, 288 (11%) nephrotic syndrome diagnoses were entered with information on kidney biopsy. A diagnosis of membranous GN was shown in 78 cases. Among them, 167 cases with information on kidney biopsy received at least one NSAID prescription in which membranous GN was found in 50 cases. The results of kidney biopsy for nephrotic syndrome cases are shown in Table 2.

Current use for 15–28 days and >28 days, recent use, and past use (discontinuation >2 months to 2 years) of conventional NSAIDs were associated with higher risk of nephrotic syndrome (adjusted OR, 1.34; 95% CI, 1.06 to 1.70; adjusted OR, 1.42; 95% CI, 0.79 to 2.55; adjusted OR, 1.55; 95% CI, 1.11 to 2.15; and adjusted OR, 1.24; 95% CI, 1.07 to 1.43, respectively) compared with nonuse. However, the risk for current use for >28 days of conventional NSAIDs was not statistically significant. Current use for 1–14 days and past use of conventional NSAIDs (discontinuation >2 years) were not associated with a higher risk compared with nonuse (Table 3). Although not statistically significant, compared with nonuse, past use of selective COX-2 inhibitors (>2 months to 2 years) was associated with higher risk (OR, 1.24; 95% CI, 0.98 to 1.58). In contrast, current and past use (>2 years) were associated with lower risk. The number of cases with recent use was too small to evaluate this association (Table 4).

According to the chemical groups of NSAIDs, current, recent, and past use (>2 months to 2 years) of acetic acid derivatives were associated with higher risk of nephrotic syndrome (adjusted OR, 1.11; 95% CI, 0.73 to 1.64; adjusted OR, 1.99; 95% CI, 1.28 to 3.10; and adjusted OR, 1.36; 95% CI, 1.13 to 1.64, respectively) compared with nonuse. The higher risk was also found for current, recent, and past use (>2 months to 2 years) of propionic acid derivatives (adjusted OR, 1.41; 95% CI, 0.90 to 2.20; adjusted OR, 1.24; 95% CI, 0.74 to 2.08; and adjusted OR, 1.14; 95% CI, 1.02 to 1.26, respectively) compared with nonuse. However, the higher risks for current use of acetic acid derivatives, and current and recent use of propionic acid derivatives were not statistically significant (Table 4).

Effect Modification by Age and Sex

Age did not modify the risk of nephrotic syndrome for the users of either conventional NSAIDs or selective COX-2 inhibitors compared with nonuse (Supplemental Table 3). Sex did not either modify the risk, except for past users of conventional NSAIDs and selective COX-2 inhibitors. Compared with women who were nonusers of any NSAIDs, women who were past users of conventional NSAIDs (>2 years) had a similar risk of nephrotic syndrome. In contrast, females who were past users of selective COX-2 inhibitors (>2 months to 2 years) were associated with a higher risk. For males, either past users of conventional NSAIDs (>2 years) or selective COX-2 inhibitors (>2 months to 2 years) were associated with lower risk of nephrotic syndrome compared with males who were nonusers of any NSAIDs (Supplemental Table 4).

Sensitivity Analyses

Our findings were similar when only cases with information on kidney biopsy were used. Recent and past use (>2 months to 2 years) of conventional NSAIDs were associated with higher risk (although not statistically significant) of nephrotic syndrome (adjusted OR, 1.83; 95% CI, 0.89 to 3.80; and adjusted OR, 1.23; 95% CI, 0.85 to 1.78, respectively) compared with nonuse. The risk for current use of conventional NSAID was not assessed according to the duration of use, because of small sample size (Supplemental Table 5). In extensive sensitivity analyses for various index dates, we found similar associations between conventional NSAIDs and nephrotic syndrome as found above. However, the higher risks were already observed during the first 2 weeks before the index date (Supplemental Tables 6–9). Excluding cases and controls with comorbidities that are well known causes of nephrotic syndrome did not change the results (Supplemental Table 10). Considering only hospitalized nephrotic syndrome patients as cases did not either change

Table 1. Baseline characteristics of patients with nephrotic syndrome and controls

Baseline Characteristics	Cases (*n*=2620)	Controls (*n*=10,454)
Age, yr, mean±SD	58±17	57±17
18–64 yr old, *n* (%)	1579 (60)	6316 (60)
>64 yr old, *n* (%)	1041 (40)	4138 (40)
Women, *n* (%)	1432 (55)	5714 (55)
Body mass index, kg/m^2, mean±SD	28.0±6.3	27.0±5.4
Underweight, <18.5 kg/m^2, *n* (%)	57 (2)	229 (2)
Normal weight, 18.5–24.9 kg/m^2, *n* (%)	783 (30)	3278 (31)
Overweight, 25.0–29.9 kg/m^2, *n* (%)	808 (31)	3453 (33)
Obesity, >30 kg/m^2, *n* (%)	753 (29)	2207 (21)
Unknown, *n* (%)	219 (8)	1287 (12)
Comorbidities associated with nephrotic syndrome, *n* (%)		
Diabetes mellitus	629 (24)	740 (7)
SLE	120 (5)	7 (0)
Rheumatoid arthritis	36 (1)	82 (1)
Amyloidosis	23 (1)	1 (0)
Leukemia	13 (1)	16 (0)
Comorbidities associated with kidney toxicity, *n* (%)		
Hypertension	1190 (45)	2655(25)
CKD	474 (18)	188 (2)
Heart failure	204 (8)	219 (2)
Chronic liver disease	42 (2)	70 (1)
Comedications within 6 mo before the index date, *n* (%)		
Cardiovascular drugs[a]	1843 (70)	3392 (32)
Systemic corticosteroids	413 (16)	316 (3)
Antibiotics[b]	98 (4)	93 (1)
Chemotherapeutic agents	83 (3)	87 (1)
Smoking status, *n* (%)		
Current	553 (21)	2272 (22)
Ever	947 (36)	3112 (30)
Never	1042 (40)	4545 (43)
Unknown	78 (3)	525 (5)
Alcohol abuse, *n* (%)	126 (5)	412 (4)

[a]Angiotensin-converting enzymes inhibitors, angiotensin II antagonists, β-blockers, diuretics, calcium channel blockers, and statins.
[b]Aminoglycosides, sulfamethoxazole and trimethoprim, vancomycin, and ciprofloxacin.

the results. For current use with duration 15–28 days, >28 days, recent use, and past use (>2 months to 2 years) of conventional NSAIDs, the adjusted ORs were 1.61 (95% CI, 0.78 to 3.32), 1.53 (95% CI, 0.59 to 3.95), 1.52 (95% CI, 0.89 to 2.59), and 1.27 (95% CI, 1.00 to 1.61), respectively, compared with nonuse (Supplemental Table 11).

Table 2. The result of kidney biopsy for a subgroup (*n*=288) of cases with nephrotic syndrome

Kidney Biopsy Result	Frequency, *n* (%)		
	NSAID Use	Non-NSAID Use	Total
Membranous GN	50 (30)	28 (23)	78 (27)
Focal and segmental glomerular lesions	34 (20)	35 (29)	69 (24)
Diffuse crescentic GN	19 (11)	12 (10)	31 (11)
Diffuse mesangiocapillary GN	18 (11)	7 (6)	25 (9)
Minimal change disease	15 (9)	13 (11)	28 (10)
Diffuse membranous GN	10 (6)	10 (9)	20 (7)
Diffuse mesangial proliferative GN	10 (6)	7 (6)	17 (6)
Minor glomerular abnormality	6 (4)	6 (5)	12 (4)
Diffuse endocapillary proliferative GN	3 (2)	0 (0)	3 (1)
Dense deposit diseases	1 (1)	1 (1)	2 (1)
Congenital nephrotic syndrome with focal glomerulosclerosis	1 (1)	0 (0)	1 (0)
Lipoid nephrosis	0 (0)	1 (1)	1 (0)
Other pathological kidney lesions	0 (0)	1 (1)	1 (0)
Total	167 (100)	121 (100)	288 (100)

NSAID, nonsteroidal anti-inflammatory drug.

Table 3. Odds ratios of nephrotic syndrome for conventional NSAID users

Exposures	Cases (n=2536)[a]	Controls (n=10,168)	Crude OR (95% CI)	Adjusted OR (95% CI)[b]
Nonuse, n (%)	1118 (44)	5142 (51)	1	1
Current use, n (%)[c]				
1–14 d	24 (1)	104 (1)	1.06 (0.68 to 1.66)	0.78 (0.46 to 1.31)
15–28 d	29 (1)	104 (1)	1.28 (0.85 to 1.95)	1.34 (1.06 to 1.70)
>28 d	21 (1)	56 (1)	1.73 (1.04 to 2.86)	1.42 (0.79 to 2.55)
Recent use, n (%)	73 (3)	182 (2)	1.85 (1.40 to 2.44)	1.55 (1.11 to 2.15)
Past use (discontinuation between >2 mo and 2 yr), n (%)	474 (19)	1477 (15)	1.48 (1.31 to 1.67)	1.24 (1.07 to 1.43)
Past use (discontinuation >2 yr), n (%)	797 (31)	3103 (31)	1.18 (1.07 to 1.31)	0.96 (0.85 to 1.09)

NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; 95% CI, 95% confidence interval.
[a]Acetic acid derivatives, propionic acid derivatives, fenamates, oxicams, and other NSAIDs.
[b]Adjusted for matching variables (age, sex, general practitioners' practice, and the index date), comorbidities, comedications, body mass index, smoking behavior, and alcohol abuse.
[c]Duration of use.

Discussion

Our study demonstrated that current use for more than 2 weeks, recent use, and past use (>2 months to 2 years) of conventional NSAIDs were associated with a higher risk of nephrotic syndrome. The higher risk seems to disappear after 2 years of discontinuation. The higher risk for conventional NSAIDs is mainly attributable to acetic acid and propionic acid derivatives. Current and past use of selective COX-2 inhibitors were not associated with a higher risk, although small sample size hampers drawing definite conclusions.

The risk estimates shown in the main analyses were confirmed when we specified our cases only for patients with available information on kidney biopsy. Furthermore, another study showed that the validity of several diagnoses in this database is high (29). When we varied the index date, we consistently found the same association between conventional NSAIDs and nephrotic syndrome. These findings strengthen

Table 4. Odds ratios of nephrotic syndrome for NSAID users according to chemical groups and selective COX-2 inhibitors

	Cases (n=2620)	Controls (n=10,454)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Nonuse, n (%)	1118 (43)	5142 (49)	1	1
Current use, n (%)				
Acetic acid derivatives	35 (1)	139 (1)	1.16 (0.80 to 1.69)	1.11 (0.73 to 1.70)
Propionic acid derivatives	33 (1)	93 (1)	1.63 (1.09 to 2.44)	1.41 (0.90 to 2.20)
Other conventional NSAIDs[b]	6 (0)	32 (1)	0.86 (0.36 to 2.07)	0.51 (0.19 to 1.33)
Selective COX-2 inhibitors	8 (0)	39 (1)	0.94 (0.44 to 2.02)	0.40 (0.24 to 0.65)
Recent use, n (%)				
Acetic acid derivatives	37 (1)	89 (1)	1.91 (1.30 to 2.82)	1.99 (1.28 to 3.10)
Propionic acid derivatives	31 (1)	77 (1)	1.85 (1.21 to 2.82)	1.24 (0.74 to 2.08)
Other conventional NSAIDs[b]	5 (0)	16 (0)	1.44 (0.53 to 3.93)	1.01 (0.56 to 1.84)
Selective COX-2 inhibitors	4 (0)	15 (0)	NA	NA
Past use (discontinuation between >2 mo and 2 yr), n (%)				
Acetic acid derivatives	239 (9)	700 (7)	1.57 (1.34 to 1.84)	1.36 (1.13 to 1.64)
Propionic acid derivatives	193 (7)	637 (6)	1.39 (1.17 to 1.66)	1.14 (1.02 to 1.26)
Other conventional NSAIDs[b]	42 (2)	140 (1)	1.38 (0.97 to 1.96)	1.13 (0.76 to 1.70)
Selective COX-2 inhibitors	37 (1)	99 (1)	1.72 (1.17 to 2.52)	1.24 (0.98 to 1.58)
Past use (discontinuation >2 yr), n (%)				
Acetic acid derivatives	379 (5)	1466 (14)	1.19 (1.04 to 1.35)	1.02 (0.88 to 1.19)
Propionic acid derivatives	347 (13)	1368 (13)	1.17 (1.02 to 1.33)	0.90 (0.77 to 1.06)
Other conventional NSAIDs[b]	71 (3)	269 (3)	1.21 (0.93 to 1.59)	1.00 (0.74 to 1.35)
Selective COX-2 inhibitors	35 (1)	133 (1)	1.21 (0.83 to 1.77)	0.77 (0.50 to 1.20)

NSAID, nonsteroidal anti-inflammatory drug; COX-2, cyclooxygenase-2; OR, odds ratio; 95% CI, 95% confidence interval; NA, not applicable.
[a]Adjusted for comorbidities, comedications, body mass index, smoking behavior, and alcohol abuse.
[b]Oxicams, fenamates, other NSAIDs not classified elsewhere.

the suggestion of a possible causal relationship. There is an indication that the higher risk might start within 2 weeks of NSAID exposure. When we excluded well known conditions associated with nephrotic syndrome in both cases and controls, the estimated risks remained similar, suggesting that NSAIDs are independently associated with the occurrence of nephrotic syndrome. The higher risk for conventional NSAIDs was also demonstrated for hospitalized patients with nephrotic syndrome. It implies that the risk of nephrotic syndrome for conventional NSAIDs was independent of their severity.

Our findings confirmed previous studies. Case reports and case series showed that NSAID-associated nephrotic syndrome occurs from the exposure duration of <1 week (30,31) to years (17,32,33). Even further, nephrotic syndrome might develop 6 months after the discontinuation of an NSAID (34). In a review of acute kidney diseases associated with NSAID use, it appeared that particularly the propionic acid derivative fenoprofen was associated with nephrotic syndrome (half of the 34 cases) (1). Our finding that current and past use (>2 years) of selective COX-2 inhibitors are not associated with higher risk of nephrotic syndrome risk corresponds with the safe administration of celecoxib to a patient with repeated episodes of nephrotic syndrome induced by NSAIDs (20).

NSAID-associated nephrotic syndrome is thought to be mediated by either the inhibition of PG synthesis or a hypersensitivity mechanism. As a chemical mediator, PGs are essential for kidney hemodynamic including glomerular filtration. In nephrotic syndrome, glomeruli are impaired by the inflammation processes that allow proteins to pass through kidney cell membranes (30,36,37). Hypersensitivity mechanisms of NSAIDs for nephrotic syndrome are caused allegedly by the shift of PG synthesis from COX to lipoxygenase paths, or the release of lymphokines that increase the production of leukotrienes. Leukotrienes can activate T helper lymphocytes that ultimately affect glomerular permeability (30).

Clinical Implications

Our results demonstrated that conventional NSAIDs, especially current, recent, and past use (>2 months to 2 years) of acetic acid derivatives (such as indomethacin, diclofenac, and ketorolac) and current, recent, and past use (>2 months to 2 years) of propionic acid derivatives (such as ibuprofen, naproxen, and ketoprofen), and past use (>2 months to 2 years) of selective COX-2 inhibitors were associated with a higher risk of nephrotic syndrome. However, this higher relative risk that was observed in our study is relatively low. Thus, health care professionals should be more alert regarding development of clinical features of nephrotic syndrome caused by other risk factors. A patient who develops nephrotic syndrome should be asked about the use of NSAIDs, including over the counter. Although our study indicated that current and past use (>2 years) of selective COX-2 inhibitors were not associated with a higher risk, the number of participants was too small to draw definite conclusions.

Strengths and Limitations

Our study has several strengths. The data were extracted over a long observation time, and the database contained longitudinal data of patient's medical history and lifestyle. Many potential risk factors were available, allowing us to adjust for many potential confounders. The routine collection of medical information and medication use lowers the risk of information bias.

Nonetheless, some limitations need to be acknowledged. We might encounter the delay in establishing the diagnosis from the first complaints. The index date was the date of diagnosis entered in the database, whereas the first complaints that cause patients to seek help might have preceded this index date. If the delay is substantial (weeks to months are not uncommon in nephrotic syndrome), and patients take a NSAID within this period, it inadvertently attributes to misclassification of the exposure status. This might also partly explain the higher risk for recent and past use (>2 months to 2 years) of conventional NSAIDs. Nevertheless, our sensitivity analyses consistently showed that the delay was unlikely to change the risk estimates. Although most diagnoses were entered without information on kidney biopsy, the analysis among cases with kidney biopsy supported our main results. When we excluded cases and controls with well known conditions associated with nephrotic syndrome for sensitivity analyses, the estimated risks remained similar. The actual NSAID use is uncertain. We had no direct measure on NSAID use because medication use is determined on the basis of prescribing information. Information on whether NSAIDs were prescribed as a regular or needed use was not available. Furthermore, we had no information on over-the-counter NSAID use. However, only ibuprofen is available as over-the-counter NSAIDs in the UK (38,39). Furthermore, we expect the use is unlikely to be different between cases and controls. Therefore, misclassification of NSAID exposure is probably nondifferential. We cannot either ignore the fact that the previous use of NSAID (either recent or past use) might affect the magnification risk for their following use (current or recent use, respectively). We had no information on patients being allergic. Because hypersensitivity reaction–mediated nephrotic syndrome is suspected to be low, this misclassification problem is unlikely to influence our results. The sample size for selective COX-2 inhibitors and an individual chemical group of NSAIDs was small, resulting in a too-low power to detect statistically significant associations. Finally, the extrapolation of our results to age groups <18 years old is less valid. Further studies to test the consistency of our findings may consider unmeasured potential confounders and a larger population.

In conclusion, the use of conventional NSAIDs was associated with a higher risk of nephrotic syndrome starting from at least 2 weeks of exposure. This higher risk was also shown for recent and past exposure up to 2 years before nephrotic syndrome diagnosis. These higher risks appeared mainly attributable to acetic acid and propionic acid derivatives. In contrast, current and past use (>2 months to 2 years) of selective COX-2 inhibitors were not associated with a higher risk.

Disclosures

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Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.14331218/-/DCSupplemental.

Supplemental Table 1. CPRD codes for nephrotic syndrome and the clinical events.

Supplemental Table 2. The Anatomical Therapeutic Chemical Classification system for NSAIDs.

Supplemental Table 3. ORs of nephrotic syndrome for NSAID users stratified by age.

Supplemental Table 4. ORs of nephrotic syndrome for NSAID users stratified by sex.

Supplemental Table 5. ORs of nephrotic syndrome defined by kidney biopsy for conventional NSAID users.

Supplemental Table 6. ORs of nephrotic syndrome for conventional NSAID users 3 months before the index date.

Supplemental Table 7. ORs of nephrotic syndrome for conventional NSAID users 6 months before the index date.

Supplemental Table 8. ORs of nephrotic syndrome for conventional NSAID users 9 months before the index date.

Supplemental Table 9. ORs of nephrotic syndrome for conventional NSAID users 12 months before the index date.

Supplemental Table 10. ORs of nephrotic syndrome for conventional NSAID users among those without comorbidities that are well known causes of nephrotic syndrome.

Supplemental Table 11. ORs of hospitalized patients with nephrotic syndrome for conventional NSAID users.

References

1. Rivosecchi RM, Kellum JA, Dasta JF, Armahizer MJ, Bolesta S, Buckley MS, Dzierba AL, Frazee EN, Johnson HJ, Kim C, Murugan R, Smithburger PL, Wong A, Kane Gill SL: Drug class combination-associated acute kidney injury. *Ann Pharmacother* 50: 953–972, 2016
2. Farker K, Merkel U, Schweer H, Haerting J, Madani SF, Eggers R, Müller UA, Seyberth HW, Hoffmann A: Effects of short-term treatment with diclofenac-colestyramine on renal function and urinary prostanoid excretion in patients with type-2 diabetes. *Eur J Clin Pharmacol* 58: 85–91, 2002
3. Cohen HJ, Walston JD, Rao SV, Schrier SL, Artz A; Partnership for Anemia: Clinical and Translational Trials in the Elderly Consortium: Renal toxicity associated with salsalate in elderly adults with anemia. *J Am Geriatr Soc* 64: 898–899, 2016
4. Chou CI, Shih CJ, Chen YT, Ou SM, Yang CY, Kuo SC, Chu D: Adverse effects of oral nonselective and cyclooxygenase-2-selective NSAIDs on hospitalization for acute kidney injury: A nested case-control cohort study. *Medicine (Baltimore)* 95: e2645, 2016
5. Chiu HY, Huang HL, Li CH, Chen HA, Yeh CL, Chiu SH, Lin WC, Cheng YP, Tsai TF, Ho SY: Increased risk of chronic kidney disease in rheumatoid arthritis associated with cardiovascular complications - a national population-based cohort study. *PLoS One* 10: e0136508, 2015
6. Dixit M, Doan T, Kirschner R, Dixit N: Significant acute kidney injury due to non-steroidal anti-inflammatory drugs: Inpatient setting. *Pharmaceuticals (Basel)* 3: 1279–1285, 2010
7. Ungprasert P, Cheungpasitporn W, Crowson CS, Matteson EL: Individual non-steroidal anti-inflammatory drugs and risk of acute kidney injury: A systematic review and meta-analysis of observational studies. *Eur J Intern Med* 26: 285–291, 2015
8. Winkelmayer WC, Waikar SS, Mogun H, Solomon DH: Nonselective and cyclooxygenase-2-selective NSAIDs and acute kidney injury. *Am J Med* 121: 1092–1098, 2008
9. Whelton A: Nephrotoxicity of nonsteroidal anti-inflammatory drugs: Physiologic foundations and clinical implications. *Am J Med* 106[5B]: 13S–24S, 1999
10. Segal R, Lubart E, Leibovitz A, Iaina A, Caspi D: Renal effects of low dose aspirin in elderly patients. *Isr Med Assoc J* 8: 679–682, 2006
11. Alper AB Jr., Meleg-Smith S, Krane NK: Nephrotic syndrome and interstitial nephritis associated with celecoxib. *Am J Kidney Dis* 40: 1086–1090, 2002
12. Chen YH, Tarng DC: Profound urinary protein loss and acute renal failure caused by cyclooxygenase-2 inhibitor. *Chin J Physiol* 54: 264–268, 2011
13. Andrews PA, Sampson SA: Topical non-steroidal drugs are systemically absorbed and may cause renal disease. *Nephrol Dial Transplant* 14: 187–189, 1999
14. O'Callaghan CA, Andrews PA, Ogg CS: Renal disease and use of topical non-steroidal anti-inflammatory drugs. *BMJ* 308: 110–111, 1994
15. Robinson J, Malleson P, Lirenman D, Carter J: Nephrotic syndrome associated with nonsteroidal anti-inflammatory drug use in two children. *Pediatrics* 85: 844–847, 1990
16. Sekhon I, Munjal S, Croker B, Johnson RJ, Ejaz AA: Glomerular tip lesion associated with nonsteroidal anti-inflammatory drug-induced nephrotic syndrome. *Am J Kidney Dis* 46: e55–e58, 2005
17. Tazoe N, Ikezaki N, Ito J, Kuwahara K, Hara M, Nakayama M, Sato T: A case of acute interstitial nephritis induced by flurbiprofen. *Jpn J Med* 26: 230–233, 1987
18. Harirforoosh S, Asghar W, Jamali F: Adverse effects of nonsteroidal antiinflammatory drugs: An update of gastrointestinal, cardiovascular and renal complications. *J Pharm Pharm Sci* 16: 821–847, 2013
19. Garini G, Mazzi A, Buzio C, Mutti A, Allegri L, Savazzi G, Borghetti A: Renal effects of captopril, indomethacin and nifedipine in nephrotic patients after an oral protein load. *Nephrol Dial Transplant* 11: 628–634, 1996
20. Mihovilovic K, Ljubanovic D, Knotek M: Safe administration of celecoxib to a patient with repeated episodes of nephrotic syndrome induced by NSAIDs. *Clin Drug Investig* 31: 351–355, 2011
21. Low CL, McGoldrick MD, Bailie GR: Successful management of steroid-resistant nephrotic syndrome using ibuprofen. *Clin Nephrol* 47: 60–62, 1997
22. Al-Waili NS: Three cases of nephrotic syndrome treated by indomethacin. *J Pak Med Assoc* 38: 54–56, 1988
23. Shehadeh IH, Demers LM, Abt AB, Schoolwerth AC: Indomethacin and the nephrotic syndrome. *JAMA* 241: 1264–1266, 1979
24. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, Smeeth L: Data resource profile: Clinical practice research datalink (CPRD). *Int J Epidemiol* 44: 827–836, 2015
25. Eddy AA, Symons JM: Nephrotic syndrome in childhood. *Lancet* 362: 629–639, 2003
26. Lennon R, Watson L, Webb NJ: Nephrotic syndrome in children. *Paediatr Child Health* 20: 36–42, 2010
27. Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P: Data resource profile: Hospital episode statistics admitted patient care (HES APC). *Int J Epidemiol* 46: 1093–1093i, 2017
28. Mathur R, Bhaskaran K, Chaturvedi N, Leon DA, vanStaa T, Grundy E, Smeeth L: Completeness and usability of ethnicity data in UK-based primary care and hospital databases. *J Public Health (Oxf)* 36: 684–692, 2014
29. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ: Validation and validity of diagnoses in the general practice research database: A systematic review. *Br J Clin Pharmacol* 69: 4–14, 2010
30. Vega J, Goecke H, Méndez GP, Guarda FJ: Nephrotic syndrome and acute tubular necrosis due to meloxicam use. *Ren Fail* 34: 1344–1347, 2012
31. Nortier J, Depierreux M, Bourgeois V, Dupont P: Acute interstitial nephritis with nephrotic syndrome after intake of naproxen and amoxycillin. *Nephrol Dial Transplant* 5: 1055, 1990
32. Tattersall J, Greenwood R, Farrington K: Membranous nephropathy associated with diclofenac. *Postgrad Med J* 68: 392–393, 1992
33. Mourad G, Mimran A, Baldet P, Barjon P: [Reversible acute renal failure and nephrotic syndrome induced by fenoprofene]. *Nephrologie* 3: 65–68, 1982
34. Radford MG Jr., Holley KE, Grande JP, Larson TS, Wagoner RD, Donadio JV, McCarthy JT: Reversible membranous nephropathy associated with the use of nonsteroidal anti-inflammatory drugs. *JAMA* 276: 466–469, 1996

35. Carmichael J, Shankel SW: Effects of nonsteroidal anti-inflammatory drugs on prostaglandins and renal function. *Am J Med* 78: 992–1000, 1985
36. Kim S, Joo KW: Electrolyte and Acid-base disturbances associated with non-steroidal anti-inflammatory drugs. *Electrolyte Blood Press* 5: 116–125, 2007
37. Ejaz P, Bhojani K, Joshi VR: NSAIDs and kidney. *J Assoc Physicians India* 52: 632–640, 2004
38. Chen Y, Bedson J, Hayward RA, Jordan KP: Trends in prescribing of non-steroidal anti-inflammatory drugs in patients with cardiovascular disease: Influence of national guidelines in UK primary care. *Fam Pract* 35: 426–432, 2018
39. Andersohn F, Schade R, Suissa S, Garbe E: Cyclooxygenase-2 selective nonsteroidal anti-inflammatory drugs and the risk of ischemic stroke: A nested case-control study. *Stroke* 37: 1725–1730, 2006

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