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Combined sabal and urtica extract compared with finasteride in men with benign prostatic hyperplasia: analysis of prostate volume and therapeutic outcome

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Objective To test the hypothesis that in patients with benign prostatic hyperplasia (BPH), the outcome of drug therapy with finasteride may be predictable from the baseline prostate volume and that positive clinical effects might be expected only in patients with prostate volumes of >40 mL, using a subgroup analysis of results from a previously reported clinical trial of finasteride and phytotherapy.

Patients and methods A subgroup of 431 patients was analysed from a randomized, multicentre, double-blind clinical trial involving 543 patients with the early stages of BPH. Patients received a fixed combination of extracts of saw palmetto fruit (*Serenoa repens*) and nettle root (*Urtica dioica*) (PRO 160/120) or the synthetic 5α-reductase inhibitor finasteride. The patients assessed had valid ultrasonographic measurements and baseline prostate volumes of either $\leqslant 40$ mL or >40 mL. All 516 patients were included in the safety analysis. The results of the original trial showed equivalent efficacy for both treatments.

Results The mean (SD) maximum urinary flow (the main outcome variable) increased (from baseline values) after 24 weeks by 1.9 (5.6) mL/s with PRO 160/120 and by 2.4 (6.3) mL/s with finasteride. There were no statistically significant group differences ($P=0.52$). The subgroups with small prostates ($\leqslant 40$ mL) showed similar improvements, with mean values of 1.8 (5.2) mL/s with PRO 160/120 and 2.7 (7.4) mL/s with finasteride. The mean values for the subgroups with prostates of >40 mL were similar, at 2.3 (6.1) and 2.2 (5.3) mL/s, respectively. There were improvements in the International Prostate Symptom Score in both treatment groups, with no statistically significant differences. The subgroup analysis showed slightly better results for voiding symptoms in the patients with prostates of >40 mL, but there were also improvements in the subgroup with smaller prostates. The safety analysis showed that more patients in the finasteride group reported adverse events and also there were more adverse events in this group than in patients treated with PRO 160/120.

Conclusion The present analysis showed that the efficacy of both PRO 160/120 and finasteride was equivalent and unrelated to prostate volume. However, PRO 160/120 had better tolerability than finasteride.

Keywords Benign prostatic hyperplasia, sabal, saw palmetto, Urtica extract, PRO 160/120, finasteride, safety, efficacy, prostate volume

Introduction

Phytotherapeutic preparations have long been considered standard therapy for the treatment of the early stages of BPH. One such preparation is PRO 160/120 (Prostagutt forte™, Dr Willmar Schwabe GmbH, Germany), a fixed combination of 160 mg of extract (WS 1473) from the fruit of the saw palmetto (*Serenoa repens*) and 120 mg of dry extract (WS 1031) from the stinging nettle, *Urtica dioica.* This herbal drug has been used for many years in BPH therapy because it has confirmed efficacy and good tolerability [1–3].

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The efficacy and safety of the 5α-reductase inhibitor finasteride has been investigated in several placebo-controlled clinical trials [4–8], but there are no data relating to the risk/benefit ratio of finasteride compared with PRO 160/120. Therefore, a randomized, multicentre, double-blind trial was carried out to compare the efficacy and tolerability of PRO 160/120 vs finasteride in patients with early BPH. The results of this clinical trial, which showed that there were no statistically significant differences between the drugs for the relevant efficacy variables, were published previously [9].

A recent report suggested that the outcome of the treatment of BPH with finasteride might be predicted by the patient's pre-existing prostate volume [10,11]. The

authors concluded that positive clinical effects might only be expected in patients with prostate volumes of >40 mL. This hypothesis has important therapeutic consequences for the treatment of patients with prostate volumes of ⩽ 40 mL and therefore this was investigated using the results from the previous trial of PRO 160/120 vs finasteride [9]. In the present paper, the main results are briefly reviewed and those from additional analyses relating to the correlation between prostate volume and drug effects presented.

Patients and methods

In all, 543 men (aged 50–88 years) were recruited from 81 medical practices in Germany and enrolled into a randomized, multicentre, double-blind study. All patients had early symptomatic BPH (stages I–II according to the classification system used by Alken [12]) with a maximum urinary flow (Q_{max}) at baseline of <20 mL/s and a voided volume of >150 mL. Patients were excluded from the trial if they had concomitant diseases or were receiving additional treatment that could interfere with the trial procedure or the outcome evaluation. All patients gave their written informed consent and the trial protocol was approved by an institutional ethical committee before study initiation.

After a 2-week placebo 'run-in', 516 patients entered the double-blind treatment period. They were randomized to treatment for a total of 48 weeks receiving either two capsules of PRO 160/120 and one placebo capsule, or one finasteride (5 mg) capsule and two placebo capsules (double-dummy method). The men were examined clinically at the beginning and the end of the run-in period (baseline), at 6-week intervals during the double-blind period and at the end of the 48-week treatment period. The following variables were recorded: Q_{max}, mean urinary flow rate, voided volume and duration, time to flow rate increase, ultrasonographically measured prostate volume, urinary symptoms using the IPSS, and a quality-of-life-score (both according to the recommendations of the International Consensus Committee [13]). Adverse events were recorded using active questioning at each medical examination.

The working hypothesis of the trial assumed that the clinical efficacy of the PRO 160/120 treatment in patients with BPH (stages I–II) was not inferior to treatment with finasteride. The change in Q_{max} was established as the primary efficacy outcome variable in the confirmatory analysis. After 24 weeks of therapy the mean improvement in Q_{max} with PRO 160/120 was less than with finasteride by ⩽ 0.5 mL/s (equivalence limit). All other measured efficacy variables were considered secondary. The efficacy analysis of Q_{max} comprised the intention-to-treat population and included data from 489 patients (245 on PRO 160/120 and 244 on finasteride).

The efficacy was also assessed in subgroups categorized by the patients' prostate volume, using data from the 431 patients with valid ultrasonographic measurements (215 on PRO 160/120 and 216 on finasteride). In this analysis, the mean changes in Q_{max} from baseline values after 24 and 48 weeks of treatment were calculated for two subgroups in each treatment group, consisting of patients with baseline prostate volumes of either ⩽ 40 mL or >40 mL. All 516 patients (261 on PRO 160/120 and 255 on finasteride) included in the active treatment period were analysed for safety. Except for the test of the equivalence hypothesis (one-sided *t*-test for equivalence), two-sided *t*-tests were used and the data expressed as the mean (SD).

Results

Prostate volumes at baseline were similar in the two groups, at 42.7 (27.8) and 44.0 (26.6) mL in the PRO 160/120 and finasteride groups, respectively; the respective values of the median and interquartile range were 23.8 (37.8–51.0) and 25.6 (38.2–54.2) mL. In the PRO 160/120 group, there was only a small change in mean prostate volume throughout the trial (42.4 mL at the end of therapy). However, in the finasteride group the prostate volume decreased to a mean of 37.2 mL at the final examination.

The Q_{max} increased during the trial in both treatment groups, but there was no statistically significant difference between them (Table 1). In the PRO 160/120 group the mean values increased until week 24 and remained stable until week 48, whereas in the finasteride group there was a further slight increase in mean flow. However, the differences were not statistically significant ($P = 0.19$) at the end of therapy. The confirmatory efficacy analysis of Q_{max} also showed very similar results for both treatment groups after 24 and 48 weeks (Table 1). The subgroup analysis with baseline prostate volume showed no relevant differences. There was a continuous improvement in IPSS with both therapies (Table 1). The mean scores decreased similarly during the trial, with no statistically significant differences. The prostate volume subgroup analysis (Table 1) showed slight differences in favour of patients with baseline prostate volumes of >40 mL in both treatment groups. However, the score also decreased in patients with prostate volumes of ⩽ 40 mL.

In the finasteride group there were 96 adverse events in 54 patients, compared with 74 in 52 patients in the PRO 160/120 group; a detailed description of the safety evaluation was reported previously [9].

Table 1 The Q_{max} during the study for all patients, the change in Q_{max} after 24 and 48 weeks of treatment compared with baseline, for all patients** and for the two subgroups of prostate volume, and the IPSS (score A) during the course of treatment for all patients and for the two subgroups of prostate volume (all intentions to treat analysis)

Mean (SD) [n] variable	*PRO 160/120*	*Finasteride*	*P*
Q_{max} (mL/s)			
Inclusion	12.4 (4.5) [244]	12.8 (4.0) [241]	0.33
Baseline	12.7 (4.4) [245]	12.7 (4.5) [244]	0.90
Week 12	14.2 (6.0) [240]	14.6 (6.6) [242]	0.46
Week 24	14.6 (6.2) [245]	15.1 (7.1) [244]	0.34
Week 36	14.6 (6.2) [231]	15.2 (7.4) [231]	0.31
Week 48	14.6 (6.4) [233]	15.4 (6.8) [232]	0.19
Change in Q_{max} (mL/s), over all patients			
After 24 weeks	1.9 (5.6) [245]	2.4 (6.3) [244]	0.52
After 48 weeks	2.0 (6.4) [233]	2.8 (6.6) [232]	0.73
Change in Q_{max} (mL/s), subgroups relating to prostate volume (mL)			
After 24 weeks, ≤ 40*	1.8 (5.2) [116]	2.7 (7.4) [112]	0.27
After 24 weeks, >40*	2.3 (6.1) [99]	2.2 (5.3) [104]	0.90
P	0.49	0.58	
After 48 weeks, ≤ 40*	1.6 (6.6) [109]	2.7 (6.8) [106]	0.22
After 48 weeks, >40*	2.1 (6.1) [94]	2.7 (6.2) [99]	0.50
P	0.60	0.96	
IPSS			
Baseline	11.3 (6.5) [258]	11.8 (6.6) [255]	0.34
Week 24	8.2 (5.8) [233]	8.0 (5.7) [230]	0.66
Week 48	6.5 (5.8) [230]	6.2 (5.2) [223]	0.54
IPSS, subgroups relating to prostate volume (mL)*			
Baseline, ≤ 40	10.5 (6.1) [116]	10.5 (6.2) [111]	0.94
Baseline, >40	11.3 (6.7) [98]	11.8 (5.8) [104]	0.62
P	0.36	0.11	
Week 24, ≤ 40	7.9 (5.9) [116]	8.1 (5.9) [111]	0.79
Week 24, >40	7.9 (5.4) [98]	7.5 (5.2) [104]	0.60
P	0.99	0.44	
Week 48, ≤ 40	7.0 (6.2) [116]	6.3 (5.3) [106]	0.38
Week 48, >40	6.3 (5.0) [93]	5.6 (3.8) [100]	0.28
P	0.42	0.31	

*Sample size for subgroup analysis was lower than for all patients because there were missing values for prostate volumes. *P* is calculated from the applied two-sided *t*-test, except for the change in Q_{max}, where the one-sided test for equivalence was applied.

Discussion

The published results of this multicentre, randomized, double-blind clinical trial comparing the effects of PRO 160/120 and finasteride on functional variables (Q_{max} and subjective voiding symptoms) showed improvements on both treatments, with no statistically significant differences [9]. The results of the present analysis of prostate volume and therapeutic outcome neither support the hypothesis that the efficacy of treatment with finasteride may be predicted by the patients' baseline prostate volumes [10,11], nor show such an effect for PRO 160/120; there were no substantial differences in clinical efficacy related to prostate size. There were clinically relevant improvements in Q_{max} and subjective symptoms in patients with prostate volumes in either category.

However, the safety data reported earlier [9] suggest that PRO 160/120 was better tolerated than finasteride. Patients treated with finasteride had more adverse events than those receiving PRO 160/120. In addition, the costs of herbal drug therapy for BPH are substantially lower than treatment with finasteride. Recently, a cost/benefit analysis was published discussing the costs and benefits of finasteride therapy compared with alternative therapies [14]. Given the relatively small benefits and side-effects of finasteride therapy, the authors concluded that it should be considered carefully by physicians and patients.

In summary, the therapeutic outcome of treatment with either PRO 160/120 or finasteride was unrelated to prostate volume in either treatment group. As PRO 160/120 was better tolerated, it might be preferable to treat patients with early BPH by phytotherapy as a first choice.

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US Pharm . 2016;41(8):36-40. ABSTRACT: Benign prostatic hyperplasia (BPH) is a common disorder in men with an incidence that increases with age. BPH often requires therapy when patients begin to experience lower urinary tract symptoms that affect quality of life. Current management strategies involve lifestyle modifications, pharmacotherapy, phytotherapy, and surgical interventions as indicated. Pharmacists are in the unique position of being accessible sources of healthcare information for the BPH patient population. Understanding the symptoms of this disorder and therapy options will be beneficial for pharmacists who have increased chances to answer BPH-related questions from their patients. Benign Prostatic Hyperplasia (BPH) - Etiology, pathophysiology, symptoms, signs, diagnosis & prognosis from the MSD Manuals - Medical Professional Version.Â Men with moderate or severe symptoms of obstruction may also have uroflowmetry (an objective test of urine volume and flow rate) with measurement of postvoid residual volume by bladder ultrasonography. Flow rate < 15 mL/sec suggests obstruction, and postvoid residual volume > 100 mL suggests retention. Prostate-specific antigen (PSA) levels. Interpreting prostate-specific antigen (PSA) levels can be complex. Combined sabal and urtica extract compared with finasteride in men with benign prostatic hyperplasia: Analysis of prostate volume and therapeutic outcome. Article. Sep 2000.Â In a double-blind placebo-controlled randomized trial between January 1999 and March 2000, 100 men with symptoms of BPH, aged < 80 years, with a maximum urinary flow rate of 5-15 mL/s for a voiding volume of 150 mL, were randomly and equally allocated to 320 mg S. repens extract or placebo (paraffin oil). The most common prostate problems include benign prostatic hyperplasia, chronic prostatitis, and prostate cancer. Treatments, when available, vary in effectiveness and carry considerable side effects. A large handful of dietary supplements has shown real promise in reducing the impact of prostate disease.Â Sokeland J. Combined sabal and urtica extract compared with finasteride in men with benign prostatic hyperplasia: analysis of prostate volume and therapeutic outcome. BJU Int. 2000;86(4):439-42. Lopatkin N, Sivkov A, Schlafke S, et al. Efficacy and safety of a combination of Sabal and Urtica extract in lower urinary tract symptoms--long-term follow-up of a placebo-controlled, double-blind, multicenter trial. Int Urol Nephrol. 2007;39(4):1137-46. Combined sabal and urtica extract compared with finasteride in men with benign prostatic hyperplasia: analysis of prostate volume and therapeutic outcome. BJU Int.Â Objective: To test the hypothesis that in patients with benign prostatic hyperplasia (BPH), the outcome of drug therapy with finasteride may be predictable from the baseline prostate volume and that positive clinical effects might be expected only in patients with prostate volumes of > 40 mL, using a subgroup analysis of results from a previously reported clinical trial of finasteride and phytotherapy. Patients and methods: A subgroup of 431 patients was analysed from a randomized, multicentre, double-blind clinical trial involving 543 patients with the early stages of BPH.