European Urology

European Urology 47 (2005) 505–510

Treatment of Benign Prostatic Hyperplasia and Occurrence of Prostatic Surgery and Acute Urinary Retention: A Population-Based Cohort Study in The Netherlands

P.C. Souverein[a,*], M.M. van Riemsdijk[b], J.J.M.C.H. de la Rosette[c], P.C.E. Opdam[d], H.G.M. Leufkens[a]

[a]*Department Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, PO BOX 80082, 3508 TB Utrecht, The Netherlands*
[b]*GlaxoSmithKline Corp., The Netherlands*
[c]*Department Urology, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands*
[d]*Zorggroep Almere, Almere, The Netherlands*

Accepted 2 November 2004

Available online 20 November 2004

Abstract

Objectives: To assess and compare the risk of prostatic surgery in (subsets of) patients with a diagnosis of BPH. We sought to expand on data of an earlier pharmacy-based study by obtaining more information on BPH disease parameters by using a Dutch GP-based research database.

Methods: A retrospective cohort study (1994–mid-year 2002) was conducted among 1430 men aged ≥45 years with ≥6 months of registration with the GP. BPH case identification was based on review of medical records.

Results: Overall, we found that there was no difference in the risk of prostatic surgery between patients on medical treatment and watchful waiting. Patients using 5α-reductase inhibitors (5-ARIs) at any stage had a statistically significant reduced risk of surgery compared to patients using α-blockers only: adjusted hazard ratio 0.35 (95%CI: 0.13-0.96). The routine collection of BPH parameters were insufficient to be useful in the analysis.

Conclusion: Patients using 5-ARIs seemed to have a reduced risk of prostatic surgery compared to patients using α-blockers. However, it was unknown whether the disease profile of 5-ARI users is different compare to non-5-ARI-treated and untreated patients with BPH, as detailed medical information necessary to characterise patients according to the BPH disease severity and development of disease parameters is not routinely recorded by GPs.

Keywords: Benign prostatic hyperplasia; Cohort study; Database; 5α-reductase inhibitors; α-adrenoceptor antagonist

1. Introduction

Benign prostatic hypertrophy (BPH) is the most frequent urological problem in ageing men, commonly resulting in increasing pressure on the urethra with subsequent obstruction of the urinary flow and lower urinary tract symptoms (LUTS). Based on histopathological and clinical criteria, the prevalence of BPH among men aged 60–70 years is 40–70% [1,2]. An enlarged prostate in the presence of moderate to severe LUTS and/or a decreased urinary flow occurs in about 25% of men in the community, rising from 14% in men aged 40–49 to 43% in men aged 60–69 years [2]. Up to a decade ago, BPH was usually treated by either watchful waiting or surgery, primarily transurethral resection of the prostate (TURP). In the last decade drug therapies,

* Corresponding author. Tel. +31 30 2536720/7324; Fax: +31 30 2539166.
E-mail Address: P.C.Souverein@pharm.uu.nl (P.C. Souverein).

0302-2838/$ – see front matter
doi:10.1016/j.eururo.2004.11.001

ELSEVIER

e.g. α-blockers and 5α-reductase inhibitors (5-ARIs) have become available and are recommended for patients with moderate to severe symptomatic symptoms. Nowadays, α-blockers are widely used as a first-line medical treatment for patients affected by LUTS. Newer α-blockers, such as alfuzosin and tamsulosin, relieve BPH symptoms equally effective as doxazosin or prazosin but have an improved safety profile relative to the classic α-blockers, like doxazosine and prazosin [3]. α-blockers generally produce a rapid relief of LUTS by relaxing smooth muscle tone in the lower urinary tract. Finasteride and dutasteride are selective inhibitors of 5α-reductase which decrease the conversion of testosterone to dihydrotestosterone, improve LUTS, reduce prostate volume and the risk of surgery and AUR, and improve quality of life [4–6].

Observational studies are important to obtain knowledge on LUTS/BPH, its treatment and long-term consequences in daily clinical practice. In a previous study, conducted in the PHARMO database, it was shown that use of 5-ARIs was associated with a decreased risk of BPH-related surgery relative to use of α-blockers [7]. The observed difference between α-blockers and 5-ARIs may be the result of differences in mode of actions between the two classes of drugs. A limitation of the previous study was that it concentrated on the use of drugs labelled for the treatment of BPH and did not have information on the indication for which the drug had been used.

In The Netherlands, three databases have so far been used earlier to study the epidemiology of BPH. The Boxmeer study and the Krimpen study are both community-based longitudinal studies in Dutch municipalities that combined questionnaire information and physical examinations of respondents [8,9], whereas the Integrated Primary Care Information (IPCI) database, a large general practitioners database, contains information on medical diagnoses, laboratory data, hospital referrals and discharge data and prescription information [10]. Recently, a new GP-based research database has become available in the Dutch municipality of Almere that combines medical diagnoses, hospital data and pharmacy dispensing data (the Quadraet database). The rationale of this study was to expand on the information obtained from the PHARMO database study by using the Quadraet database in order to get improved information on medical diagnoses and clinically important parameters. The objective was to estimate the risk of prostatic surgery and/or acute urinary retention (AUR) in patients with a diagnosis of BPH and to compare the risk between three possible treatment strategies (watchful waiting, α-blocker use and 5-ARI use).

2. Methods

2.1. Setting

The data for this study were obtained from ''Stichting Quadraet'', that holds the research database of ''Zorggroep Almere''. The database is a longitudinal observational database, which contains information from computer-based records of GPs, pharmacies and nursing homes in Almere. All inhabitants registered at a GP have a unique identifying patient number and the record for each patient can be assumed to contain all medical information on that patient. The database is maintained by the department Informatisering of Zorggroep Almere. The first pharmacy was enrolled in December 1991 and the first GP practice followed in 1994. Since then, the cumulative number of practices contributing data has increased to 20 and the database now contains information on approximately 150,000 patients.

Computer records contain information on patient demographics, symptoms (free text in the notes field of the electronic record), diagnoses (using the International Classification for Primary Care), specialist referrals, hospital admissions, laboratory values (e.g. PSA, cholesterol, fasting glucose levels), measurements (e.g. prostate volume (PV), blood pressure), drug prescriptions plus their ICPC-coded indications. Summaries of the hospital discharge letters and information from specialists are entered in a free text format. Information on drug prescription comprises brand name, quantity, strength, indication, prescribed daily dose, dispensing date and the Anatomical Therapeutical Chemical classification (ATC) code.

2.2. Study design and patient identification

Within this database, a retrospective cohort study was conducted among all men, aged 45 years and older, who had been registered with their GP for at least 6 months (''at risk study base''). The study covered a period from 1994 to mid-year 2002. Patients with pre-existing prostate or bladder cancer or a history of prostate surgery were excluded. In order to estimate the incidence of BPH, a ''run-in'' period was applied to exclude from the cohort anyone with a record of BPH during the first 6 months following his registration with the GP. In this way, it was assumed that the first record of BPH represented the first presentation of the patient and that all patients were incident cases. Implicitly, the first record of drug treatment was assumed to represent the first period of BPH therapy.

Cases of BPH cannot be identified solely by a specific ICPC code. Therefore, all medical records were reviewed manually by a medical doctor and patients were classified as definite cases of BPH if they had a diagnosis of BPH or LUTS in their records in combination with a remark about prostatic enlargement (established by rectal examination, ultrasound or cystoscopy) without mentioning of pain (as this symptom is associated with prostatitis, rather than BPH). If the data were inconclusive, or merely indicated LUTS that could be attributed to other urological conditions (e.g. dysuria related to meatal stenosis or urethral stricture), the patient was excluded. The first date of evidence for BPH marked the start of follow-up.

2.3. Drug exposure

During the study period, 6 drugs were registered for the treatment of BPH in The Netherlands (the α-blockers alfuzosin, tamsulosin, terazosin, prazosin, doxazosin and the 5α-reductase inhibitors finasteride). All prescriptions for α-blockers and 5α-reductase inhibitors were identified from the pharmacy records.

The duration of BPH drug use was described as a treatment episode. Treatment episodes were defined as a series of subsequent prescription refills for BPH, independent of switching to another type of drug or dose regimen. A new episode was assumed if an interval of 30 days or more occurred between the theoretical end date of a prescription and the dispensing date of the next prescription for the same patient.

2.4. Study outcomes

Information on the occurrence of surgical procedures (TURP, prostatectomy) and/or AUR was extracted from each patient's GP record and/or hospital discharge letters. The date of the procedure or AUR diagnosis was the event date.

2.5. Statistical analyses

The incidence rate of BPH was calculated by dividing the number of patients with a diagnosis of BPH by the number of person-years of follow-up by the at-risk study base. The 95% confidence limits for the incidence rate were calculated using the Poisson distribution.

All patients in the study were followed from the time they met the inclusion criteria until the occurrence of either the outcome of interest (prostatic surgery or AUR), death, the end of follow-up or the end of the study. Kaplan–Meier survival curves and Cox proportional hazards analysis was used to assess the relation between use of BPH drugs and prostatic surgery or AUR. Hazard ratios were used to estimate relative risks (RR) and 95% confidence intervals (CI). Hazard ratios were adjusted for age and calendar year. Watchful waiting or α-blocker use was used as a reference category.

3. Results

From the database, 1430 men aged 45 years and older with sufficient clinical evidence for the presence of BPH were identified. The denominator of patients was 20,635. The overall incidence of BPH was 17.3/1000 person-years. The characteristics of the study population are displayed in Table 1. The median duration of follow-up was 2.4 years. The mean age of the study population was 69 years (SD 10) with 85% of the patients aged between 55 and 85 years. There were 656 patients (45.9%) who were dispensed drugs for BPH and 615 patients (43.0%) were referred to an urologist. α-blockers, in particular alfuzosin and tamsulosin, were the most commonly dispensed BPH drugs.

The characteristics of BPH drug use are shown in Table 2. Only 78 patients used finasteride during follow-up, 40 (2.8%) of them had a history of finasteride use only and 38 (2.7%) had a history of α-blocker use as well. There were 172 patients (12.0%) who had BPH-related surgery during follow-up. There was no difference in the proportion of patients having BPH-related surgery between patients who were on watchful waiting ($n = 91$, 11.8%) and patients who used BPH drugs ($n = 81$, 12.3%). The 656 prescription drug users had a total of 1056 treatment episodes with BPH drugs. Using Kaplan–Meier survival curves, the median duration of a treatment episode was 697 days (95%CI: 632–762). In the first treatment episode, 7.5% of all patients were on 5-ARI monotherapy. There was no difference between patients using α-blockers or 5-ARI with respect to age and there was no significant difference in the duration of treatment episodes between both type of drugs, except for a longer dura-

Table 1
Characteristics of the study population (n=1430)

Characteristics	Number (%)
Mean age (years)	64.5 (SD 9.7)
Age category (years)	
<55	145 (10.1)
55–64	400 (28.0)
65–74	448 (31.3)
75–84	380 (26.6)
≥85	57 (4.0)
Any drug treatment	656 (45.9)
α-blockers only	578 (40.4)
5α-reductase inhibitor only	40 (2.8)
Combination therapy	38 (2.7)
Referral to urologist	617 (43.1)
Prostatic surgery	172 (12.0)
Urinary retention	49 (3.4)

Table 2
Characteristics of BPH drug treatment among 656 patients

Characteristics	Number (%)
Type of treatment	
α-blockers	580 (88.4)
Alfuzosin	343 (52.3)
Tamsulosin	337 (51.4)
Terazosin	14 (2.1)
Prazosin	71 (10.8)
Doxazosin	14 (2.1)
5-ARI	78 (11.9)
Number of treatment episodes	
1	449 (68.3)
2	112 (16.8)
>2	95 (14.3)
Median duration of treatment episode (95%CI)	697 (632–762)
First treatment episode	
Any drug changes in episode	103 (15.7)
Switching between α-blockers only	73 (11.1)
Switching from α-blocker to 5-ARI	11 (1.7)
Switching from 5-ARI to α-blocker	8 (1.2)
Combination of α-blocker/5-ARI	3 (0.5)

5-ARI: 5α-reductase inhibitor.

Table 3
Hazard ratio of having BPH-related prostatic surgery according to treatment type

Characteristic	Prostatic surgery (*n*, %)	Crude HR (95%CI)	Adjusted HR (95%CI)*
All patients			
Watchful waiting	91 (11.8)	1.00 (reference)	1.00 (reference)
Drug treatment	81 (12.3)	1.03 (0.76–1.39)	1.01 (0.75–1.36)
α-blockers only	77 (13.3)	1.09 (0.80–1.48)	1.16 (0.85–1.58)
5-ARI only	1 (2.5)	0.22 (0.03–1.57)	0.21 (0.03–1.48)
Both	3 (7.9)	0.56 (0.18–1.76)	0.55 (0.17–1.73)
Watchful waiting	91 (11.8)	1.00 (reference)	1.00 (reference)
α-blockers only	77 (13.3)	1.09 (0.80–1.48)	1.16 (0.85–1.58)
Any use of 5-ARI	4 (5.1)	0.40 (0.15–1.09)	0.39 (0.14–1.06)
BPH drug users only			
α-blockers only	77 (13.3)	1.00 (reference)	1.00 (reference)
Any use of 5-ARI	4 (5.1)	0.34 (0.13–0.93)	0.35 (0.13–0.96)

* Adjusted for age and calendar year.

tion of use for patients who switched or co-used drugs during a treatment episode (data not shown). In the first treatment episode, 103 patients (15.7%) changed to another BPH drug, mostly from one type of α-blocker to another (Table 2).

Table 3 shows the hazard ratios of BPH-related surgery in the study population. The risk of having BPH-related surgery was not different between patients on watchful waiting and patients on drug therapy (adjusted HR 1.01, 95%CI: 0.75–1.36). Stratification according to the class of BPH drug dispensed showed adjusted HRs of 1.16 (95%CI: 0.85–1.58) and 0.21 (95%CI: 0.03–1.48) for patients using α-blockers only and patients using 5-ARIs only, respectively. We found no differences with respect to the type of α-blocker used (data not shown). Compared with patients on watchful waiting, the risk of BPH-related surgery was reduced by 60% for patients using 5-ARIs: adjusted HR 0.39 (95%CI: 0.14–1.06). When excluding patients undergoing BPH-related surgery within two months of the first diagnosis of BPH, results were not substantially different and still indicated a lower risk among patients using 5-ARIs (data not shown). The risk of BPH-related surgery for patients using 5-ARI (alone or in combination with α-blockers) versus α-blockers use alone was significantly reduced: adjusted HR 0.35 (95%CI: 0.13–0.96).

Apart from BPH-related surgery, the occurrence of AUR before prostatic surgery was considered as an alternative outcome. Thirty-five AURs (4.5%) occurred in the watchful waiting group, and 14 AURs (2.4%) in the α-blocker group. There were no AURs among patients using 5-ARI. The risk of AUR was significantly lower among α-blocker users compared with patients on watchful waiting (adjusted HR 0.42, 95%CI: 0.22–0.78). However, when the analysis was restricted to AURs that did not occur within 30 days of the first BPH diagnosis, the point estimate of the hazard ratio increased to 1.33 (95%CI: 0.58–3.07).

4. Discussion

In this population-based study it was found that the risk of having BPH-related surgery was significantly reduced among patients being treated with 5-ARIs (either as monotherapy or in combination with α-blockers) compared to patients being treated with α-blocker monotherapy. This finding is in line with an earlier population-based study conducted in The Netherlands, that used data from the PHARMO Record Linkage System. In this study on 5671 men using drugs that are indicated for the treatment of BPH (terazosin, tamsulosin and alfuzosin), an increased risk of prostatic surgery was found for users of α-blockers compared to patients using 5-ARIs (hazard ratio 1.52, 95%CI 1.24–1.88) [7]. A recent trial where the efficacy of treatment with an α-blocker alone, a 5-ARI alone or a combination of both also showed that the incidence of prostatic surgeries was significantly lower in the 5-ARI group [11]. Furthermore, a study in the GPRD database in the United Kingdom on 4,500 patients treated with α-blockers or 5-ARIs revealed similar findings [12]. Boyle et al. found that patients using α-blockers were significantly more likely to experience surgery (hazard ratio 1.78, 95%CI: 2.30–2.44) than patients using 5-ARIs. Therefore, the Quadraet database provided similar results to other studies that contained information on a larger number of patients.

The risk of AUR was not different for patients using α-blockers and those on watchful waiting, whereas the results initially indicated a significantly lower risk when not taking the time of AUR in relation to the start of study follow-up into account. The most likely explanation for this finding might be that patients suffered with LUTS for some time, but present themselves to their GP with AUR as the first major voiding problem and complication of BPH. However, the number of patients in this analysis was low, making it difficult to draw strong conclusions. Furthermore, the influence of 5-ARI therapy could not be assessed in the AUR-analysis, because no AURs were observed among 5-ARI users.

A strength of this study is that we used medical data from general practices, community pharmacies, as well as information on referrals to medical specialists and hospitalisations. During patient selection, effort was taken to ensure that patients had sufficient evidence of BPH; meaning that patients had to have evidence for an enlarged prostate during either rectal examination, ultrasound or cystoscopy. The incidence rate of 17.4 per 1000 person-years found in our study is in line with earlier an earlier reported incidence of BPH of 15 per 1000 person-years found by Verhamme et al. in The Netherlands using a similar case identification strategy [10].

The aim for this study was to obtain more detailed information on clinical parameters important for classifying BPH severity compared to an earlier study only using information on drug dispensing and hospital admissions. We used data from a new research database from the municipality of Almere, combining GP, hospital data and pharmacy data. When comparing the data with other data sources in The Netherlands that have been used to conduct BPH epidemiology, the Almere database closely resembles the design of the Dutch Integrated Primary Care Information (IPCI) database [14]. The problem with GP-based databases in this particular disease area is that detailed information on BPH, including prostate size, urinary flow rates, symptom scores, and PSA-value, is unlikely to be systematically accrued and recorded by a GP. Therefore, although there were incidental cases where such data were available, the overall reliability of this information was too limited to be used in an epidemiological study. As a consequence, we were not able to control for differences in baseline disease characteristics in this study, as we aimed a priori. Patients being prescribed 5-ARIs are likely to be different with respect to disease characteristics compared to patients on other treatment strategies (e.g. with respect to disease/symptom severity, prostatic size). Hence, the likelihood of such patients having prostatic surgery might be different from patients not being treated with 5-ARIs. Thus, it can not be ruled out that other characteristics can explain the observed difference between α-blockers and 5-ARI with respect to the risk of having prostatic surgery.

This study has some other important limitations. First, the number of patients using 5-ARI was low, which is in line with earlier data on BPH drug use in The Netherlands [13]. Patients were only eligible for inclusion in the study when they had at least 6 months of history prior to the first record indicative for BPH in the medical records, however, it is possible that patients had symptoms earlier, were treated earlier by another GP, or that prior history of BPH was not listed in the patient medical files. Another concern is that inclusion of false-positive BPH cases can not be ruled out, as we had to rely on the recorded medical information, including the doctors interpretation of the problems. However, this would have led to an underestimation of the true effect.

In conclusion, this study showed and confirmed data from the literature that patients using 5-ARIs are less likely to have BPH-related surgery compared to patients being treated with α-blockers. The question remains whether this effect is due to the drug or is caused by differences in underlying disease differences. More research into the natural history and progression of BPH in a population-based setting can generate more knowledge on BPH in daily clinical practice. Moreover, it was experienced in this study that although GP-based research databases may contain a wealth of information for epidemiological research, their use in BPH epidemiology seems to be restricted to rather basic research questions, as the detailed medical information necessary to characterise patients according to the BPH disease severity and development of disease parameters is not routinely recorded by GPs. More detailed urological information, like (repeated) standard clinical measurements and symptom questionnaires, as used in both the Boxmeer and the Krimpen studies provide the more detailed information on BPH that seems necessary. The drawback of these types of studies is that they rely on the active participation of study subjects, which might cause problems with (selectivity of) non-response, loss to follow-up, and study costs.

Acknowledgements

This study was supported by an unconditional educational grant from GlaxoSmithKline Corp.

References

[1] Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. J Urol 1984; 132(3):474–9.

[2] Garraway WM, Collins GN, Lee RJ. High prevalence of benign prostatic hypertrophy in the community. Lancet 1991;338(8765): 469–71.

[3] Djavan B, Marberger M. A meta-analysis on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. Eur Urol 1999;36(1):1–13.

[4] Gormley GJ, Stoner E, Bruskewitz RC, Imperato-McGinley J, Walsh PC, McConnell JD, et al. The effect of finasteride in men with benign prostatic hyperplasia. The Finasteride Study Group. N Engl J Med 1992;327(17):1185–91.

[5] McConnell JD, Wilson JD, George FW, Geller J, Pappas F, Stoner E. Finasteride, an inhibitor of 5 alpha-reductase, suppresses prostatic dihydrotestosterone in men with benign prostatic hyperplasia. J Clin Endocrinol Metab 1992;74(3):505–8.

[6] Boyle P, Gould AL, Roehrborn CG. Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: meta-analysis of randomized clinical trials. Urology 1996;48(3):398–405.

[7] Souverein PC, Erkens JA, de la Rosette JJ, Leufkens HG, Herings RM. Drug treatment of benign prostatic hyperplasia and hospital admission for BPH-related surgery. Eur Urol 2003;43(5):528–34.

[8] Sonke GS, Kolman D, de la Rosette JJ, Donkers LH, Boyle P, Kiemeney LA. Prevalence of lower urinary tract symptoms in men and its influence on their quality of life: Boxmeer Study. Ned Tijdschr Geneeskd 2000;144(53):2558–63.

[9] Blanker MH, Groeneveld FP, Prins A, Bernsen RM, Bohnen AM, Bosch JL. Strong effects of definition and nonresponse bias on prevalence rates of clinical benign prostatic hyperplasia: the Krimpen study of male urogenital tract problems and general health status. BJU Int 2000;85(6):665–71.

[10] Verhamme KM, Dieleman JP, Bleumink GS, van der Lei J, Sturkenboom MC, Artibani W, et al. Incidence and prevalence of lower urinary tract symptoms suggestive of benign prostatic hyperplasia in primary care-the Triumph project. Eur Urol 2002;42(4):323–8.

[11] McConnell JD, Roehrborn CG, Bautista OM, Andriole Jr GL, Dixon CM, Kusek JW, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med 2003;349(25): 2387–98.

[12] Boyle P, Roehrborn C, Harkaway R, Logie J, de la Rosette J, Emberton M. 5-alpha reductase inhibition provides superior benefits to alpha blockade by preventing AUR and BPH-related surgery. Eur Urol 2004;45(5):620–6 [Discussion 626–7].

[13] Erkens JA, Herings RM. Drug and surgical treatment of BPH. Utrecht: PHARMO Institute for Drug Outcomes Research; 2002.

[14] Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med 1999;38(4–5):339–44.