FUROSEMIDE USE AND HOSPITALIZATION FOR BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT

Objective
Recent studies have shown that furosemide may have anti-inflammatory properties. We explored whether exposure to furosemide would reduce the risk of being hospitalized with prostatism, a marker of benign prostatic hyperplasia.

Methods
Using record linkage and the computerized health insurance databases of the province of Québec, Canada, we identified a cohort of men 65 years of age and older within which we conducted a case-control study. Cases were individuals hospitalized with prostatism (ICD-9 code 600) between January 1991 and June 1993, with the index date taken as the date of hospitalisation. Controls were those not having experienced the event during the study period, with an index date selected randomly during their follow-up. Cases and controls were required to have at least 2 ½ years of health coverage prior to index date in order to identify risk factors for benign prostatic hyperplasia and establish baseline medical history. We assessed the subjects' exposure to furosemide and various other diuretics in the period 180 to 900 days preceding the index date. Logistic regression was used to evaluate the association between the use of furosemide and hospitalization for prostatism, adjusting for potential confounders.

Results
The cohort included 8,814 subjects, of which 231 were cases and 8,583 controls. The rate of hospitalization for prostatism was lower for users of furosemide compared to non-users (adjusted rate ratio 0.49; 95% CI: 0.25–0.95). There was no association with the use of thiazide or potassium sparing diuretics (adjusted rate ratio 0.95; 95% CI: 0.65–1.37). Results suggestive of a protective effect associated with corticosteroid use were observed (adjusted rate ratio 0.64; 95% CI: 0.44–0.93).

Conclusions
This study supports the hypothesis that furosemide can reduce the risk of hospitalization for prostatism, a marker of benign prostatic hyperplasia.

Key Words: *Case-control studies, elderly, epidemiology, benign prostatic hyperplasia, furosemide, diuretic*

Benign prostatic hyperplasia (BPH) is a common condition that affects one in two men over the age of 65, nearly a third of whom will have lower urinary tract symptoms.[1] Left untreated, BPH can cause recurrent urinary tract infections, urinary obstruction and lead to eventual loss of renal function. In addition, the quality of life of both the affected individual and his partner can be significantly affected by this condition.[2-3] Little is known about the etiology of BPH although age, androgenic function, and family history are believed to be important risk

factors.[1,4] Other factors that have been proposed include diet, alcohol consumption, and low body mass index. More recently, inflammation has been shown to play an important role in the pathology of this disease.[5]

Furosemide is a loop diuretic that is commonly used for the symptomatic management of congestive heart failure, cirrhosis of the liver and renal disease. Recent studies have shown that this drug possesses anti-inflammatory properties as a result of its ability to inhibit the release of tumour necrosis factor (TNF) and cytokines.[6,7] Furosemide also stimulates the production of endogenous ouabain-like substance (EOLS) in the urinary tract. EOLS has a molecular structure similar to that of glucocorticoids and in turn may exert anti-inflammatory effects.[8] However, the potential clinical relevance of these findings is currently unknown. We therefore sought to assess and quantify the relationship between the use of furosemide and the risk of being hospitalized due to BPH in older men.

METHODS

To study the possible association between the use of furosemide and hospitalization for BPH, we followed a cohort of 8,814 elderly men in the province of Quebec, Canada between January 1st, 1991 and June 1st, 1993**.** The study population was identified using the computerized health insurance databases of the province of Québec. Briefly, all permanent residents aged 65 years or older are eligible for health insurance coverage provided by the *Régie de l'Assurance Maladie du Québec* (RAMQ). This publicly funded program covers the cost of prescription drugs and both inpatient and outpatient medical services. As such, information on all such services is available from the RAMQ database. In addition, the hospitalization (*Med-Echo*) and vital statistics databases maintained by the *Ministère de la Santé et des Services Sociaux* (MSSS) provide detailed information on all hospital admissions and discharges and deaths. The information in these various databases can be linked using an encrypted unique identification number and has been widely used for research purposes.[9-12]

Study subjects had to be at least 65 years of age on July 1st, 1988, male, and community dwelling. Within this cohort of elderly men, cases were those admitted to hospital with a primary diagnosis of prostatism (ICD-9 code 600) between January 1st, 1991 and June 1st, 1993. An admission for prostatism was used as a marker for the presence of BPH. Controls were all those who did not experience the endpoint during the study period. We took the index date for the cases as the date of a *first* hospitalization for prostatism during the study period. For the controls, we selected a random date in the two and half year study period (with exposure assessed in the two and half years prior to the randomly assigned index date). Individuals with a hospitalization for the diagnosis of interest (ICD-9 code 600) in the 2 ½ years preceding the index date (baseline period) as well as those receiving drug therapy for BPH (i.e., alpha-adrenergic antagonists) were excluded. In order to identify baseline risk factors, health status, and patterns of health care utilization cases and controls had to have at least 2 ½ years of RAMQ coverage prior to index date.

Data on drug exposure was obtained from the prescription drug claims of the RAMQ database. This source of exposure data has been independently assessed for veracity and completeness.[13] Individuals classified as "exposed" to furosemide were those having received at least one prescription for this agent in the 180 to 900 days before the index date. All other subjects were considered "unexposed" to furosemide. Because hospitalization for prostatism is more likely to occur in an individual with pre-existing benign prostatic hyperplasia, drug exposure immediately preceding such an admission cannot possibly exert a protective effect. Therefore, we did not consider those having received a prescription for furosemide within six months (i.e., from 1 to 179 days) of the index date as "exposed".

The rate ratio (RR) and 95% confidence interval (CI) for the association between use of furosemide and hospitalization for prostatism was estimated from the odds ratio (OR) using logistic regression. Multivariable logistic regression was used to adjust for the potentially confounding effects of age (by year), use of androgenic drugs, use of non-steroidal anti-inflammatory drugs (NSAIDs), several neurological disorders including stroke (ICD-9 codes 431-434, 436), diabetes (use of oral hypoglycemics or insulin or ICD-9 code 250), and cardiovascular diseases

including angina (ICD-9 code 413 or use of a nitrate either alone or combined with a calcium channel blocker or a beta blocker), myocardial infarction (ICD-9 codes 410 and 412), and congestive heart failure (ICD-9 codes 402 and 428 or use of digoxin and an ACE inhibitor).

In addition, the previously validated Chronic Disease Score (CDS) method was used to adjust for the possible influence of overall disease severity.[14] This measure of comorbidity is based on both the presence of disease (identified by the use of disease-specific drugs) and an indicator of disease severity (based on the number of drugs from different therapeutic categories). Only information in the two and a half years preceding the index date (i.e., baseline period) was considered to identify the presence of these potential confounders. Finally, the number of hospitalizations during this baseline period was used as a measure of health care utilization and a proxy for contact with health care professionals. For all of these analyses, the reference group was non-users (i.e., unexposed) of furosemide.

To assess the robustness of our results, secondary analyses were performed in users of potassium sparing and thiazide diuretics compared to non-users. These agents were chosen for comparison as they share similar contraindications with furosemide and have not been shown to possess anti-inflammatory properties. We used the diuretics commonly used in our study population, namely amiloride, hydrochlorothiazide, methyclothiazide, spironolactone, and triamterene as our diuretic contrast group. The exposure time window for these analyses was the same as that used for the primary analysis. All analyses were performed using SAS version 8.2.[15]

RESULTS

During the two and a half year study period, a total of 231 individuals had a first hospitalization with a primary diagnosis of prostatism. In the 2 ½ years preceding the index date, cases were similar to controls in a univariate analysis (Table 1). Fewer cases than controls had used furosemide 180 to 900 days before the index date but these results were not significantly different (univariate analysis). Users of furosemide averaged 14 prescriptions in this time period with an average duration of 28 days. Usage of androgenic drugs was equally low in both cases and controls and both groups had a similar chronic disease score. The proportion of subjects having a history of acute myocardial infarction, angina, and congestive heart failure were also similar for cases and controls.

TABLE 1 Baseline characteristics of cases and controls

	Cases (n=231)	**Controls (n=8583)**	**Univariate P-Value**
Age, mean years (SD)	73.7 (1.0)	73.8 (1.3)	0.05
Chronic Disease Score, mean (SD)	2.74 (2.72)	2.64 (2.80)	0.58
Co-morbidity			
Congestive Heart Failure	4.3%	4.5%	0.90
Angina	1.7%	1.8%	0.90
Diabetes	11%	10%	0.70
Previous Myocardial Infarction	3.0%	2.6%	0.68
Previous Stroke	1.7%	1.3%	0.59
Medication use			
NSAIDs or corticosteroids	60.0%	56.0%	0.24
Diuretics	16.4%	16.8%	0.87
Androgens	0.4%	0.4%	0.98
Furosemide	6.3%	9.4%	0.07
Furosemide prescriptions among users, mean (SD)	13.7 (11.9)	14.0 (16.6)	0.17

Furosemide users had a lower rate of hospitalization for prostatism relative to non-users (adjusted rate ratio 0.49; 95% CI: 0.25-0.95). The use of thiazide and potassium-sparing diuretics was not associated with a protective effect (adjusted RR: 0.95; 95% CI: 0.65-1.37) (Table 2). Corticosteroid use (with exposure defined identically to that of furosemide) was associated with a lower rate of hospitalization for prostatism (adjusted RR: 0.64; 95% CI: 0.44-0.93).

TABLE 2 Crude and adjusted rate ratios of hospitalization for benign prostate hyperplasia with medications used in the time window 180 to 900 days prior to index date

Drug Exposure	Cases*	Controls*	Crude RR	Adjusted RR** (95% CI)
Non-users	154	5099	Reference	Reference
Furosemide	14	805	0.63	0.49 (0.25 – 0.95)
Other Diuretics***	38	1441	0.98	0.95 (0.65 – 1.37)
Corticosteroids	36	1827	0.68	0.64 (0.44 – 0.93)

* It is possible for patients to be exposed to more than one of the drugs in the list across our exposure period
**Adjusted for one another as well as age, congestive heart failure, angina, myocardial infarction, stroke, diabetes, CDS, androgen use and NSAIDs.
***Other diuretics include: amiloride, hydrochlorothiazide, methyclothiazide, spironolactone and triamterene

DISCUSSION

We observed an association between the use of furosemide and a decrease in hospitalization with prostatism. This result is in keeping with some recent evidence suggesting that inflammation may play an important role in the pathology of BPH and that furosemide may exert anti-inflammatory effects.[5-8] The validity of this association is strengthened by the observed lack of a protective effect among users of thiazide and potassium-sparing diuretics, agents with some similar indications and contraindications but no known anti-inflammatory properties. In addition, the latter finding demonstrates that the beneficial effect from exposure to furosemide is most likely due to the specific pharmacological effects of this agent rather than a general property of diuretics. Corticosteroid use was also associated with a reduced risk of hospitalization for prostatism, further supporting the anti-inflammatory hypothesis.

We were unable to investigate a dose-response relationship due to the small number of cases using furosemide and insufficient variation in exposure levels. On the other hand, given the majority of those exposed to furosemide were regular users, the observed protective effect is based on continued exposure rather than receipt of a few prescriptions over a prolonged period of time. Some aspects of the study design and associated limitations require further discussion. Benign prostatic hyperplasia is a disease with an insidious onset for which a significant proportion of men are not diagnosed and do not seek treatment.

Consequently, we used hospitalization with a primary diagnosis of prostatism as a marker for the presence of BPH. The use of this endpoint increased the likelihood that subjects were at a more similar point in the natural progression of this disease. However, we had no information on the exact date of diagnosis for BPH. For this reason, it is possible that a proportion of control subjects had advanced BPH for which they had not yet been hospitalized. It is unlikely that clinicians would alter their prescribing of furosemide based on the presence of BPH given that the reported beneficial effect is unknown. The resulting misclassification of the subject's case/control status would therefore be non-differential and bias the results towards the null.

The definition of hospitalization for BPH as a marker for BPH severity is a conservative assumption. As many of the controls will have varying degrees of BPH they will be more similar

to the cases and so this will tend to drive any effect of the drug towards the null by making cases and controls more similar. It is possible that there is an underlying confounding factor that explains both the prescription of furosemide and increases the likelihood of a subject being hospitalized for BPH. Further investigation and validation of this endpoint could increase our understanding of this effect.

In any observational study of drug effects, bias due to confounding by indication needs to be considered as an alternative explanation for the observed results. We did not have any information on the specific indication for the use of furosemide. Although we controlled for the presence of comorbid conditions and used a measure of overall health (i.e. CDS), we cannot exclude the possibility of residual confounding in this study.

Our findings raise the possibility that use of furosemide may decrease the risk of being hospitalized for prostatism. For this reason, this study provides evidence of a beneficial effect on the progression of BPH but provides no information on the role of this agent on the development of this condition. This association may be due to anti-inflammatory properties of the drug, another unknown causal factor, or it may be a chance association. Also, we have no evidence that the drug provides any beneficial effect on the progression of the disease and it may provide purely symptomatic relief. Additional studies are needed to further explore the potential benefit of furosemide in the prevention of a hospital admission due to benign prostatic hyperplasia, as this study is primarily an exercise in hypothesis generation. It is important to note that furosemide has been implicated in serious side effects in other studies, which might reduce its attractiveness as a primary intervention.[16]

Still, if there were further evidence to support this novel and interesting effect, such information would have to be considered by clinicians when choosing a diuretic for individuals with or at risk for BPH.

Acknowledgements

This research was funded by Canadian Institutes of Health Research (CIHR). Dr Suissa is the recipient of a Distinguished Investigator award from the CIHR.

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