COMPARISON OF ONCE AND TWICE DAILY DOSAGE FORMS OF *Pygeum africanum* EXTRACT IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA: A RANDOMIZED, DOUBLE-BLIND STUDY, WITH LONG-TERM OPEN LABEL EXTENSION

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ABSTRACT

Objectives. To compare the efficacy and safety of *Pygeum africanum* extract, 50 mg twice daily and 100 mg once daily.

Methods. Patients with symptomatic benign prostatic hyperplasia (BPH) entered a 2-month randomized, parallel-group, double-blind, comparative phase (group A, 50 mg twice daily; group B, 100 mg once daily), followed by a 10-month, open phase (100 mg once daily). Main efficacy assessment parameters included International Prostate Symptom Score (IPSS), quality of life (QOL), and maximum urinary flow rate (Qmax).

Results. Two hundred nine patients completed the comparative phase in compliance with the protocol; 174 were included in the open phase. Both treatments had similar efficacy. IPSS (baseline 17 in both groups) improved by 38% in group A and 35% in group B. QOL improved by 28% in both groups. Qmax increased by 1.63 mL/s (16%) in group A and 2.02 mL/s (19%) in group B. After 12 months, the IPSS fell from 16 (baseline) to 9 (−46%). Half of the patients had an IPSS below 8. Mean Qmax increased by 1.65 mL/s (15%). The safety profile was similar between groups and study phases.

Conclusions. *P. africanum* extract at 50 mg twice daily and 100 mg once daily proved equally effective and safe at 2 months. Further improvements in efficacy with a satisfactory safety profile were documented after 12 months. UROLOGY **54:** 473–478, 1999.

Phytotherapeutic drugs are widely used[1,2] as medical treatment for benign prostatic hyperplasia (BPH).[3–6] This study compared the efficacy and safety of two dosage regimens of *Pygeum africanum* (Tadenan) extract (either 50 mg twice daily or 100 mg once daily). The long-term maintenance of the effects and the safety of the 100-mg once daily dose were also investigated for a total duration of 12 months.

MATERIAL AND METHODS

The study featured three phases: after a 1-month run-in phase without treatment, patients still meeting the inclusion criteria were randomized into a 2-month double-blind, double-placebo, parallel-group phase and received *P. africanum* 100 mg/day either once daily (one 100-mg capsule in the evening, group B) or twice daily (one 50-mg capsule morning and evening, group A). All patients continuing beyond the 2-month period received *P. africanum* 100 mg once daily for 10 additional months.

Visits took place at inclusion, after the run-in period (randomization visit), after 1 and 2 months of treatment (comparative phase), and after 5, 8, and 12 months for the extension phase (follow-up visits).

The medical history, physical examination, vital signs, routine blood tests, and urinalysis, as well as the main inclusion and noninclusion criteria, were confirmed at the randomization visit. The International Prostate Symptom Score (IPSS), quality of life (QOL), vital signs, and side effects were assessed at all follow-up visits. Investigations performed at entry and after 2 and 12 months included digital rectal examination, maximum urinary flow rate (Qmax) and voided volume (flowmeter), postvoid residual volume (transabdominal ultrasound), and sexual function (qualitative assessment of

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TABLE I. ***Demographic and baseline data of the 209 patients completing the 2-month double-blind comparative phase***

	Pygeum africanum Extract	
	50 mg BID (n = 101)	**100 mg OD (n = 108)**
Age (yr)	65.7 ± 7.2	66.2 ± 7.5
Urinary symptoms (mo)	60.4 ± 49.5	54.4 ± 43.6
IPSS	17.18 ± 4.89	16.65 ± 4.50
QOL	4.32 ± 0.96	4.08 ± 0.83
Qmax (mL/s)	10.17 ± 2.75	10.89 ± 2.66
Voided volume (mL)	261.5 ± 92.5	272.6 ± 120.9
Residual volume (mL)	48.3 ± 42.9	50.2 ± 37.2
Prostate volume (cm^3)	45.1 ± 16.6	45.1 ± 13.5

KEY: BID = twice daily; OD = once daily; IPSS = International Prostate Symptom Score; QOL = quality of life; Qmax = maximum urinary flow rate.
Data presented as mean value ± SD at randomization.
No comparisons between groups were statistically different.

changes, three-item questionnaire). Prostate volume and prostate-specific antigen (PSA) serum level were assessed at entry into the study and after 12 months.

The main inclusion criteria were age 50 years or older; clinical symptoms of BPH (urinary symptoms, IPSS 10 or greater, and QOL 3 or greater), confirmed by digital rectal examination and transrectal ultrasound (prostate volume 30 cm^3 or greater); Qmax 15 mL/s or less (voided volume 140 mL or greater); residual volume 150 mL or less; PSA less than 10 ng/mL; and serum creatinine less than 160 μmol/L. The main noninclusion criteria included indication for or previous prostate or bladder surgery, prostate and/or bladder cancer, urinary symptoms due to other causes, and treatment during the 3 months preceding inclusion with finasteride, *P. africanum*, or *Serenoa repens* or with any alpha-blocker during 1 month before inclusion.

The IPSS[7–10] was the primary efficacy parameter. A clinically significant improvement was prospectively defined[11,12] as a 40% or greater reduction of mean IPSS from baseline (randomization visit); the main efficacy end point was the percentage of patients reaching this goal. Secondary outcome measures included global IPSS, nocturia (IPSS item 7), QOL, Qmax, residual volume, and prostate volume. Safety was assessed on side effects, vital signs, clinical biology, serum PSA at 12 months, and patients' satisfaction with their sexual function. The study was conducted according to Good Clinical Practice as defined by the International Conference on Harmonisation and the French legislation. The protocol was approved by the Ethics Committee of the Pitié-Salpétrière Hospital (Paris, France). All patients gave their written consent.

Statistical Analysis

The primary criterion was analyzed using a simultaneous testing of two one-sided hypotheses[13]: the first hypothesis tested for one-sided equivalence; the second tested whether the 100-mg once daily dose had a greater efficacy than 50 mg twice daily dose. The limit of equivalence was 20%. For all efficacy and safety parameters, the 90% confidence interval (CI) for the difference between treatment groups was calculated. Analyses of efficacy at 2 months were performed both on the per-protocol population and as an intention-to-treat; results being both quantitatively and statistically comparable, the results presented are those obtained on the per-protocol population. Efficacy and safety analyses at long term were performed on the intention-to-treat populations.

RESULTS

Patient Population

Two hundred thirty-five patients were randomized into the comparative phase, 12 patients (5.1%) dropped out, 11 (4.7%) because of an adverse event and 1 (0.4%) for a nonmedical reason; of the 223 patients who completed this phase, 209 patients (101 in group A and 108 in group B) were valid for the per-protocol analysis, and 14 were not (poor compliance, interruption of treatment, visit performed outside the accepted time frame). The two groups were homogenous for all the demographic and baseline characteristics (Table I).

As defined by the protocol, only the first 174 patients completing the comparative phase entered the open-label extension; 151 patients completed this phase, and 23 patients dropped out: 8 (4.6%) because of an adverse event and 15 (8.6%) for nonmedical reasons. The baseline characteristics of this subgroup of patients and of the patients who participated in the comparative phase were similar.

Efficacy Results

Comparative Phase. The IPSS decreased similarly in both groups. The percentage of patients reaching the therapeutic goal was 42.6% (95% CI 33% to 53%) and 40.7% (95% CI 31% to 51%) in groups A and B, respectively. The 90% CI of the difference between treatments was −13%, +9% ($P = 0.004$ for the one-sided demonstration of equivalence and $P = 0.606$ for the testing of superiority).

Secondary outcome measures (Table II) underwent similar changes in both groups. The mean IPSS was significantly reduced from 17.2 (group A) and 16.7 (group B) to 10.7 (−37.6%) and 10.9 (−34.6%), respectively. The 95% CI of the before-after differences did not include zero, confirming a

TABLE II. *Analysis of changes in secondary outcome measures from baseline to final visit at 2 months*

Group	n	Baseline Mean	Mean Within-Group Change from Baseline (95% CI)	Mean Between-Group Comparison (90% CI)
IPSS				
Pa 50 mg BID	101	17.18	−6.46 (−7.44, −5.47)	−0.70 (−1.75, 0.36)
Pa 100 mg OD	108	16.65	−5.76 (−6.55, −4.96)	
QOL				
Pa 50 mg BID	101	4.32	−1.19 (−1.44, −0.93)	−0.06 (−0.34, 0.22)
Pa 100 mg OD	108	4.08	−1.13 (−1.35, −0.91)	
Qmax (mL/s)				
Pa 50 mg BID	87	10.20	1.63 (0.68, 2.57)	0.40 (−0.82, 1.62)
Pa 100 mg OD	95	10.89	2.02 (0.92, 3.12)	
Residual volume (mL)				
Pa 50 mg BID	87	49.9	0.3 (−12.4, 12.9)	3.0 (−11.5, 17.5)
Pa 100 mg OD	94	52.8	3.3 (−8.8, 15.3)	

KEY: *Pa* = Pygeum africanum *extract; CI = confidence interval; other abbreviations as in Table I.*

TABLE III. *Secondary efficacy parameters (baseline mean values and per visit results), long-term phase*

Visit	IPSS (n = 174)	QOL (n = 174)	Nocturia (n = 174)	Qmax (mL/s)	Residual Volume (mL)	Prostate Volume (cm^3)
Baseline	16.2	4.1	2.3	10.87 (n = 168)	53.3 (n = 168)	42.0 (n = 174)
1 month	12.3	3.4	1.7	—	—	—
2 months	10.5	3.1	1.5	13.26 (n = 141)	60.0 (n = 140)	—
5 months	9.5	2.6	1.5	—	—	—
8 months	8.7	2.3	1.4	—	—	—
12 months	8.7	2.4	1.4	12.58 (n = 123)	57.9 (n = 123)	39.9 (n = 145)

KEY: *Abbreviations as in Table I.*

significant reduction of IPSS in each group. The difference of the IPSS reduction between groups was −0.7 and the limit of the 90% CI was less than 2 points, confirming the equivalence of treatments.

All individual items of the IPSS decreased similarly in both groups. Nocturia improved equally in both groups, from 2.3 to 1.5 in both groups. QOL improved in both groups, from 4.3 (group A) and from 4.1 (group B) at baseline to 3.1 and 3.0, respectively. The 90% CI of the difference of the means between the two groups was centered on zero (−0.34, +0.22). Qmax increased by 1.63 mL/s (16.0%) in group A and by 2.02 mL/s (18.6%) in group B. The changes from baseline were statistically and clinically significant in each group, but not different between groups. Residual volume did not vary significantly.

Open Label Extension Phase. Given the equivalence in efficacy during the comparative phase between groups, patients from group A (n = 83) and from group B (n = 91) were pooled for the long-term analysis. Analyses by initial treatment groups showed similar evolutions over the long-term period.

The percentage of patients reaching the therapeutic goal increased with time: 20.1% at 1 month, 42.0% at 2 months, 57.1% at 5 months, 65.4% at 8 months, and 62.8% at 12 months.

The mean IPSS fell from 16.2 at baseline to 8.7 (−46.3%) (Table III). All individual items of the IPSS improved with time. Nocturia decreased from 2.3 to 1.4 after 12 months. QOL improved from 4.1 at baseline to 2.4 (−41.5%). Although no patient scored 2 or lower (mostly satisfied, pleased, or delighted) at baseline, after 12 months, 58.1% of patients had a QOL of 2 or lower; 31.6% of patients scored 5 (unhappy) or 6 (terrible) at entry compared with 10.9% after 12 months. Qmax and other urinary parameters improved significantly after the first 2 months of treatment, and this improvement was maintained after 12 months (Table III). Prostate volume was slightly but significantly reduced at the end of the study, from 42.0 to 39.9 cm^3 (−6.8%).

Safety Assessment

Side effects had similar distributions between groups during the comparative phase and were comparable for both phases of the trial. Few side effects (Table IV) led to patient withdrawal (4.7%

TABLE IV. *Safety profile of side effects leading to premature withdrawal and treatment-emergent serious side effects: 2-month comparative and 12-month long-term phases*

	Two Months (n = 235)				Twelve Months (n = 174)	
	Pa 50 mg BID		Pa 100 mg OD		Pa 100 mg OD	
	SE (n)	SSE (n)	SE (n)	SSE (n)	SE (n)	SSE (n)
Nausea, dizziness	1					
Dyspepsia			1		1	
Constipation	2					
Epistaxis						1
Cardiac arrhythmia						1
Inguinal hernia		1		1		1
Stenosis of colon						1
Joint prosthesis		1				2
Muscular and joint pain			1*	1	1*	1
Back pain						1
Pelvic pain			1			
Increase in urinary symptoms	1					
Dysuria	1*	1	1*	1	3*	3
Urinary retention		1	1*	1	1*	1
Bladder polyp ablation						1
Renal disorder						1
Hematuria					1*	1
Subcutaneous abscess						1
Cataract						1
Phlebitis						1
Headache/migraine						1
Meningeal carcinoma			1*	1		
Subdural hematoma					1*	1
Total	5	4	6	5	8	20

KEY: SE = side effect leading to premature withdrawal; SSE = treatment-emergent serious side effect; other abbreviations as in Table II.
** SE considered by the investigator as an SSE at the same time.*

of patients during the comparative phase and 4.6% of patients during the long-term phase). Treatment-emergent side effects were mostly gastrointestinal; most were not treatment related. Side effects that were possibly drug related were observed in 2.6% of patients in the comparative phase and 2.9% in the 12-month phase. Most serious side effects (Table IV) involved the urogenital system (1.3% and 4.0% of patients in, respectively, the comparative and the long-term phases).

No significant changes were noted in blood or urinalyses in either group or during the study. There was no significant variation of the PSA level at 12 months. Sexual activity was not significantly affected after either 2 or 12 months.

COMMENT

One of the first aims of treatment in BPH is the alleviation of the symptoms, which impair the patients' QOL[14–16] and are usually the initial reason for seeking treatment. The existing clinical evidence[17] confirms the efficacy and safety of *P. africanum* for this indication. Results reported with *P. africanum* administered most often as a 50-mg twice daily dose in open and placebo-controlled clinical trials showed a rapid and significant improvement both in clinical symptoms and in objective parameters. Clinical studies and postmarketing safety data show that the drug is well tolerated, with only mild to moderate side effects, mostly gastrointestinal.

Patients' compliance with the treatment may be improved by a simple dosage regimen (single versus multiple intake per day). A 100-mg capsule was therefore developed; the present study compared the efficacy and safety of the two dosage regimens after 2 months of treatment, as well as the long-term effects of the 100-mg once daily regimen.

The IPSS was chosen both as the main inclusion and evaluation criterion. The strict entry criterion of an IPSS of 10 or greater (and QOL of 3 or greater) ensured the enrollment of patients with symptomatic BPH and impaired QOL, who are the most appropriate candidates for pharmacologic

treatment.[18] The success criterion, arbitrarily defined as a reduction in IPSS of 40% or more from baseline, can be considered as high; this criterion is justified by the absence of a placebo arm in the study and the aim of identifying only those patients whose response was markedly greater than the usually accepted placebo response (Hansen *et al.*[11] estimated this response to reach 24% reduction of the score at 2 months). The percentage of patients who reached this target in the present study was significant (40% at 2 months and 63% at 12 months). Simultaneously, the decrease in the IPSS seen in the present study (6 units after 2 months and 8 units after 12 months) significantly exceeded that usually reported on placebo in randomized studies, which averages approximately 3 points.[4,12] This symptomatic response to *P. africanum* after both 2 and 12 months can be considered favorably in comparison with that observed in randomized trials with alpha-blockers[1,12,19] or 5-alpha reductase inhibitors.[3,20] The absence of a placebo arm in our study limited the evaluation of the net effect of the product tested, and the observed effects must be considered as the aggregate of the drug and placebo effects. However, this study was designed with the objective to compare two daily regimens of the same drug, the efficacy versus placebo having been documented in the past.[17] The clinical effects and the safety profile were similar between the two groups and two treatment periods. There were no significant changes either in the PSA levels or in sexual function of studied patients.

CONCLUSIONS

The results of this study confirm those previously obtained in randomized double-blind, placebo-controlled and open trials.[17] It can be concluded that *P. africanum* extract offers an alternative for the treatment of patients with mild to moderate symptoms of BPH; the effects of once daily administration of 100 mg of *P. africanum* extract are similar to those of the currently recommended dosage regimen of 50 mg twice daily.

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