Nonsteroidal Anti-inflammatory Drugs and Increased Risk of Acute Urinary Retention

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Background: Acute urinary retention (AUR) is characterized by the sudden inability to urinate, which is usually extremely painful and requires catheterization. Prostaglandins play an important role in the genitourinary function as they provoke contractions of the detrusor muscle. Relaxation of the detrusor muscle, via the inhibition of the prostaglandin synthesis, could result in AUR.

Methods: We conducted a population-based case-control study within the Integrated Primary Care Information project in the Netherlands to investigate whether the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with an increased risk of AUR. All men 45 years or older registered in the database between 1995 and 2002 and with at least 6 months of valid history were included. Cases were all men with a validated diagnosis of AUR. To each case, up to 10 controls were matched on age and calendar time.

Results: Within the source population of 72,114 men, we identified 536 cases of AUR and 5348 matched controls. Risk of AUR was 2.02-fold higher in current users of NSAIDs than in nonusers (95% confidence interval, 1.23-3.31). The highest risk for AUR (adjusted odds ratio, 3.3; 95% confidence interval, 1.2-9.2) was observed in patients who recently started using NSAIDs and in those using a dose equal to or higher than the recommended daily dose.

Conclusion: This study shows that the risk of AUR is about 2-fold higher in men who use NSAIDs.

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A CUTE URINARY RETENTION (AUR) is a condition characterized by the sudden inability to urinate, which is usually painful and requires catheterization. Mechanisms such as increased resistance of the urinary flow, interruption of the sensory innervation of the bladder, weakness of the detrusor muscle, and overdistention of the bladder are involved in the pathogenesis of AUR. The incidence of AUR is higher in men than in women, especially in older age categories, because men more often have comorbidities known to provoke AUR.

In vitro studies have shown that prostaglandins, especially prostaglandin E2, play an important role in the genitourinary function. The prostaglandin synthesis in the bladder works via cyclooxygenase-2 (COX-2) and is up-regulated by stimuli such as inflammation, trauma, and overdistention. Slow tonic contractions of the bladder muscle result from these processes enabling the bladder to empty. As nonsteroidal anti-inflammatory drugs (NSAIDs) are known to have a direct effect on prostaglandin synthesis, they have been tested in clinical trials for the treatment of detrusor instability. Gruenenfelder et al9 recently reported 3 cases of AUR that occurred within 1 week after starting treatment with COX-2 inhibitors, which suggests that NSAIDs impair bladder contraction, eventually resulting in AUR. The objective of the present case-control study in a population of men 45 years or older was to investigate whether the use of NSAIDs is associated with an increased risk of AUR.

METHODS

SETTING

This study was conducted using the Integrated Primary Care Information (IPCI) database in the Netherlands, which is a general practice research database containing information from electronic patient records of 150 general practitioners covering a total of approximately 500,000 patients. In the Dutch health care system, patients are registered with a single

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general practitioner who acts as a gatekeeper of medical care and information. The electronic records contain coded and anonymous data on patient demographics, symptoms and diagnoses (using the International Primary Care Classifications and free text), clinical findings, referrals, laboratory findings, and hospitalizations. Summaries of the hospital discharge letters and information from specialists are entered in a free text format, and hard copies can be provided on request. Information on drug prescription includes brand name, quantity, strength, indication, prescribed daily dose, the Anatomical Therapeutic Chemical classification code, and the physician-linked indication. To maximize completeness of the data, general practitioners who participate in the IPCI project are not allowed to use paper-based records. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmacoepidemiologic research. The scientific and ethics advisory group of the IPCI project approved the study.

SOURCE POPULATION

The source population comprised all men 45 years or older with at least 6 months of valid database history. A valid history meant that the practice had been contributing data to the IPCI database for at least 6 months and that the patient had been registered with the general practitioner for at least 6 months. Follow-up started on January 1, 1993, or the date at which 6 months of valid history was obtained, whichever was latest. Patients having a history of AUR or radical cystectomy prior to study entry were excluded. All subjects were observed from study entry until the first episode of AUR, the end of the study period (December 2002), the time of transfer out of the practice, or death, whichever event occurred first.

CASE IDENTIFICATION AND VALIDATION

Acute urinary retention is defined as the sudden inability to pass any urine, requiring catheterization. All potential cases of AUR were manually reviewed by a physician (K.M.C.V.) and categorized into 3 groups (definite AUR, possible AUR, or no AUR). An end point committee of 3 physicians (J.L.H.R.B., B.H.C.S., and M.A.M.V.W.) reviewed all cases from the possible AUR category. Independently, the physicians classified the cases into 3 categories (AUR, no AUR, or AUR unknown). If at least 2 of the 3 physicians agreed, the respective category was assigned. If none of the physicians agreed, the AUR case remained within the possible AUR category. A sample of possible AUR cases (5%) was verified with the general practitioner, and the diagnosis was confirmed in 93% of all cases.

Review of cases was blinded for exposure to drugs throughout the entire validation process. The index date was defined as the date of the first AUR.

CONTROLS

For each case, we sampled up to 10 male controls from the source population in follow-up at the time the case occurred. The controls were matched for age (year of birth) and calendar time (index date).

EXPOSURE DEFINITION

From the prescription records of both cases and controls, all prescriptions for NSAIDs prior to the index date were retrieved. The hazard curves for AUR during the use of NSAIDs are not known. Based on the proposed mechanism, we assumed a priori an acute effect with a short carryover. Hence, exposure to NSAIDs was classified as current (last prescription covers the index date or ends less than 2 days prior to the index date) or past (last prescription ended more than 2 days and less than 6 months prior to the index date). For current users of NSAIDs, the dose effect in defined daily dose (DDD) (<1 DDD, 1 DDD, >1 DDD) and the treatment-duration effect were studied. The DDD is the recommended average dose of a drug for an adult for the main indication, as defined by the World Health Organization.

To study the effect of time since first use we categorized current users of NSAIDs into recent starters (patients who received their prescription for an NSAID within 1 week prior to the index date) and long-term users (patients currently using NSAIDs for more than 1 week or patients who had used NSAIDs in the past 6 months and who received their prescription for an NSAID within 1 week prior to the index date). To investigate the influence of affinity to COX-2, we compared COX-2-selective inhibitors with nonselective COX inhibitors.

In addition, we retrieved all prescriptions for acetylsalicylic acid prior to the index date and examined the effect of current use of acetylsalicylic acid, using the same definitions as stated herein, either as analgesic or as platelet-inhibiting agent.

COVARIATES

Data on the presence of different risk factors for AUR were extracted from the computerized patient records. These concerned current use of concomitant drugs known to cause AUR (drugs with anticholinergic effect, narcotic analgesics, and benzodiazepines) and a recent (within 30 days prior to the index date) history of urinary tract infection, nephrolithiasis, constipation, surgery, immobility, or acute neural injury. In addition, we checked for a history of benign prostatic hyperplasia (BPH), prostate cancer, incontinence, diabetes mellitus, cardiac diseases, cancer, stroke, dementia, or other neuropsychologic disorders (eg, multiple sclerosis or Parkinson disease) prior to the index date. Finally, we checked all indications for current use of NSAIDs from the patient's prescription records.

STATISTICAL ANALYSIS

The incidence of AUR within this population was calculated by dividing the number of men with AUR by the number of man-years accumulated by the source population. Ninety-five percent confidence intervals (CIs) estimates were calculated around the estimates based on the Poisson distribution.

Conditional logistic regression analysis was used to assess the matched unadjusted and adjusted risk estimates for the association between risk factors and AUR and exposure to NSAIDs and the occurrence of AUR. In the adjusted model, we first included, 1×1, all covariates that were univariately associated with the outcome (P<.05). Risk factors that changed the relative risk of AUR following current use of NSAIDs by more than 5% were maintained in the final model.

To estimate the proportion of AUR in the total population that could be attributed to the current use of NSAIDs, we calculated the population attributable risk (PAR) using the following formula: \( \text{PAR} = \frac{\text{attributable risk} \times \text{proportion exposed}}{\text{incidence rate}} \)

In this formula, the \text{attributable risk} is the incidence rate among the exposed minus the incidence rate among the unexposed. The \text{proportion exposed} is the proportion of current NSAID users among the controls (assumed to be representative of the general population).

All statistical analyses were conducted with the statistical software packages SPSS/PC 11.5 (SPSS Inc, Chicago, Ill).
RESULTS

Within the source population of 72,114 men 45 years or older, we identified 536 definite and 25 possible cases of AUR; the incidence was 2.4 per 1000 man-years (95% CI, 2.25-2.65). To avoid false-positive misclassification of the outcome, we included only the definite cases in our case-control analyses. These 536 definite AUR cases were matched to 5348 controls.

The mean (SD) age in cases was 73.0 (10.4) years. Compared with controls, case patients had a higher prevalence of comorbidity such as BPH, prostate cancer, neurologic disorders, and cancer and more often had a history of urinary tract infections, constipation, surgery, and immobility (Table 1). Current use of drugs with anticholinergic effects, narcotic analgesics, and benzodiazepines was also higher among case patients than among controls (Table 1).

The unadjusted odds ratio (OR) for AUR was 2.26 (95% CI, 1.49-3.45) for current use of NSAIDs compared with no use. This increase in risk remained after adjustment for other AUR risk factors (OR, 2.02; 95% CI, 1.23-3.31) (Table 2). Past use of NSAIDs was not associated with an increased risk of AUR. Among current users, the risk was highest for persons who were new NSAIDs users (adjusted OR, 3.3; 95% CI, 1.2-9.2), whereas the risk was highest for persons who were new NSAIDs users with an increased risk of AUR. Among current users, the risk was higher risk for persons who were new NSAIDs users (adjusted OR, 3.3; 95% CI, 1.2-9.2), whereas the risk for long-term users was 1.77 (95% CI, 1.01-3.10) (Table 2).

The risk of AUR was not linearly related with dose. No association with current use of low doses of NSAIDs (<1 DDD) was observed, and there was a similar increase in risk for patients taking NSAIDs at a dose of 1 DDD or higher (Table 2).

In a further attempt to explore whether any potential effect would be restricted to NSAIDs with high affinity for COX-2, we estimated the AUR risk for the COX-2–selective inhibiting NSAIDs and the nonselective NSAIDs. Use of COX-2–selective inhibitors was associated with a somewhat higher risk of AUR than use of nonselective NSAIDs, although the difference was not statistically significant (Table 3).

The risk of developing AUR in patients currently using acetylsalicylic acid was not increased (OR, 1.25; 95% CI, 0.98-1.60). However, most people (95%) used it in low doses (<100 mg) (Table 3).

The indications for NSAID use were not substantially different between case patients and controls: in more than 70% of each group, the NSAIDs were used to relieve locomotoric pain. Among the case patients, none of the recent starters of NSAIDs had a urologic condition or an acute neural injury as an indication to start treatment.

We explored effect modification by age, presence of urinary tract infection, history of BPH, prostate cancer, and use of concomitant medication such as anticholinergic agents or narcotics. We did not identify significant effect modification by any of these variables.

Finally, based on an AUR incidence rate of 4.73 per 1000 man-years among the exposed and 2.34 per 1000 man-years among the unexposed, we calculated a PAR of 57.4 per million population per year. Using demographic data from the Dutch Central Bureau of Statistics and based on an overall AUR incidence rate of 2.4 per 1000 man-years in men 45 years or older, this would mean that for 1998, 6548 new cases of AUR were expected in men 45 years or older, of which 156 (2.4%) could be attributed to the current use of NSAIDs.

COMMENT

In this study, we showed that current use of NSAIDs is associated with an increased risk of AUR. The risk is highest in patients who recently started using NSAIDs and those who use high daily dosages. To our knowledge, this is the first epidemiologic study to report the association between the use of NSAIDs and the risk of AUR. The hypothesis as postulated by Gruezenfelder et al. was that the inhibition of COX-2 might result in AUR. We observed an increased risk, not only for the COX-2–selective inhibitors but also for the nonselective NSAIDs, and after adjusting for all risk factors, the increased risk remained only for nonselective NSAIDs. The fact that the relationship is not restricted to the current use of COX-2–selective inhibitors seems plausible, since COX-2 will be inhibited by both COX-2–specific inhibitors and nonselective NSAIDs. We did not find an association between current use of acetylsalicylic acid and the risk to develop AUR, probably because acetylsalicylic acid was mainly used at low cardioprotective doses and thus had minimal anti-inflammatory activity.
Although we found an association between the use of NSAIDs and risk of AUR in this population-based study, our results must be interpreted with caution. Our exposure assessment was based on longitudinally collected general practitioner prescriptions rather than dispensing or patient-reported intake and did not include use of over-the-counter medications. Therefore, we may have misclassified at least some of the exposure to NSAIDs. However, it is likely that the exposure misclassification was nondifferential, and thus the reported risk estimate was an underestimate. To avoid misclassification of the outcome, we manually validated all cases and included only definite cases of AUR in our analysis. In addition, the physicians who reviewed and classified the cases were blinded to the patient’s drug exposure. Diagnostic bias was limited because the first case reports on a possible association between the use of NSAIDs and AUR were published in September 2002 and, moreover, a diagnosis of AUR was unlikely to be missed.

Confounding by indication could be a concern in this study because NSAIDs are used for the treatment of various urologic conditions (eg, urinary tract infections and nephrolithiasis) or acute neural injury (eg, acute lumbar disc herniation or symptomatic lumbar spinal canal stenosis), which by themselves could precipitate AUR.\(^{16,17}\) To control for confounding by indication, we checked the indication for all current use of NSAIDs in both cases and controls. Only 1 patient among the cases used NSAIDs for a urologic condition (chronic prostatitis), and this patient initiated therapy months prior to the index date, which suggests little or no influence of confounding by indication. Among the case patients, 3 were diagnosed as having acute neural injury in the 1 month prior to the index date. None of these 3 patients received an NSAID but instead were treated with strict bed rest and paracetamol. The highest risk of AUR that was found among recent users of NSAIDs was probably not confounded by indication because none of these patients used NSAIDs for urologic conditions or acute neural injury.

### Table 2. Use of NSAIDs, Excluding Acetylsalicylic Acid, and Risk of AUR

<table>
<thead>
<tr>
<th>NSAID Use Status</th>
<th>AUR Cases, No. (%)</th>
<th>Controls, No. (%)</th>
<th>Matched OR* (95% CI)</th>
<th>Adjusted OR† (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>No use</td>
<td>448 (83.6)</td>
<td>4715 (88.2)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Current use</td>
<td>28 (5.2)</td>
<td>131 (2.4)</td>
<td>2.26 (1.49-3.45)</td>
<td>2.02 (1.23-3.31)</td>
</tr>
<tr>
<td>Past use</td>
<td>60 (11.2)</td>
<td>502 (9.4)</td>
<td>1.26 (0.95-1.67)</td>
<td>0.98 (0.70-1.37)</td>
</tr>
<tr>
<td>Duration of use</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No use</td>
<td>448 (83.6)</td>
<td>4715 (88.2)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Current use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Started within 1 wk</td>
<td>6 (1.1)</td>
<td>16 (0.3)</td>
<td>3.9 (1.5-9.9)</td>
<td>3.3 (1.2-9.2)</td>
</tr>
<tr>
<td>Started &gt;1 wk prior</td>
<td>22 (4.1)</td>
<td>115 (2.2)</td>
<td>2.02 (1.27-3.24)</td>
<td>1.77 (1.01-3.10)</td>
</tr>
<tr>
<td>Past use</td>
<td>60 (11.2)</td>
<td>502 (9.4)</td>
<td>1.26 (0.95-1.67)</td>
<td>0.98 (0.70-1.37)</td>
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<tr>
<td>NSAID DDD</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No use</td>
<td>448 (83.6)</td>
<td>4715 (88.2)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Current use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 DDD</td>
<td>3 (0.5)</td>
<td>41 (0.7)</td>
<td>0.8 (0.2-2.5)</td>
<td>0.7 (0.2-2.6)</td>
</tr>
<tr>
<td>1 DDD</td>
<td>12 (2.2)</td>
<td>45 (0.8)</td>
<td>2.82 (1.48-5.37)</td>
<td>2.60 (1.24-5.46)</td>
</tr>
<tr>
<td>&gt;1 DDD</td>
<td>13 (2.4)</td>
<td>45 (0.8)</td>
<td>3.10 (1.65-5.83)</td>
<td>2.55 (1.21-5.39)</td>
</tr>
<tr>
<td>Past use</td>
<td>60 (11.2)</td>
<td>502 (9.4)</td>
<td>1.26 (0.94-1.67)</td>
<td>0.99 (0.70-1.38)</td>
</tr>
</tbody>
</table>

Abbreviations: AUR, acute urinary retention; BPH, benign prostatic hyperplasia; CI, confidence interval; DDD, defined daily dose; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; UTI, urinary tract infection.

*Matched for year of birth and index date.

†Adjusted for BPH, prostate cancer, UTI, surgery, immobility, and use of narcotic analgesics and benzodiazepines.

### Table 3. Type of NSAID or Acetylsalicylic Acid and Risk of AUR

<table>
<thead>
<tr>
<th>NSAID Use Status and Type</th>
<th>AUR Cases, No. (%)</th>
<th>Controls, No. (%)</th>
<th>Matched OR* (95% CI)</th>
<th>Adjusted OR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No use</td>
<td>448 (83.6)</td>
<td>4715 (88.2)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Current use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COX-2 selective</td>
<td>3 (0.6)</td>
<td>8 (0.1)</td>
<td>4.4 (1.1-17.9)</td>
<td>3.1 (0.5-17.6)</td>
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<td>Non-COX-2 selective</td>
<td>25 (4.7)</td>
<td>123 (2.3)</td>
<td>2.15 (1.38-3.34)</td>
<td>1.96 (1.17-3.26)</td>
</tr>
<tr>
<td>Past use</td>
<td>60 (11.2)</td>
<td>502 (9.4)</td>
<td>1.26 (0.95-1.68)</td>
<td>0.96 (0.70-1.37)</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use</td>
<td>90 (16.8)</td>
<td>756 (14.1)</td>
<td>1.25 (0.98-1.60)</td>
<td>0.99 (0.74-1.32)</td>
</tr>
<tr>
<td>Past use</td>
<td>30 (5.6)</td>
<td>257 (4.8)</td>
<td>1.22 (0.83-1.81)</td>
<td>0.86 (0.54-1.38)</td>
</tr>
</tbody>
</table>

Abbreviations: AUR, acute urinary retention; BPH, benign prostatic hyperplasia; CI, confidence interval; COX-2, cyclooxygenase-2; DDD, defined daily dose; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; UTI, urinary tract infection.

*Matched for year of birth and index date.

†Adjusted for BPH, prostate cancer, UTI, surgery, immobility, and use of narcotic analgesics and benzodiazepines.
All known risk factors for AUR were considered potential confounders, but residual confounding by unknown risk factors for which we did not control might remain.

Although we observed that the risk of AUR was about 2-fold higher in male patients currently using NSAIDs than in those not taking NSAIDs, there have been numerous reports on various medical conditions and use of concomitant medications that note a higher risk of provoking AUR. Particularly, narcotic agents and drugs with anticholinergic effects increase the risk of AUR. Medical conditions associated with an increased risk of AUR are mainly those that increase the resistance to the urinary flow (eg, BPH, prostate cancer, urethral stricture, and constipation). In addition, surgery, homebound lifestyle, and various neurologic conditions increase the risk of AUR. In our study, we confirmed these other risk factors for AUR, and we observed that patients using narcotic analgesics were especially at risk for developing AUR.

Acute urinary retention occurs mainly in aging men as a consequence of comorbidity and the use of concomitant medications. In our study, we found that the risk of AUR is about 2-fold higher in patients currently using NSAIDs than in those not taking NSAIDs. We believe that physicians should be informed about the possibility of provoking AUR in patients using NSAIDs, especially in high-risk patients.

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**REFERENCES**