CURRENT
THERAPEUTIC
RESEARCH
VOL. 55, NO. 7, JULY 1994

THE EXTRACT OF *SERENOA REPENS* IN THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA: A MULTICENTER OPEN STUDY

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ABSTRACT

Because prostatic surgery is not the treatment of choice for most patients with benign prostatic hyperplasia (BPH), the therapeutic effect of a 160-mg, twice-daily, oral dose of *Serenoa repens* extract was studied during a 3-month open trial in 505 patients with mild-to-moderate symptoms of BPH. The efficacy of the regimen was evaluated in 305 of these patients. Traditional parameters for quantifying prostatism, such as the International Prostate Symptom Score, the quality of life score, urinary flow rates, residual urinary volume, and prostate size, were found to be significantly improved after only 45 days of treatment. After 90 days of treatment, a majority of patients (88%) and treating physicians (88%) considered the therapy effective. In addition, the serum prostate-specific antigen concentration was not modified by the drug, thus limiting the risk of masking any possible development of prostate cancer during treatment. The incidence of side effects (5%) was low and compares favorably with that reported for existing medical therapies used in BPH patients. The extract of *Serenoa repens* appears to be an effective and well-tolerated pharmacologic agent in treating the mictional problems accompanying BPH.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is characterized by prostate gland enlargement sufficient to produce obstruction of the urethra.[1–3] The histologic changes that typify BPH may appear as early as the third decade of life and are prevalent in 75% of men by 60 years of age.[3]

While numerous theories have been proposed to explain the spontaneous development of BPH, two primary etiologic factors—in addition to advancing age—have been identified. First, the presence of functioning testes as well as a critical level of androgen are required. Second, a shift in the complex prostatic androgen metabolism occurs, which then favors prostatic accumulation of dihydroxytestosterone (DHT).[4,5] Another major change in gonadal steroid physiology that typically accompanies aging is

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Received for publication on February 17, 1994. Printed in the U.S.A.

0011-393X/94/$3.50

an increase in the ratio of plasma estrogens to androgens.[6] Because 17-beta-estradiol is known to enhance progesterone receptor production,[7] it is assumed that it may also play a role in regulating the activity of androgen receptor protein.[8] An estrogen effect in the pathogenesis of BPH would explain why the process continues with aging despite declining testicular androgen secretion.

Transurethral and open surgical prostatectomy are the most widely used treatments for BPH patients with severe symptoms such as urinary retention. However, the incidence of complications such as blood loss, urinary tract infection, urethral stenosis, incontinence, impotence, and the need for reintervention is clinically significant after prostatic surgery, and thus excludes its use as routine treatment for all BPH patients.[9–11] This has been an important motivating factor in the development of medical treatment alternatives.

Extract of *Serenoa repens** is obtained from the fruit of the American dwarf palm tree under supercritical conditions with carbon dioxide as a solvent and reportedly has antiandrogenic properties when used as a pharmacologic agent through a direct action at the level of the cytosolic androgen receptor.[12,13] This effect is achieved without significantly influencing testosterone, follicle-stimulating hormone, or luteinizing hormone levels.[14] In addition, *Serenoa repens* extract has an inhibitory effect on 5-alpha-reductase, resulting in reduced transformation of testosterone into DHT.[15] A recent study[16] demonstrated that the 5-alpha-reductase inhibitory potential of the Serenoa extract was very low compared with that of an alternative pharmacologic agent, finasteride (5600 times less potent). A recent study by Di Silverio et al[17] showed that the extract of *Serenoa repens* displays an inhibitory effect both on androgen and estrogen nuclear receptors, and evidence exists that it also acts as an anti-inflammatory and antiedematous agent.[18,19]

The efficacy and safety of the Serenoa extract have already been demonstrated in several clinical trials.[20,21] In a recent double-blind, placebo-controlled study of 238 patients with BPH, superiority of *Serenoa repens* extract over placebo was shown to be significant after only 1 month of treatment (unpublished data, J. Braeckman et al, 1994). Not only were overall clinical symptoms such as pollakiuria, nocturia, hesitancy, dysuria, and urgency significantly improved, but there was similar improvement in the total symptom score, the prostatic volume, and the major urinary flow parameters. The agent appeared to be well tolerated, with only 3% of patients receiving the active drug reporting minor side effects compared with 4% of those receiving placebo.

The aim of the present study was to confirm the therapeutic benefits,

* Trademark: Prostaserene® (Therabel Pharma, Brussels, Belgium).

efficacy, and safety of the extract of *Serenoa repens* in a large number of patients with BPH.

PATIENTS AND METHODS

Between December 23, 1992, and October 17, 1993, 112 urologists contributed to the enrollment of 505 patients with BPH into this study. The study patients received daily oral doses of the extract of *Serenoa repens* in 160-mg capsules administered twice daily for a 3-month period. Medical visits for evaluations were scheduled for days 0, 45, and 90.

The inclusion criteria for the study included hyperplasia of the prostate gland, no evidence of cancer after digital rectal examination and transrectal echography, absence of any abnormalities in urine culture, and a maximal urinary flow rate between 5 mL/s and 15 mL/s for a voided volume of $\geq$100 mL. Patients older than 80 years, those with a postmictional urine volume >100 mL, or any malformation, tumor, or infection of the genitourinary system were excluded from the study. Patients who had undergone previous endoscopy of the lower urinary tract or prior treatment for BPH, and those in debilitated physical condition resulting from the presence of other chronic disease were also excluded. Patients were also excluded if they were being treated with antibiotics.

All patients accepted into the study provided oral informed consent before participating. Study participants were asked to refrain from consuming excessive amounts of alcoholic beverages or coffee, and from eating spicy foods, particularly on the day before the first medical evaluation.

In addition to a routine clinical examination, specific parameters were examined at each visit. These included measurement of the mean and maximal urinary flow rates, the mictional volume, residual urine volume (as measured by transabdominal echography), prostatic volume (as classified by rectal toucher into the following three categories: 1 = <40 g; 2 = 40–60 g, 3 = >60 g). More precise measurement of prostatic volume was performed by transrectal echography, according to the formula described by Terris and Stamey ((anteroposterior diameter $\times$ [laterolateral diameter]^2 Π)/6).[22]

At each visit, culture and microscopic urine examinations were performed, and determinations of the International Prostate Symptom Score (I-PSS; on a scale of 0 to 35), and quality of life score measurements (seven categories), as recommended by the International Consensus Committee, were made.[23] On days 45 and 90, the patients and physicians were asked to give their global evaluation of the treatment (five categories), and were asked about side effects. In addition, serum prostate-specific antigen (PSA) concentrations were measured on days 0 and 90.

The effect of treatment on continuous variables was evaluated, using analysis of variance for repeated measures with the factor time as classification criterion, followed by Dunnett's post hoc tests. Student's *t* test was

used to analyze the effect of treatment on PSA concentration. The noncontinuous variables were analyzed using the chi-square or the Wilcoxon's two-sample test.

RESULTS

Of the 505 patients enrolled in the study, there was a total of 16 dropouts (7 after 45 days of treatment and 9 between day 45 and day 90 of treatment) (Table I). These patients were included in the safety evaluation but were excluded from the efficacy evaluation. An additional 184 patients who did not fulfill all inclusion criteria were excluded from the efficacy evaluation, leaving 305 patients in whom efficacy could be evaluated.

The effect of treatment on the maximal and mean urinary flow rates was significant ($P < 0.0001$) (Table II). The increase in these two parameters was already evident after 45 days at 17% for each of the two parameters and remained significant to day 90, when 25% and 27% increases, respectively, were measured. A slight, but nonsignificant ($P > 0.05$), increase was noted for the mictional volume, but residual urinary volume was found to be significantly decreased ($P < 0.0001$) by the treatment. The latter effect was maximal after 45 days (20% decrease) and remained approximately the same at day 90.

The prostatic volume, as measured by transrectal echography, was found to be significantly decreased ($P < 0.0001$) during the study. This was evidenced by a mean 9% decrease after 45 days, followed by a mean 10% decrease on day 90. In addition, a significant improvement ($P < 0.0001$) of mean I-PSS was noted, with a 22% improvement after 45 days which increased to 35% by 90 days. The quality of life score was also significantly affected ($P < 0.0001$) by treatment. After 45 days, it remained unchanged in 33% of patients, improved in 65%, and worsened in only 2%. At 90 days, this parameter remained unchanged in 19%, was improved in 78%, and had worsened in only 3% of patients (Figure 1). Importantly, the treatment did not significantly ($P > 0.05$) alter PSA concentrations in these patients.

The subjective evaluations of treatment made by patients after 45 and 90 days of treatment were favorable ($P < 0.0001$). After 45 days, 83% of

Table I. Number of patients available for the efficacy and safety evaluations of treatment with the extract of *Serenoa repens* (160 mg orally, twice daily).

Total no. of patients	505
Dropouts	
Total	16
On day 45	7
Between day 45 and day 90	9
No. of patients available for safety evaluation	505
No. of patients who did not fulfill all inclusion criteria	184
No. of patients available for efficacy evaluation	305

Table II. Efficacy of treatment with the extract of *Serenoa repens* (160 mg orally, twice daily) in patients with benign prostatic hyperplasia as measured by various study parameters. (Values are expressed as mean ± SD.)

Parameters	Day 0	Day 45	Day 90
Maximal urinary flow rate (mL/s)	9.78 ± 2.25	11.42 ± 4.42*	12.19 ± 4.19*
Mean urinary flow rate (mL/s)	5.83 ± 1.79	6.81 ± 2.45*	7.41 ± 2.88*
Mictional volume (mL)	225.6 ± 97.9	226.5 ± 94.6 NS	234.2 ± 104.7 NS
Residual urinary volume (mL)	35.8 ± 22.8	28.6 ± 27.9*	28.6 ± 32.0*
Prostatic volume (mm^3)	40,348 ± 30,526	36,644 ± 26,722*	36,246 ± 26,555*
Prostate-specific antigen concentration (ng/mL)	3.44 ± 5.22	Not determined	3.28 ± 4.76 NS
International Prostate Symptom Score	19.0 ± 6.9	14.8 ± 6.9*	12.4 ± 6.7*

NS = not significant. *$P < 0.0001$, analysis of variance followed by post hoc Dunnett's t tests. Student's t test for paired samples in the case of prostate-specific antigen concentrations.

patients estimated that the drug was effective (very, moderately, or slightly), and this percentage increased to 88% after 90 days. Similarly, global evaluations made by physicians after 45 days and after 90 days were favorable ($P < 0.0001$). After 45 days, 81% of physicians estimated that the drug was effective (very, moderately, or slightly), and this percentage increased to 88% after 90 days (Figure 2).

No serious adverse events were reported. The total of 32 side effects recorded occurred in 25 (5%) patients and were limited primarily to gastrointestinal symptoms (50%) such as gastralgia, nausea, vomiting, constipation, and diarrhea. Other reported effects were dizziness, insomnia, fatigue, muscular pain, tachycardia, angina pectoris, extrasystole, angiopathy, breathlessness, urinary infection, dry mouth, testicular pain, and vesical tenesmus. Side effects warranted premature discontinuation of therapy in only 11 (2%) patients.

DISCUSSION

The results obtained in this open study largely corroborate those recently reported in a placebo-controlled, double-blind, randomized clinical trial (unpublished data J. Braeckman et al, 1994) showing that the extract of *Serenoa repens* is an effective treatment for the mictional problems associated with BPH. Both studies showed that the parameters as defined by international urologist committees for quantifying prostatism,[3,24] such as the I-PSS, the quality of life score, urinary flow rates, residual urinary volume, and prostate size, were significantly improved with administration of this pharmacologic agent. A large majority of patients in our study reported benefit from the therapy on subjective evaluations, and this was corroborated by the evaluations of the urologists administering the treatment.

Several large-scale clinical investigations have documented the effi-

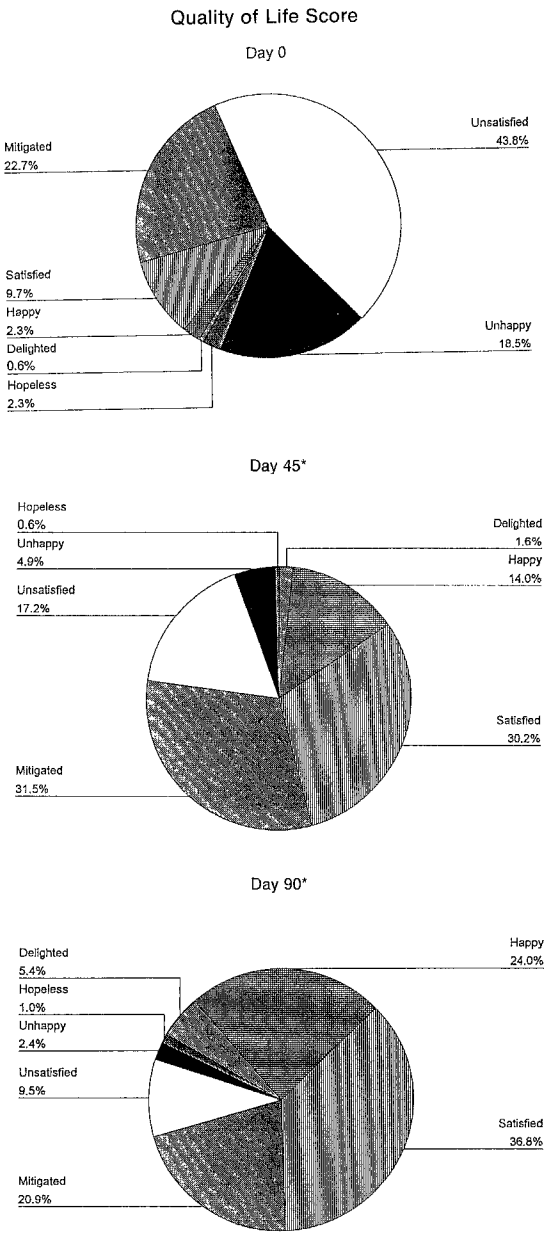

Figure 1. Quality of life scores (percentage) after 45 days and after 90 days of treatment with the *Serenoa repens* extract (160 mg orally, twice daily) compared with day 0 scores. *$P < 0.0001$, Wilcoxon's test for paired samples.

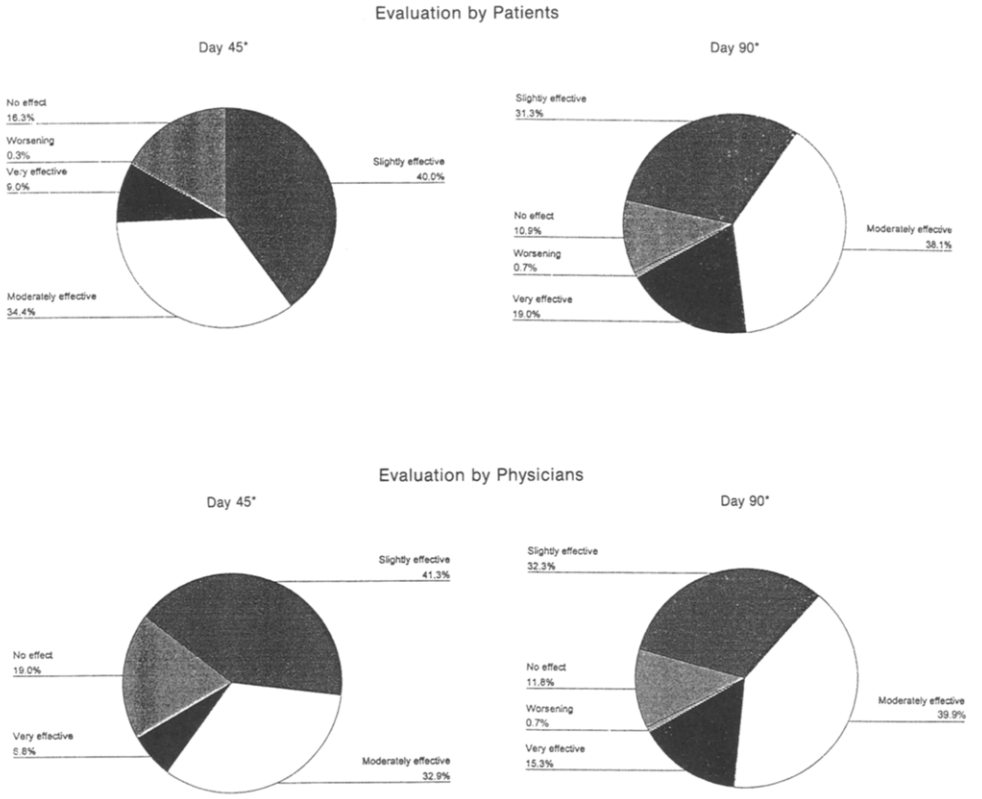

Figure 2. Evaluation of treatment with the *Serenoa repens* extract (160 mg orally, twice daily) as judged by patients and by physicians after 45 days and after 90 days of administration. *$P < 0.0001$, chi-square test.

cacy of serum PSA levels as an aid to diagnosing prostate cancer.[25–28] The underlying principle is that only minute quantities of PSA enter the general circulation under normal physiologic conditions; however elevated levels signal the presence of prostate malignancy, acute prostatitis, and BPH.[29] Because administration of finasteride is accompanied by significant decreases in PSA levels (about 50% with a 5-mg dose),[30] this treatment carries the risk of masking the development of prostate cancer during treatment. Our study clearly demonstrated the absence of such a risk with administration of *Serenoa repens* extract, as the agent does not modify the serum PSA concentration. The clinical implications of this conservative effect on PSA levels remains to be determined.

The results of this trial in a relatively large study population indicate that *Serenoa repens* extract is relatively well-tolerated by most patients. Its onset of action occurs after 30 to 45 days of treatment, and this constitutes an advantage over most currently available drugs for which delays

may be as high as 6 to 12 months.[31] We conclude that *Serenoa repens* extract, 160 mg administered twice daily, is a safe and effective treatment for the mictional problems associated with BPH. Consequently, it appears to offer a potential pharmacologic alternative capable of improving BPH symptoms in patients with mild-to-moderate disease.

Acknowledgments

The following urologists, cited in alphabetical order, participated in this multicenter trial and are gratefully acknowledged: Abi-Aad, Ackaert, Ampe, Assenmacher, Baert, Bar Moshe, Barreau, Billiet, Blaze, Blondin, Boeckx, Bouffioux, Braeckman, Jan Casselman, Coolsaet, Corbusier, Cornelissen, Cornet, D'Hoedt, D'Udekem, Dardenne, Darimont, De Boe, De Bruyne, De Galan, De Maeyer, DeNollin, De Pierpont, De Schrijver, De Wilde, Dekkers, Denys, Derluyn, Desirotte, Desmet, Detry, Dewilde, Doupagne, Ferrant, Gillis, Hallemans, Hans, Hardy, Hauzeur, Hawotte, Hublet, Hurard, Jorion, Kluge, Lahousse, Ledent, Leonard, Letawe, Libert, Maes, Maquet, Massart, Mathys, Mattelaer, Meneth, Merckx, Mestdag, Minnaert, Naome, Naudin, Nemeth, Nicolas, Nys, Oboy, Opsomer, Pacco, Pietquin, Pontus, Rager, Renard, Rettmann, Ringoir, Robyns, Roelandt, Schuyten, Smet, Smeuninx, Steyaert, Stouffs, Stragier, Tailly, Thibeau, Timmermans, Valcke, Van Belle, Van Brien, Van de Gucht, Van den Branden, Van Nueten, Van Oyen, Van Ruyssevelt, Van Vliet, Vandervaeren, Vandewalle, Vanhoucke, Verhamme, Verleyen, Vervecken, Vossaert, Vrancken, Welvaert, Werbrouck, Wildschutz, Willem, Willemen, Wilmus, and Witters.

This study was supported in part by Therabel Research, Brussels, Belgium.

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