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Effects of NSAIDs on the Incidence of Hospitalisations for Renal Dysfunction in Users of ACE Inhibitors

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Abstract

Introduction: Although relatively safe, both NSAIDs and ACE inhibitors can cause renal dysfunction in patients with compromised renal function. Case reports indicate that the combined use of ACE inhibitors and NSAIDs increases the risk of renal dysfunction. It is not known how often and when renal dysfunction occurs in patients using a combination of ACE inhibitors and NSAIDs.

Objective: The objective of the study was to investigate the effects of NSAIDs on the incidence of hospitalisations due to renal dysfunction in patients treated with ACE inhibitors.

Study Design: Case-control study nested within a cohort of users of ACE inhibitors.

Participants: All participants had at least two consecutive prescriptions for an ACE inhibitor. One hundred and forty-four cases were admitted to hospital for renal insufficiency during use of ACE inhibitors. There were 1189 randomly sampled control patients who did not have any hospital admission for renal dysfunction during use of ACE inhibitors.

Main Outcome Measures: The risk for hospitalisation for renal dysfunction associated with exposure to NSAIDs in patients receiving ACE inhibitors was expressed as odds ratios (OR).

Results: Of 144 cases, a total of 32 (22.2%) received NSAIDs in the 90 days before hospital admission for renal dysfunction. Recent start (<90 days) of an NSAID was associated with an increased risk of admission for renal dysfunction (adjusted OR 2.2; 95% CI 1.1–4.5). The increased risk was most pronounced in patients aged >70 years (adjusted OR 2.7; 95% CI 1.0–7.2). For patients who started NSAIDs and were dispensed at least three prescriptions in the 90 days preceding hospitalisation an adjusted OR of 7.1 (95% CI 1.8–28.7) was observed.

Conclusions: This study strongly suggests an increased risk for hospitalisation for renal insufficiency in patients receiving ACE inhibitors who start using NSAIDs. Elderly patients receiving several prescriptions for NSAIDs in a short period of

time are particularly at risk. Renal function should be closely monitored in these patients.

The positive effects of ACE inhibitors in hypertension and diminished left ventricular function are well established. ACE inhibitors block the conversion of angiotensin I to angiotensin II. Angiotensin II has a vasoconstrictive effect on the efferent arteriole. ACE inhibitors can blunt this vasoconstrictive effect and diminish efferent arteriolar resistance. By dilating the efferent renal arteriolar glomerular filtration rate can decrease. This can lead to moderate increases in serum creatinine levels. These changes are usually no reason to withdraw ACE inhibitor therapy.[1,2] However, in special situations such as renal artery obstruction, low cardiac output or hypovolaemia, severe renal dysfunction can occur. Renal dysfunction during treatment with ACE inhibitors is not uncommon in daily practice.[3]

The effects of moderate use of NSAIDs on renal function in relatively healthy persons, not using ACE inhibitors, are probably negligible.[4] However, several studies have shown that the use of NSAIDs is associated with an increased risk for acute renal failure (ARF).[5] Although the absolute risk on renal dysfunction in the general population is low, this risk could increase substantially in patients with already compromised renal function or using concurrent medication that is potentially nephrotoxic.[6] Even use of topical NSAIDs can lead to renal failure in patients with compromised renal function.[7] Use of both NSAIDs and ACE inhibitors is a common cause of ARF. In a study of 109 patients with hospital admissions for ARF, ARF was drug related in 39 patients. Either NSAIDs or ACE inhibitors were the cause of ARF in 24 and 8 patients, respectively.[8]

The combination of NSAIDs and ACE inhibitors can result in ARF as a consequence of decreased glomerular filtration by their combined effects on renal blood flow. NSAIDs inhibit cyclo-oxygenase (COX) and thereby reduce the production of renal vasodilating prostaglandins. This phenomenon is especially important in kidneys dependent on these vasodilating effects of prostaglandins. ACE inhibitors inhibit the vasoconstrictor effect of angiotensin II on the efferent arteriole and make control of glomerular filtration more dependent on prostaglandins.[9,10]

Other risk factors of renal insufficiency such as pre-existing renal disease, congestive heart failure, ageing, and hypovolaemia increase the risk on renal dysfunction during the simultaneous use of ACE inhibitors and NSAIDs. Both NSAIDs and ACE inhibitors are frequently used in the general population. We aimed at quantifying the risk of hospital admission for renal dysfunction in patients using NSAIDs while exposed to ACE inhibitors.

Participants and Methods

Setting

Data were used from the PHARMO record linkage system, a database containing drug dispensing records from community pharmacies and linked hospital discharge records of a defined population of 300 000 residents of six medium-sized cities in The Netherlands. Medication histories and hospital data were collected from 1987–1998. Drugs were coded according to the WHO anatomical therapeutic chemical (ATC) classification. Hospital discharge records were coded according to the International Classification of Diseases (ICD), 9th Ed., clinical modification.[11]

Participants

Within a cohort of ACE inhibitor users, aged >40 years, with at least two consecutive prescriptions for an ACE inhibitor, we identified 144 cases, admitted to the hospital because of renal insufficiency (ICD 584 or 586) during the use of an ACE inhibitor. From the remainder of the cohort we randomly sampled (case : control ratio: 1 : 8) 1189 control patients without any hospital admission for renal

problems (ICD 580 to 588). An index date was assigned to each control matching the hospitalisation date of the case. Patients with a hospital admission for renal problems (ICD 580 to 588) before the start of an ACE inhibitor were excluded among both cases and controls.

Exposure Definition

In The Netherlands prescriptions are dispensed for a maximum period of 3 months. A patient was defined as a current user when there was at least one prescription filled for a given drug in the 3 months before hospital admission for the cases or the corresponding index date for the controls.

A patient was defined as a former user when there was at least one prescription for a given drug between 3 and 12 months before hospital admission for the cases or the corresponding index date for the controls.

New use or start of use was defined as current use without former use.

Data Analysis

We performed a case-control analysis comparing exposure in cases versus controls. Odds ratios (OR) were calculated for exposure to NSAIDs, at the time of the hospitalisation due to renal dysfunction (cases) or matched index date (controls). Since age, gender, comorbidity and co-medication can influence the occurrence of renal dysfunction and may be associated with NSAID use, and thus, may confound the relationship between NSAID use and renal dysfunction, we applied multivariable logistic regression techniques to adjust for these potential confounders. All statistical analysis was performed with Egret software (Egret for Windows, Version 2.0, Cytel Software Corporation).

Results

A total of 144 hospital admissions for renal insufficiency were observed during the study period. The majority of these (132 of 144 admissions) were classified as renal insufficiency not otherwise specified (ICD-9 586). The remaining 12 of 144 admis-

Table I. Association between use of NSAIDs and risk of hospitalisation for renal dysfunction

	Cases (n = 144)	Controls (n = 1189)	Crude OR[a] (95% CI)	Adjusted OR[a,b] (95% CI)
Exposure to NSAIDs in the 90 days before index date	32 (22.2)	236 (19.8)	1.2 (0.7–1.8)	0.9 (0.6–1.5)
Former use of NSAIDs in the year before index date[c]	38 (26.4)	385 (32.4)	0.7 (0.5–1.1)	0.7 (0.4–1.1)
Start of NSAIDs in the 90 days before index date[c]	13 (9.0)	53 (4.5)	2.1 (1.1–4.2)	2.2 (1.1–4.5)
Start of NSAIDs in the 90 days before index date and at least two prescriptions in this period	6 (4.2)	15 (1.3)	3.4 (1.3–8.9)	2.7 (0.9–3.4)
Start of NSAIDs in the 90 days before index date and at least three prescriptions in this period	5 (3.5)	5 (0.4)	8.5 (2.1–34.4)	7.1 (1.8–28.7)
Exposure to prophylactic aspirin (acetylsalicylic acid) in the 90 days before index date	40 (27.8)	286 (24.1)	1.2 (0.8–1.8)	0.9 (0.5–1.3)
Start of prophylactic aspirin in the 90 days before index date	4 (2.8)	29 (2.4)	1.1 (0.4–3.3)	0.8 (0.2–2.6)

a Reference group is complementary (e.g. patients without exposure to NSAIDs in the 90 days before index date).

b Adjusted for age and gender, prior hospital admissions for congestive heart failure, diabetes and for concomitant use of diuretics, low-dose aspirin, antibiotics, paracetamol (acetaminophen), epoetin, corticosteroids, opioids, digoxin, antigout drugs and duration of use of ACE inhibitor.

c Mutually exclusive.

OR = odds ratio.

Table II. Comparison between patients using ACE inhibitors who were admitted to hospital for renal dysfunction (cases) and a random sample of patients not admitted for renal dysfunction (controls)

	Cases (n = 144) [no (%)]	Controls (n = 1189) [no (%)]
Age category (y)		
<60	18 (12.5)	395 (33.2)
60–69	23 (23.6)	333 (28.0)
>70	92 (63.9)	461 (38.8)
Gender		
Male	92 (63.9)	540 (45.4)
Co-morbidity		
Diabetes	43 (29.9)	203 (17.1)
History of heart failure at hospital admission	38 (26.4)	66 (5.6)
Medication used in 90 days before index date		
Loop diuretics	96 (66.7)	288 (24.2)
Thiazide diuretics	4 (2.8)	64 (5.4)
Spironolactone	21 (14.6)	44 (3.7)
Antibiotics	53 (36.8)	172 (14.5)
Antigout drugs	14 (9.7)	23 (1.9)
Corticosteroids	11 (7.6)	61 (5.1)
Digoxin	52 (36.1)	138 (11.6)

sions were coded ICD-9 584 for acute renal insufficiency.

Of the 144 cases and 1189 controls, 32 (22.2%) and 236 (19.8%), respectively, were treated with any NSAID in the 90 days preceding the hospital admission or index date. There was no increased risk for renal dysfunction related hospital admission for current use of NSAIDs (crude OR 1.2; 95% CI 0.7–1.8). However, the start of a NSAID in the 90 days prior to hospital admission for renal dysfunction was associated with an increased risk (crude OR 2.1; 95% CI 1.1–4.2) [table I].

Cases and controls showed differences in age, gender, co-morbidity and comedication (table II). Adjustment for these potential confounders did not change the OR for starting an NSAID (2.2; 95% CI 1.1–4.5). In order to determine a dose response relationship we calculated separate ORs for patients who started NSAIDs and received at least two or at least three prescriptions within 90 days before the hospitalisation. The adjusted odds-ratio in these groups were 2.7 (95% CI 0.9–3.4) and 7.1 (95% CI 1.8–28.7), respectively.

Ninety-two of 144 cases (64%) were >70 years old. After stratification for age the increased risk for renal dysfunction after starting NSAIDs was most pronounced in the subgroup of patients aged >70 years (adjusted OR 2.7; 95% CI 1.0–7.2).

We did not find an association between the use of low-dose aspirin (acetylsalicylic acid) and the development of renal dysfunction (table I). Only five patients started aspirin in analgesic dosages.

Discussion

This study suggests an increased risk (OR 2.2; CI 95% 1.1–4.5) for hospitalisation for renal insufficiency in patients using ACE inhibitors who start an NSAID. Patients who are newly exposed to several prescriptions for NSAIDs have a higher chance of renal dysfunction. We hypothesise therefore that susceptible individuals (i.e. elderly patients with heart failure) are at increased risk for renal dysfunction when starting NSAIDs during exposure to ACE inhibitors. Greater use of NSAIDs increases this risk. However, when patients do not develop renal dysfunction and become long-term users of NSAIDs, the increased risk of the development of renal dysfunction disappears. There even seems to be a slight protective effect of former use of NSAIDs. This is probably the result of depletion of

susceptible patients in this group. In this study only the effect on renal function requiring hospital admission was assessed. Smaller decrease of renal function, not leading to hospital admission, will probably occur much more frequently.

On first glance our findings seem conflicting with prior studies that have not found an effect on renal function by NSAIDs[4] or an additive effect of NSAIDs and ACE inhibitors.[12] Rexrode et al.[4] observed no association between long-term analgesic use and reduced renal function in relatively healthy males. This finding is confirmed by our results that long-term use of NSAIDs is not a risk factor for renal dysfunction. Stürmer et al.[12] found no interaction between ACE inhibitors and NSAIDs in long-term users of NSAIDs. We also found that long-term use of NSAIDs was not a risk factor for the occurrence of renal dysfunction in users of ACE inhibitors. Neither Rexrode et al.[4] nor Stürmer et al.,[12] however, studied patients who had started NSAID use as we did.

The fact that we did not find an association between the use of low-dose aspirin (acetylsalicylic acid) use and the development of renal dysfunction in users of ACE inhibitors may contribute to the discussion regarding the safety of the combination of low-dose aspirin and ACE inhibitors.[13] Of note, low-dose aspirin in The Netherlands is defined as 30–80 mg/day whereas dosages up to 325 mg/day are used in other countries.

Covariates and Possible Confounders

Since this is a nonrandomised study there will always be a risk for confounding. Renal function as well as NSAID use is related to age, gender and a broad range of comorbidities and medications. Age itself or comorbidity often reduces renal function in elderly patients.[14]

Our analysis showed several differences between patients with hospital admissions for renal dysfunction and controls. Notably patients with renal dysfunction were older, more often male and more frequently had a history of heart failure and diabetes mellitus. Also, patients with renal dysfunction used several drugs (loop diuretics, spironolactone, digoxin, antigout drugs and antibiotics) more frequently. Patients with a hospitalisation for renal dysfunction had used ACE inhibitors for a longer period of time, probably reflecting more serious underlying disease.

Calculation of ORs for these possible confounders showed an increased risk on renal dysfunction for several of these factors. We corrected for these potential confounders by including age, gender, presence of diabetes, any hospital admission for heart failure, the use of aforementioned drugs in the 3 months prior to the index date and the duration of treatment with ACE inhibitors in the multiple regression model. We also adjusted for the use of five other drugs (low-dose aspirin, paracetamol [acetaminophen], opioids, corticosteroids and epoetin) that may be associated with the presence of renal disease on the one hand and the use of NSAIDs on the other. After adjustment for these possible confounders the ORs did not change appreciably. These findings remain suggestive of a causal relation between starting NSAIDs and hospital admission for renal dysfunction in users of ACE inhibitors. Since information on important confounders was available, we believe that the chance of important residual confounding is negligible.

We were only partly able to take into account over-the-counter (OTC) use of NSAIDs. However we expect that this use is relatively low, since NSAIDs were reimbursed fully in The Netherlands in the study period and most Dutch (elderly) patients used these drugs on prescription. NSAIDs bought in the pharmacy will often be added to the medication history of the patient. Only NSAIDs bought in so-called 'druggists' (non-pharmacies in The Netherlands that are allowed to sell certain OTC medicines) will not be found in patients' medication history. Even when some patients did use OTC NSAIDs it is unlikely that OTC use will be unevenly distributed among cases and controls. Therefore we do not expect that OTC use of NSAIDs will influence our findings. Paracetamol on the other hand is only reimbursed for chronic conditions in The Netherlands. Incidental use is therefore especially difficult to measure with pharmacy data, since most patients will buy paracetamol OTC.

Stratification for Age

The majority of cases (64%) were aged over 70 years. After stratification for age the increased risk for renal dysfunction was most pronounced in this subgroup. As the absolute risk for renal dysfunction is higher in elderly patients, it is especially important to monitor elderly users of ACE inhibitors who start NSAIDs.

Limitations of the Study

We used discharge diagnoses as outcome variable. Ideally discharge diagnoses should have been validated in a subsample of patients. A certain degree of misclassification is therefore possible. A recent study showed that false positive cases are less likely to occur than false negative cases.[15] We therefore believe that the use of discharge codes is most likely to lead to an underestimation of the association between the start of NSAIDs and renal dysfunction. A study with validated cases might find an even stronger association.

Conclusion

NSAIDs are often combined with ACE inhibitors without leading to a deterioration in renal function. However, this study strongly suggests an increased risk of hospitalisation for renal dysfunction in patients treated with ACE inhibitors who start using NSAIDs. Elderly patients who receive several prescriptions for NSAIDs in a short period of time are particularly at increased risk for developing renal dysfunction. Patients with diabetes, a history of heart failure and using diuretics might be at an even higher risk. The use of NSAIDs should be avoided as much as possible in (elderly) patients receiving ACE inhibitors. Paracetamol seems to be preferred as an alternative for NSAIDs. Preliminary data from COX-2-selective inhibitors suggest that they also affect renal prostaglandins.[16,17] Renal failure has already been reported after high doses of COX-2 inhibitors.[18,19] Therefore, the same precautions should be exercised with their use as with traditional NSAIDs.[20] Literature suggests that renal function is only monitored in 30% of patients after the start of ACE inhibitors.[3] This study emphasises the importance of monitoring renal function in (elderly) patients already using ACE inhibitors who start NSAIDs.

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