Randomised, placebo-controlled, double-blind clinical trial of β-sitosterol in patients with benign prostatic hyperplasia

*R R Berges, J Windeler, H J Trampisch, Th Senge and the β-sitosterol study group**

Summary

Medical treatments have become available for benign hypertrophy of the prostate, including alpha-receptor blocking agents and 5-alpha-reductase inhibitors. Drugs derived from plants, for which no precise mechanism of action has been described, are widely used for this purpose in Europe.

In a randomised, double-blind, placebo-controlled multicentre study, 200 patients (recruited between April and October 1993) with symptomatic benign prostatic hyperplasia were treated with either 20 mg β-sitosterol (which contains a mixture of phytosterols) three times per day or placebo. Primary end-point was a difference of modified Boyarsky score between treatment groups after 6 months; secondary end-points were changes in International Prostate Symptom Score (IPSS), urine flow, and prostate volume. Modified Boyarsky score decreased significantly with a mean of −6·7 (SD 4·0) points in the β-sitosterol-treated group versus −2·1 (3·2) points in the placebo group $p<0.01$. There was a decrease in IPSS (−7·4 [3·8] points in the β-sitosterol-treated group *vs* −2·1 [3·8] points in the placebo group) and changes in urine flow parameters: β-sitosterol treatment resulted in increasing peak flow (15·2 [5·7] mL/s from 9·9 [2·5] mL/s), and decrease of mean residual urinary volume (30·4 [39·9] mL from 65·8 [20·8] mL). These parameters did not change in the placebo group ($p<0.01$). No relevant reduction of prostatic volume was observed in either group.

Significant improvement in symptoms and urinary flow parameters show the effectiveness of β-sitosterol in the treatment of benign prostatic hyperplasia.

Lancet 1995; **345:** 1529–32

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Introduction

The natural history of benign prostatic hyperplasia (BPH) is a slow enlargement of fibromuscular and epithelial structures within the gland, eventually leading to obstructive urinary symptoms experienced to some extent by most men over the age of 50.[1,2]

Transurethral resection of the prostate in men with symptoms of obstruction is the standard treatment for this condition, against which alternative treatments options have to be compared in terms of safety and effectiveness.[3] In recent years, new medical treatments have become available, including alpha-receptor blocking agents[4] and 5-alpha-reductase inhibitors,[5] which have been shown to be effective in randomised clinical trials.[6–8]

Drugs derived from plants have a long tradition in the medical treatment of BPH in Europe; although no mechanism of action nor precise classification of the active compounds for many of these drugs have yet been established, substantial symptom improvement has been reported.[9] We tested β-sitosterol (Harzol, Hoyer, Germany), a phytopharmacological drug containing phytosterols. Although the active substance is termed β-sitosterol, the mixture contains a variety of phytosterols, mainly β-sitosterol, with smaller amounts of campesterol, stigmasterol and other sterols along with their glucosides (Harzol contains 10 mg of β-sitosterol [including standardised 0·1 mg β-sitosterol-β-D-glucosidase], glucose, lactose, talc, gelatin, erythrosin E127, quinoline yellow E104, and titanium dioxide E171). It is not known which of its components are responsible for its effect in BPH.

This study was designed in accordance with the suggestions of the international committee on the therapy of BPH held at the 2nd international consultation on benign prostatic hyperplasia in Paris, 1993.[10] Treatment endpoints were chosen so as to match studies on alpha-receptor blocking agents and 5-alpha-reductase inhibitors.

Patients and methods

Patients

Patients were recruited from eight private urological practices (table 1). For those currently on medication for prostatic symptoms, a 4-week wash-out period was required. Written informed consent was given by each patient eligible for the trial. Approval was obtained from the ethics committee of the Rühr University. Treatment with hormones, cimetidine, anticholinergics, psychotherapeutics, sympathicomimetics, parasympathicolytics, anticoagulants, diuretics, alpha-receptor-blocking agents, or other phytopharmacological drugs was not allowed during and four weeks before the trial.

Initial assessment

A history was taken and subjective symptoms evaluated by modified Boyarsky score[11] and IPSS questionnaire.[12] Urinary flow

Inclusion	Peak urine flow <15 mL/s at a voiding volume of ≥150 mL
	Residual volume ≥30 mL over ≤150 mL
	<75 years old
Exclusion	History of acute retention
	Prostate cancer
	PSA >10 mg/mL
	History of transurethral resection
	Prostatitis
	Urinary infection
	Haematuria
	Urethral stricture
	Bladder stones
	Diabetes
	Abnormal GOT, GPT, or alkaline phosphatase
	Severe cardiopulmonary disease
	Neurological or psychological disorders

PSA=prostate specific antigen, GOT= glutamic-oxaloacetic transaminase, GPT= glutamic-pyruvic transaminase.

Table 1: **Inclusion and exclusion criteria**

(maximum flow, median flow, voiding time, and volume) were recorded with a minimum voiding volume of 150 mL, followed by trans-abdominal ultrasound measurement of residual volume. Prostatic volume was assessed by trans-abdominal or trans-rectal ultrasound.

Each centre was supplied with numbered bottles containing either 20 mg of β-sitosterol in capsules or placebo in capsules of the same size and shape, according to a previously randomised sequence. One copy of the code break (in case of emergency) was held by the responsible investigator at each centre in a sealed envelope.

Laboratory tests included liver function tests, blood urea, creatinine, prostate specific antigen (PSA), blood-cell counts, and urine culture.

Follow-up

Patients were assessed monthly. On each visit, compliance, side effects, and modified Boyarsky-score were recorded. After 3 and 6 months, the IPSS questionnaire was recorded as well as urinary flow measurements and prostatic volume. Laboratory testing was repeated after 6 months.

Endpoints

The primary outcome variable was the difference in modified Boyarsky scores after 6 months of treatment compared with initial value. IPSS, urine flow, residual urine volume, and prostatic size were secondary end-points.

Analysis

To detect a difference of 2·5 modified Boyarsky-score points between the two groups, 100 patients were needed in each treatment group to give a power of 80% (unpaired *t* test, α=0·05 two sided, sigma=5).

The statistical method used for the analysis of the primary and secondary outcome variables was the unpaired *t* test. The level of significance was defined as α=0·05 (two sided).

For the primary outcome variable, data were analysed on an intention-to-treat basis including all randomised patients. For patients with incomplete follow-up the last obtainable value of the modified Boyarsky score was used for analysis. If the last obtainable value was lower than the initial value, a difference of 0 points was recorded. If the last obtainable value was higher than the initial value, this last value was recorded. Therefore, all 200 patients enrolled in the study were considered for final analysis of the primary outcome variable Boyarsky score. Reported p values for secondary outcome variables are considered as descriptive only. Centre effects were measured by a two-factor analysis of variance (centre, treatment), with initial values and end-of-study values as independent parameters.

Characteristic	Treatment group	
	Placebo	β-sitosterol
Age (years)	65·5 (7·0)	65·2 (6·6)
Height (cm)	173·4 (6·1)	174·7 (6·2)
Body weight (kg)	79·6 (10·9)	78·7 (9·3)
Heart rate (beats/min)	72·4 (5·8)	73·6 (6·6)
BP systolic (mm Hg)	141·6 (15·0)	142·3 (13·1)
BP diastolic (mmHg)	83·8 (9·0)	85·3 (9·0)
Pre-treatment drug therapy (%)	51	51
History of urological surgery/diseases (%)	9	16
Mean voiding vol (mL)	218·5 (84·6)	209·1 (58·7)
Mean urinary flow (mL/s)	5·7 (2·1)	5·7 (2·1)
Peak flow (mL/s)	10·1 (2·8)	9·9 (2·5)
Voiding time (s)	45·5 (2·3)	48·7 (33·3)
Residual volume (mL)	64·8 (24·0)	65·8 (20·8)
Modified Boyarsky score (points)	14·9 (3·7)	15·0 (4·1)
IPSS (points)	15·3 (4·3)	14·9 (4·7)
QOL (points)	3·0 (0·8)	3·1 (0·8)
Prostate volume (mL)	48·7 (29·9)	44·6 (19·4)

Numbers are mean (SD) unless indicated. QOL=quality or life assessed by the IPSS questionnaire.

Table 2: **Demographic and urinary characteristics of placebo and β-sitosterol-treated patients at time of recruitment**

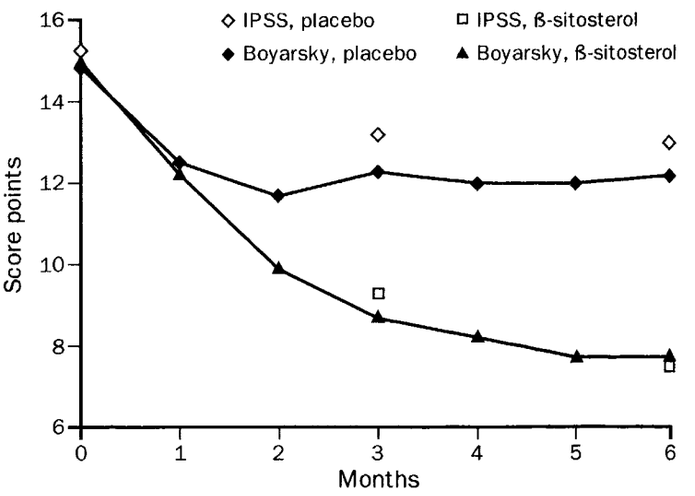

Figure: **Modified Boyarsky and IPSS scores during treatment**

Results

Recruitment and baseline characteristics

Between April, 1993, and October, 1993, 200 patients were included. All but one centre recruited at least 20 (range 20–40). Inclusion criteria were violated once, by a patient aged 75·6 years. No exclusion criteria were violated. Characteristics were well balanced between the two treatment groups (table 2).

Follow-up

2, 4, and 6-months follow-ups were completed in 95% of patients. Times of evaluation were at a mean of 93 (SD 25) days for 3-month and 183 (25) days for 6-month evaluation, with no differences between treatment groups.

Withdrawals

All 200 patients were included in analysis for the primary outcome variable. For secondary outcome variables, only patients with values at six months were considered. Six patients of the placebo group and four patients of the β-sitosterol group did not appear for final evaluation. Four patients underwent surgical interventions during the study period, all in the placebo group, and were excluded. Thus, 91 patients in the placebo group and 96 patients in the β-sitosterol group were considered for analysis of secondary outcome variables. 1 patient in this latter group was unable to void at 6 months; however, residual urinary volume was obtained.

Prostatic volume was not assessed in all participating centres, reducing the number of patients available for

Time of withdrawal (days)	Treatment group	Reported reason	Modified Boyarsky score at time of stopping treatment	Intention to treat value used for analysis
na	Placebo	Better voiding without medication	13	0
34*	Placebo	No relief under medication	20	2
125*	Placebo	Two episodes of transurethral bleeding	4	0
1	Placebo	Allergic reactions after medication	16	0
43*	Placebo	Acute urinary retention, suprapubic fistula	25	4
61*	Placebo	Increase of hair growth (hands and eyebrows)	19	3
29*	Placebo	Subjective worsening of symptoms	8	0
52*	Placebo	Hospital admission	15	0
47*	Placebo	Epigastric pain	11	0
1*	Placebo	Not known	13	0
37	Placebo	Pelvic tenderness after medication	13	0
14*	Placebo	Dizziness, finger trembling	11	1
115	Placebo	PSA >10 ng/mL, ?prostate carcinoma	12	0
73	Placebo	Allergic reaction after medication	20	0
14*	β-sitosterol	No relief, patient requested another treatment	22	5
111	β-sitosterol	Not known	19	1
14*	β-sitosterol	Too many medications, no relief	14	1
11	β-sitosterol	Nausea after medication	14	0
na*	β-sitosterol	Acute heart attack, change of medication	11	0
107*	β-sitosterol	Relief of symptoms, medication discontinued	8	0

*Withdrawn from analysis of secondary outcome variables. na=not assessible.

Table 3: **Patients who stopped treatment**

analysis of this parameter to 80 in the placebo and 83 in the β-sitosterol groups. 20 patients stopped treatment (table 3).

Outcome

There was a significant improvement of modified Boyarsky score in the β-sitosterol group (table 4). Divergence between placebo and treatment group did not occur until about 4 weeks of treatment but was thereafter stable throughout follow-up. Comparison of symptoms with the IPSS questionnaire at 3 and 6 months confirmed the extent and time course of improvement in β-sitosterol treated patients compared with the placebo group (figure).

The quality of life score also improved more in the β-sitosterol treated group (table 1). Urinary flow measurements improved with β-sitosterol: peak flow by 5·2 (4·9) mL/s versus 1·1 (4·1) mL/s in the placebo group; median flow by 3·0 (3·5) mL/s versus 0·3 (25·5) mL/s; and mean voiding time by 15·5 (33·5) versus 2·8 (34·9) s, $p<0·01$.

Residual urinary volume decreased with β-sitosterol therapy from 35·4 (45·2) mL to 11·6 (28·4) mL in the placebo group, $p<0·01$. As with symptom scores, changes in urine flow occurred during the first half of the trial, with no further changes towards the end of the study.

There was a mean decrease of 3·1 (8·8) mL in the β-sitosterol group compared with 0·3 (9·0) mL in the placebo group, which makes it unlikely that β-sitosterol has a substantial effect on prostatic volume.

Adverse effects

There were no severe adverse reactions attributed to β-sitosterol. One patient observed erectile dysfunction, and another reported loss of libido, both after 2 months of medication. One patient reported constipation from day 1. One patient experienced several episodes of nausea after 11 days of treatment and stopped medication. In the placebo group, one patient complained of increasing hair growth on hands, abdomen, and eyebrows, leading to discontinuation of medication. One patient suffered from generalised skin rash after the second day of placebo treatment. Both groups experienced minor side-effects and withdrew from the study. Two patients experienced some degree of dizziness on day 3 for 3 h and on day 103 lasting for 10 days. Two patients complained of epigastric pain after medication, starting on day 52 and recurring for several weeks in one case, starting on day 3 and lasting for 30 min in the other case (table 3).

Discussion

The effect of phytopharmaceuticals on BPH is controversial because no clear mechanisms of action have been established, and their effect has been attributed to placebo responses. Nevertheless, these drugs are commonly prescribed.[9] Since other forms of medical treatment of BPH have been shown to be effective, it is questionable whether phytopharmaceutical drugs should continue to be prescribed.

In this trial, we investigated the effects of a typical phytopharmaceutical, a plant extract whose composition

	Placebo				β-sitosterol			
	n	At start	After 6 months	Difference	n	At start	After 6 months	Difference
Primary outcome variable								
Modified Boyarsky score (points)	100	14·9 (3·7)	12·2 (3·9)	2·1 (3·2)	100	15·0 (4·1)	7·7 (4·2)	6·7 (4·0)*
Secondary outcome variables (mean [SD])								
IPSS (points)	91	15·1 (4·2)	12·8 (4·5)	2·1 (3·8)	96	14·9 (4·7)	7·5 (4·4)	7·4 (3·8)*
QOL (points)	91	3·0 (0·8)	2·8 (0·9)	0·2 (1·0)	96	3·1 (0·8)	1·8 (0·8)	1·4 (0·8)*
Peak flow (mL/s)	91	10·2 (2·8)	11·4 (4·7)	−1·1 (3·9)	95	9·9 (2·5)	15·2 (5·7)	−5·2 (4·9)*
Median flow (mL/s)	91	5·8 (2·4)	6·2 (3·1)	−0·3 (2·5)	95	5·7 (2·2)	8·8 (4·2)	−3·0 (3·5)*
Voiding time (s)	91	45·4 (22·2)	47·5 (34·4)	−2·8 (34·9)	95	48·7 (33·9)	33·2 (18·9)	15·5 (33·5)*
Residual volume (mL)	91	64·8 (23·5)	54·3 (27·6)	11·6 (28·4)	96	65·8 (20·8)	30·4 (39·9)	35·4 (45·2)*
Prostate volume (mL)	80	48·0 (27·9)	48·8 (26·5)	0·3 (9·0)	83	44·6 (19·4)	42·3 (18·2)	3·1 (8·8)

Note that modified Boyarsky scores were analysed on an intention-to-treat basis including all randomised patients (see text). For all other indices, patients with missing values were excluded from analysis. P values reported for these indices are considered descriptive only. *$p<0·01$ compared with placebo.

Table 4: **Outcome variables at initial presentation and 6 months of placebo or β-sitosterol treatment**

is not exactly defined, and which may vary between doses. Futhermore, no exact biochemical mechanism of action has been established for the various phytosterols in β-sitosterol. The trial was designed as suggested by the international consensus-conference on therapy of BPH in Paris in 1993.[10] The results show a significant effect of β-sitosterol in patients with symptomatic BPH on symptoms, as measured by the modified Boyarsky-score questionnaire. Objective parameters of urine flow were also improved more than in the placebo group.

Finasteride, a 5-alpha-reductase inhibitor reduced prostatic volume by up to 30% over 12 months and improved Boyarsky scores with a reduction of up to 4 points,[6] which is within the range we achieved with β-sitosterol. Finasteride also increased peak urinary flow by a mean of 1·3 mL/s. The increase reached 3·6 mL/s after 36 months in the uncontrolled long-term follow-up,[6] similar to that observed in patients treated for 6 months with β-sitosterol (5·2 [4·9] mL/s). Median flow and residual urinary volume also improved. This improvement was achieved with β-sitosterol with no reduction of prostatic volume, demonstrating again that obstruction and subjective symptoms are not necessarily correlated with prostatic size. It should be noted that our study investigated few patients and only over 6 months. It is well known that subjective as well as obstructive symptoms may vary within the first 6 months after initial appearance of symptoms in patients with symptomatic BPH, leading to substantial improvement in many patients even without any form of therapy.[13]

Data from randomised trials with alpha-receptor blocking agents are also comparable with our results. Jardin et al[14] investigated alfuzosine in 518 patients, and reported a 3·1 mL/sec improvement of peak urinary flow. Doxazosine, a long-acting alpha-receptor blocker, improved peak flow up to 1·5 mL/s in a study of Christensen et al,[15] and to 2·6 mL/s in a study by Chapple et al.[16] The best results were reported by Caine et al[7] with phenoxybenzamine (improvement of peak flow by 6·2 mL/sec),[7] and Martorana et al[17] with prazosine (improvement of peak flow 6·9 mL/s). However, both studies had a short follow-up of only 2 weeks and no evaluation of residual volume or symptom score was reported. By contrast with β-sitosterol treatment, adverse effects such as dizziness, decreasing blood pressure, tachycardia, or orthostatic problems, were reported frequently.

Investigation should now focus on evaluating specific compounds within the mixture of phytosterols in β-sitosterol, and on possible biochemical mechanisms. The effects of long-term treatment with β-sitosterol have also to be assessed.

The β-sitosterol study group: B Aeikens, J Albrecht, C Becker, P Brundig, D Dreyer, W Kaldewey, H Latka, A Reek, HJ Schneider, P Schöter, C Schumacher.

This study was sponsored by Hoyer GmbH & Co, Neuss, Germany.

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British Journal of Urology (1997), **80**, 427–432

A multicentric, placebo-controlled, double-blind clinical trial of β-sitosterol (phytosterol) for the treatment of benign prostatic hyperplasia

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Objective To report the results of a double-blind, placebo-controlled trial to evaluate Azuprostat®, a β-sitosterol, in patients with symptoms of outlet obstruction caused by benign prostatic hyperplasia (BPH).

Patients and methods A randomized, double-blind and placebo-controlled clinical trial was conducted to assess the efficacy and safety of 130 mg free β-sitosterol (phytosterol) daily, using the international prostate symptom score (IPSS) as the primary outcome variable. In total, 177 patients with BPH were recruited for 6 months of treatment in 13 study centres. In addition to the relative difference in the IPSS, changes in quality of life, peak urinary flow rate (Q_{max}) and post-void residual urinary volume (PVR) were recorded. The drug used in the trial consisted of a chemically defined extract of phytosterols, derived for example from species of *Pinus*, *Picea* or *Hypoxis*, with β-sitosterol as the main component.

Results There were significant ($P<0.01$) improvements over placebo in those treated with β-sitosterol; the mean difference in the IPSS between placebo and β-sitosterol, adjusted for the initial values, was 5.4 and in the quality-of-life index was 0.9. There were also significant improvements in the secondary outcome variables, with an increase in Q_{max} (4.5 mL/s) and decrease in PVR (33.5 mL) in favour of β-sitosterol when adjusted for the changes after placebo.

Conclusion These results show that β-sitosterol is an effective option in the treatment of BPH.

Keywords β-sitosterol therapy, symptom score, benign prostatic hyperplasia

Introduction

Therapies with confirmed efficacy in treating BOO caused by BPH should be minimally invasive, economical and of low risk [1–4]; TURP is the 'gold standard' against which these alternative treatments must be compared for efficacy and safety [5]. An interest in medicinal alternatives to surgical intervention led to the development of 5-α-reductase inhibitors [6–8] and alpha adrenergic blockers [9–12] that are now established treatments for symptomatic BPH in many countries.

There has been a long tradition in some European countries for the use of drugs of plant origin in the treatment of BPH. A mixture of constituents from plant products, some of which may be active and others not, has drawn criticism of these agents and their mode of action. Few have been evaluated in controlled clinical trials, but this deficiency is now being addressed [1,13,17].

This study was designed in accordance with the recommendations of the International Consultation on BPH (1991 and 1993) [13,14] and reports the results of a double-blind, placebo-controlled trial to evaluate Azuprostat®, a β-sitosterol, in patients with symptoms of BOO caused by BPH. The drug used in this trial consists of a chemically defined extract of phytosterols, derived for example from species of *Pinus*, *Picea* or *Hypoxis*, with β-sitosterol as the main component.

Patients and methods

Patients

The study was conducted between October 1993 and September 1994 at 13 private urological centres in Germany, with a total recruitment of 177 patients; 89 patients were allocated randomly to receive placebo and 88 to β-sitosterol. A 4-week wash-out period was required for all patients currently on symptomatic medication for benign prostatic disorders. Concomitant medication with drugs acting on the hormonal axis of the prostate, cimetidine, anticholinergics, sympathomimetics and psychotropic drugs were discontinued in patients 2 weeks before entering the trial. The conduct of the study was supervised

‡Listed at the end of the paper.
Accepted for publication 30 April 1997

Table 1 Patients characteristics at recruitment

Characteristic	*Placebo*	*β-Sitosterol*	P *(t-test)*
Mean (SD)			
Age (years)	65.9 (7.43)	64.8 (8.06)	0.355
Height (cm)	174.6 (6.11)	173.9 (5.36)	0.484
Body weight (kg)	78.7 (7.91)	77.4 (8.05)	0.274
Pre-treatment drug therapy (%)	35.9	45.9	0.112*
Concomitant allowed therapies (%)	23.5	27.5	0.624*
IPSS (points)	14.9 (5.17)	16.0 (4.58)	0.144
Quality of life (points)	3.0 (0.91)	3.2 (0.79)	0.158
Peak flow (mL/s)	11.3 (2.70)	10.6 (3.33)	0.116
Mean voided volume (mL)	246.8 (98.8)	236.5 (94.5)	0.477
Residual urine volume (mL)	63.1 (26.36)	63.4 (28.97)	0.935

*Chi-square test.

by extensive monitoring; in addition, the responsible specialists in each centre nominated a second person (study assistant) to supervise the patients' appointments and internal quality control. Table 1 lists the patients' characteristics of both groups at the beginning of the study.

Methods

After taking the patients' history at the initial visit, the symptom score and quality-of-life (QOL) index were recorded using the IPSS questionnaire. The post-void residual urinary volume (PVR) was measured by transabdominal ultrasonography after measuring urinary flow rate and voiding volume. The prostatic volume was not assessed by ultrasonography. Patients underwent a DRE and blood was sampled for laboratory tests including liver and renal function, PSA level and a blood cell count; a urine sample was also cultured. Inclusion and exclusion criteria are shown in Table 2.

During the follow-up, each patient was evaluated monthly (seven visits in total) and on each visit compliance was recorded by counting the capsules not used in the previous month. Side-effects and possible concomitant medication were recorded and evaluated according to the exclusion criteria. The IPSS and QOL index were assessed, the PVR and urinary flow rate measured, and the medication for the following month supplied. Laboratory tests, conducted at the initial visit, were repeated after 6 months. A subjective assessment of efficacy was obtained by questionnaire at the final follow-up visit.

Medication

The term β-sitosterol represents a chemically defined extract of phytosterols with β-sitosterol as the main component. In contrast to the glycosidic phytosterols originally in plant sources, the drugs used in current therapy are defined compositions of free phytosterolic components (aglycons) produced by current manufacturing processes (Pharmaceutical Monograph for the European Pharmacopoeia, in preparation). Each patients took two capsules per day, each containing 65 mg either of β-sitosterol (Azuprostat®, Azupharma, Germany) or placebo over a period of 6 months.

Each centre had been supplied with one package of medication for each patient, numbered according to a randomized sequence, with each of these containing smaller boxes with the medication calculated for one month of therapy. All capsules were manufactured to meet the requirements of the study; there were no differences in size, shape, colour, weight, smell or taste between active or placebo capsules and all were packaged in the same blister-packs.

Table 2 Inclusion and exclusion criteria

Inclusion criteria
IPSS of at $\geqslant 6$ points
Residual urinary volume 30–150 mL
$Q_{max} \leqslant 15$ mL/s, at a voiding volume of $\geqslant 150$ mL
Benign enlargement of the prostate (DRE)
Age 50–80 years
Body weight 55–100 kg

Exclusion criteria
IPSS of < 6 points
Prostatic malignancy
PSA level > 10 ng/mL
Bacterial prostatitis
Urinary infection
History of acute urinary retention
History of surgical prostatic intervention
Need for surgical intervention in case of urethral stricture or bladder diverticulae
Bladder stones
Phimosis and meatal stenosis
Insulin-dependent diabetes
Abnormal laboratory values, e.g. glutamic-pyruvic transaminase, glutamic-oxaloacetic transaminase, alkaline phosphatase, creatinine
Severe cardiopulmonary disease
Neurological or psychological disorders
Concomitant prostatotropic treatment
Abuse of alcohol or drugs
Expected non-compliance

Statistical analysis

The primary endpoint of the study was the relative difference in the IPSS between the groups, measured by the percentage change from the initial to the final follow-up visit. The QOL index, PVR and peak urinary flow rate

(Q_{max}) were assessed as secondary outcome variables. To detect a difference of 3 points (SD of 5 points) in the mean IPSS during the 6 months of treatment between the groups (considered as clinically relevant), 61 patients were needed in each treatment group to give a power of 95% ($\alpha = \beta = 0.05$). With an expected withdrawal rate of about 15 patients per treatment arm and the reduced efficiency of the non-parametric method, the planned size of the treatment groups was increased to 90 patients. The IPSS scores were analysed statistically using the one-sided Mann–Whitney test at the 5% level of significance. All other tests of significance were considered descriptive. The intention-to-treat analysis was used to evaluate the results for the IPSS; for patients who did not complete the 6 months of treatment, the last value obtained was carried forward to 6 months.

Table 3 Primary and secondary outcomes after 6 months of therapy with β-sitosterol or placebo (mean [SD])

	Initial	*6 months*	*Difference*
β-sitosterol			
IPSS (points)	16.0 (4.58)	7.8 (4.93)	−8.2 (5.74)
Quality of life (points)	3.3 (0.79)	1.4 (0.65)	−1.8 (1.02)
Q_{max} (mL/s)	10.6 (3.33)	19.4 (8.62)	8.9 (8.86)
PVR (mL)	63.4 (29.0)	25.6 (28.8)	−37.5 (37.2)
Placebo			
IPSS (points)	14.9 (5.17)	12.1 (5.56)	−2.8 (4.18)
Quality of life (points)	3.1 (0.91)	2.2 (0.98)	−0.9 (0.91)
Q_{max} (mL/s)	11.3 (2.7)	15.7 (6.12)	4.4 (5.87)
PVR (mL)	63.1 (26.36)	59.1 (44.12)	−4.1 (33.57)

Results

All but three centres recruited a median of 18 (range 11–24) patients. There were no violations of the exclusion criteria, but some inclusion criteria were not met. One patient (on β-sitosterol) was 49 years old at the beginning of the study and five others exceeded the age limit (two on placebo, three on β-sitosterol). Two patients had a PVR of < 30 mL (one on placebo, 10 mL, and one on β-sitosterol, 20 mL) and one patient had a PVR of 194 mL.

Withdrawals and side-effects

Twenty-two patients did not complete the 6 month period of treatment, 11 in each group. In the placebo group, one patient was excluded after an acute myocardial infarction. In the β-sitosterol group, one patient was withdrawn because of recurrent indigestion under medication. Two patients had sudden cardiac infarction, one suffered a stroke with hemiparesis and one patient decided to withdraw because he felt a rapid worsening of symptoms. All other withdrawals were for non-compliance caused by the patient's decision, or by being unable to attend regular follow-up checks in the centres; this is a general problem in out-patient trials with older participants, rather than a consequence of the treatment. None of the severe incidents in the β-sitosterol group was attributable to the drug and decoding of the randomization was unnecessary.

Outcome

Most (87.5%) of the patients completed the study in accordance with the protocol to the 6-month follow-up; the earlier withdrawals were incorporated into the

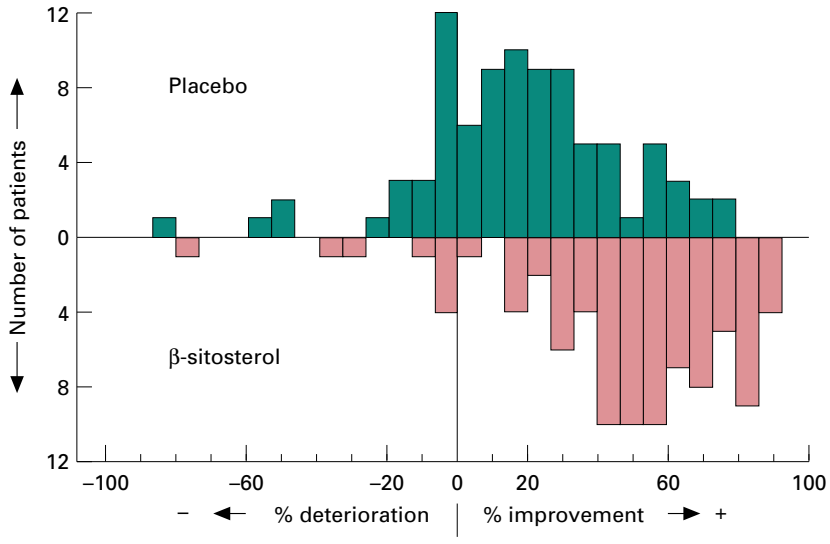

Fig. 1. Individual relative changes (%) in the IPSS from the initial to final visit. Green, Placebo. Red, β-sitosterol.

intention-to-treat analysis. Both the IPSS and the secondary variables showed significant ($P<0.01$) improvements in the β-sitosterol group, but improvements to unexpected levels also occurred in the placebo group (Table 3). The improvement in the IPSS with β-sitosterol and placebo was 51% and 19%, respectively.

To assess the improvement with β-sitosterol over placebo, adjusting for the initial values in IPSS, the difference in the changes in the IPSS (and other variables) for the groups was also calculated; the mean advantage of β-sitosterol was then 5.4 IPSS points and the corresponding advantage in QOL index was 0.9 points, for Q_{max} 4.5 mL/s and PVR 33.5 mL in favour of β-sitosterol (Table 3).

Nearly half of the total improvement had occurred in the first month in both groups; the improvement increased more slowly to 6 months in both groups, but with less variation in the profile of the β-sitosterol group. The advantage with β-sitosterol increased from 2.6 at 1 month to 4.5 and 5.4 at 3 and 6 months, respectively. The better performance of β-sitosterol is illustrated in Fig. 1; two histograms, one above and one below the baseline, show the frequency (number of patients) with similar individual relative percentage changes from the initial to the final visit in both treatment groups.

Discussion

Plant-derived drugs, although well established in the treatment of BPH, are rarely considered in international scientific discussion on the treatment strategies for BPH. In 1991, the International Consensus Committee on BPH stated that 'Although these extracts have been widely used for many years in various countries, they have not yet been studied adequately to determine their exact effectiveness and their mode of action.' [13]. Since then, pharmacological and clinical research on phytotherapeutic compounds for BPH has increased with the growing interest of health professionals and patients in such low-risk, low-cost drugs [1,16]. Berges *et al.* reported the use of β-sitosterol (phytosterols) in patients with BPH [17]; in this randomized, placebo-controlled, double-blind trial, the efficacy, safety, benefits and risks of β-sitosterol therapy were clearly established.

The present multicentre trial used the IPSS as the primary outcome variable, according to international recommendations [13,14] and showed a significant advantage of β-sitosterol over placebo and a favourable benefit-risk ratio. There was a significant reduction in the IPSS in patients receiving β-sitosterol compared with those receiving placebo and an improvement in the subjective evaluation of quality of life; Q_{max} and PVR were also significantly improved compared with placebo. No relevant side-effects were observed in the treatment group.

The results from the present trial are comparable with those in an earlier pilot study with β-sitosterol [15] and with the outcome reported by Berges *et al.* [17]. The design of the latter and the present trial were similar [13,14], but differed in the symptom score used and in the dosage regimen. Berges *et al.* used a modified Boyarsky score [18] as the primary and the IPSS as a secondary variable, recorded only three times during the follow-up; the dose regimen was 20 mg three times daily, whereas 65 mg was administered twice daily in the present study. The limited availability of dose-response relationships for such phytotherapeutic drugs remains a point of criticism. In the present study, the higher dose used has been confirmed in practice by almost 15 years of empirical experience and is fully within the registered dose range for the BPH indication in Germany.

In both trials, treatment with β-sitosterol produced a greater improvement than did placebo for the symptom score, Q_{max} and QOL index. The PVRs were comparable at recruitment but were reduced significantly in both trials (by 33 mL more than placebo in the present study and by 24 mL in [17]).

The improvement in the assessed variables was more rapid in the first month of therapy than later (with β-sitosterol and placebo). Such improvement profiles are similar to those reported in other studies of BPH treatment using alpha-blocking agents or finasteride [8,12,19]. The present trial showed slightly more rapid changes initially than did that by Berges *et al.* [17], with a difference of 2.6 points over placebo after 4 weeks.

However, the statistically defined endpoint in the present trial was not the absolute IPSS profile but the relative difference in the IPSS between the placebo and β-sitosterol groups measured as the percentage change from the initial to the final visit (Fig. 1). This analysis highlights the individual changes in IPSS and shows the 'benefit' to patients in both groups.

In contrast with the present study, randomized trials with finasteride have used the change in prostatic volume as the endpoint [6,8,21]. Considering the mechanism of action of finasteride, this is the primary and most important outcome variable in studies with this drug. In the present trial, it was not deemed necessary to assess this variable because no reduction could be expected with β-sitosterol [24]. This was also confirmed by the results of Berges *et al.* [17] where improvements occurred with no change in prostatic volume. For finasteride, the reported change from baseline in Q_{max} was up to 4 mL/s after 10–12 months [20] and the improvement in symptom score was 3.6 after 36 months of long-term follow-up [8] or 6.4 (4 in placebo) as reported by others [22,23]. These outcomes, calculated from baseline, are similar to the improvements over placebo observed in the present study.

Trials with alpha-receptor blocking agents show a range of mostly significant improvements, lower or higher than those in the present study. With alfuzosin, Jardin *et al.* [10] reported an improvement of 4 points in the symptom score, 3.1 mL/s in Q_{max} and 31 mL (39%) in PVR. The results reported for doxazosin were an improvement of 39% for the total score [19] and 82% and 90% for the irritative and obstructive symptoms, respectively [11], while the changes in Q_{max} were up to 2.9 mL/s [19] or 45% [11]. PVRs were monitored in two of the studies [9,11] and showed reductions of 15–72%. Similar results were observed with prazosin [11], while the results for terazosin [12,25] showed improvements in the symptom score of up to 5.0 and up to 5.4 mL/s for Q_{max}. Other reported changes from baseline in Q_{max} showed improvements of 10, 6.9 and 6.2 mL/s for indoramin, prazosin and phenoxybenzamine, respectively [26–28]. However, all these results should be compared with the corresponding changes in the associated placebo groups to calculate the actual improvement over placebo.

It is well known that placebo effects occur in pharmacological therapies in general and particularly in patients with BPH who wish to avoid operative intervention [29]; responses of up to 40% or more have been reported [30–32]. The placebo response in the present study was about 19% in the IPSS, 29% in the QOL index and 43% in Q_{max}, with no effect on PVR. This placebo effect is comparable with that obtained in the pilot study with the same drug [15] and to the results for other drugs used to treat BPH. The corresponding placebo response reported by Berges *et al.* [17] was lower with their chosen symptom score, but was more apparent in the PVR. Thus, the placebo response can be accounted for by normal statistical variability and appears to be a usual response for patients with BPH as characterized in this study. Further research should now focus on the possible biochemical mechanisms of β-sitosterol action in patients with BPH.

Acknowledgement

This work was sponsored by Azupharma, Germany and supported by the DGO (German Society For Oncology). The efforts of Mrs Patricia Davies and Dr E. Ruckdäschel are gratefully acknowledged for improving the grammar of the manuscript.

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BJU International (2000), **85**, 842–846

Treatment of symptomatic benign prostatic hyperplasia with β-sitosterol: an 18-month follow-up

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Objectives To determine the long-term effects of phytotherapy with β-sitosterol (the trade name for β-sitosterol used in this study is Harzol®) for symptomatic benign prostatic hyperplasia (BPH).

Patient and methods At 18 months after enrolment in a 6-month multicentre double-blind placebo-controlled clinical trial with β-sitosterol (reported previously), patients were re-evaluated using the modified Boyarsky score, the International Prostate Symptom Score and quality-of-life index, the maximum urinary flow rate (Q_{max}) and postvoid residual urine volume (PVR). In this open extension of the original trial (after 6 months of treatment or placebo), patients were free to chose their further treatment for BPH.

Results In all, 117 patients (59%) were eligible for analysis during the follow-up. Of the former β-sitosterol group, 38 patients who continued β-sitosterol treatment had stable values for all outcome variables between the end of the double-blind study and after 18 months of follow-up. The 41 patients choosing no further therapy had slightly worse symptom scores and PVR, but no changes in Q_{max}. Of the former placebo group, 27 patients who started β-sitosterol after the double-blind trial improved to the same extent as the treated group for all outcome variables. The 18 patients choosing no further therapy showed no signs of improvement.

Conclusion The beneficial effects of β-sitosterol treatment recorded in the 6-month double-blind trial were maintained for 18 months. Further clinical trials should be conducted to confirm these results before concluding that phytotherapy with β-sitosterol is effective.

Keywords Benign prostatic hyperplasia, phytotherapy, β-sitosterol, long-term outcome, symptom score

Introduction

Phytotherapy has a long tradition in the medical treatment of BPH in Europe. Despite there being no established mechanism of action and no precise classification of the active compounds for many of these drugs, substantial symptom improvement has been reported in previous studies [1,2]. However, as modern drug therapies are becoming significantly more effective (e.g. α1-receptor blocking agents, 5α-reductase inhibitors), there is an obvious need for valid clinical testing of phytosterol drugs to confirm their claimed benefits.

Currently only two clinical trials have been reported that meet most of the study criteria of the WHO consensus conference for the treatment of BPH [3]. Both studies used β-sitosterol (the trade name for β-sitosterol used in this study is Harzol®) as the active treatment in their protocols [4,5]. The study design (multi-centred, placebo-controlled and double-blind) was similar in both trials and showed statistically significant improvements in BPH-related symptoms and urodynamic values during a 6-month study period.

Results for the 18-month follow-up of our previous trial [4] are now available for the primary (modified Boyarsky symptom score) and other outcome variables, e.g. IPSS, the quality-of-life (QoL) index, maximum urinary flow (Q_{max}) and postvoid residual urine volume (PVR) of the 200 patients originally recruited in the study group.

Patients and methods

After unblinding the 6-month randomized trial [4] both placebo and treated patients were free to choose further treatment or discontinue therapy of any kind. Inclusion criteria for the follow-up evaluation were designed to exclude possible false-positive effects and to maximize the number of patients eligible for evaluation. Therefore, all patients with a follow-up of $\geqslant 16$ months (486 days) after recruitment for the double-blind trial were included. To be eligible for analysis patients had to be continuously treated for at least 90% of the follow-up and no changes

Accepted for publication 28 February 2000

in treatment were allowed within the last 6 weeks before the follow-up visit. Patients were excluded from analysis if there was: loss to follow-up; surgical intervention for BPH; discontinuation of study medication during the double-blind trial; α1-blocker or finasteride therapy during the follow-up; any combination of β-sitosterol with other phytotherapy; and insufficient follow-up.

For the 18-month follow-up analysis, six groups resulted from the patients' choice of further therapy. Patients from the former β-sitosterol arm accounted for groups 1–3 according to their further treatment in the open extension and those in the former placebo arm accounted for groups 4–6 (Table 1).

During the follow-up patients were evaluated according to the original protocol of the double-blind trial. The magnitude of their symptoms was assessed using the modified Boyarsky score and the IPSS, and their Q_{max} and PVR were recorded.

Exclusion criteria applied in 83 patients (36 of the former β-sitosterol group and 47 from the former placebo group) of whom 32 had more than one reason for exclusion (Table 2). Eleven patients were excluded for BPH-related surgery, another seven because they discontinued study medication during the double-blind trial and seven because they were treated with α1-blockers or finasteride during the follow-up. Thirty-three patients were excluded from analysis as they were lost to follow-up. From the remaining 152 eligible patients, a further 25 were excluded because of insufficient follow-up. Table 2 also details the distribution between the original groups of patients excluded for each criterion.

The unpaired *t*-test was used to assess differences between all the variables in the original double-blind trial. The modified Boyarski score in the placebo-controlled study was originally evaluated in an intention-to-treat analysis. Other *P* values reported (compared with placebo) were considered descriptive only [4], as are all *P* values reported in the present analysis. The level of significance was defined as $\alpha = 0.05$ (two-sided).

Results

Of the 200 patients from the original protocol, 117 (59%) were eligible for the 18-month follow-up analysis; 41% were excluded for various criteria (Table 2). The treatment outcome for the primary and secondary variables is shown in Table 3. Those in group 1 continued to have a favourable outcome, with all values remaining stable from the end of the double-blind study to the 18-month follow-up. There was no additional effect from the longer treatment period. All improvements at 18 months were significantly better (except for PVR) than in those who never received active treatment (group 5).

Of the former placebo group, those in group 4 improved to the same extent as the treated group in the double-blind trial for all variables (Table 3). Symptoms and QoL improved more than in those who remained on watchful waiting (group 5), but the changes in Q_{max} and PVR were not significant because there were too few patients. Those in group 5 and those in group 6 (data not shown) had no or minor signs of improvement between the end of the double-blind study and at 18 months of follow-up.

Patients in group 2 showed mild worsening of symptoms and PVR (Table 3), but compared with the baseline values of the original trial, the improvement remained substantial. Comparing the 18-month follow-up values between group 2 and group 5, the changes in symptoms and QoL (IPSS) were significant. Patients in group 3 (data not shown) improved slightly compared with those who took no further medication.

Of the initial 200 patients, 15 (7.5%) reported undergoing surgery for BPH during the 18-month follow-up; 12 (6%) of these patients belonged to the former placebo group and three (1.5%) to the former β-sitosterol group. The mean time to surgery was 201 days in the patients on placebo and 441 in those taking β-sitosterol.

Discussion

To date, β-sitosterol has been tested in two randomized, placebo-controlled, double-blind clinical trials [4,5], and in many other trials of different design over the last two decades [6–8]. The first two trials were conducted following the WHO consensus criteria [3], except that

Table 1 The treatment groups in the open-extension trial

	Treatment during double-blind trial (n = *200*)	
Treatment in open extension trial (n = *117*)	*β-sitosterol* (n = *100*)	*Placebo* (n = *100*)
Group *N* (*n*)		
β-sitosterol	1 (38)	4 (27)
Watchful waiting	2 (14)	5 (18)
Other phytotherapy (data not shown)	3 (12)	6 (8)

Table 2 Reasons for exclusion from the 18-month follow-up evaluation. Note that exclusion criteria were applied in the order given, e.g. 15 patients had surgical interventions for BPH but four were already excluded as follow-up data were missing, thus the total number of excluded patients increased by only 11

	Excluded former:		*Additional event, however already excluded*		
Reason and order for exclusion	*Sitosterol*	*Placebo*	*Sitosterol*	*Placebo*	*Cumulative total*
Lost to follow-up	14	19	–	–	33
Surgical intervention	3	8	–	4	44
Medication discontinued during randomized trial	1	6	5	8	51
α-blocker or finasteride therapy	2	5	–	1	58
Combination phytotherapy	0	0	1	1	58
Follow up <486 days	16	9	4	8	83
Total	36	47	–	–	83

the study duration was 6 months in both. Both trials have shown β-sitosterol to be better than placebo over the study period for symptoms and uroflow variables. With the criticism that the study duration was insufficient to provide enough information about the long-term results, the present study was designed to investigate the outcome of the original study population of the β-sitosterol group one year after the end of the double-blind protocol [4].

From the 64 eligible patients taking β-sitosterol in the original study, only 19% chose to discontinue it after unblinding; most of the rest (59%) remained on β-sitosterol treatment. In these patients, the results were stable over the 18-month follow-up. Of the 53 eligible former placebo patients, most (66%) chose phytotherapy over watchful waiting (34%). Interestingly, when starting β-sitosterol therapy (group 4), the patients had the same extent of symptom relief as had those taking β-sitosterol during the randomized study. Despite the small groups, in general all those who chose sitosterol for further therapy (group 1 and 4) had significantly better symptom relief and QoL scores than those who remained on watchful waiting during the open extension (group 5). Of all eligible patients, most chose drug therapy after unblinding in both the β-sitosterol and placebo groups; overall, these patients had a substantial and lasting favourable effect compared with the symptom severity at randomization. Active treatment was generally better than watchful waiting.

To interpret the present results correctly, the sub-

Table 3 Results for the Boyarski score, IPSS, QoL, Q_{max} and PVR at various times during the study

	Mean (SD)				
Group/assessment	*Boyarsky score*	*IPSS*	*QoL*	*Qmax (mL/s)*	*PVR (mL)*
Group 1					
At randomization	14.9 (4.5)	13.7 (4.6)	3.0 (0.8)	10.5 (2.6)	62.2 (23.6)
After double-blind trial	6.9 (4.0)a,b*	6.8 (4.1)a,b	1.4 (0.8)a,b	17.8 (5.7)a,b	22.1 (29.5)b
At 18-month follow-up	7.1 (3.4)b	6.3 (3.1)b	1.4 (0.7)b	18.7 (5.9)b	23.3 (28.2)
Group 2					
At randomization	13.0 (3.2)	13.6 (2.7)	3.1 (0.9)	9.0 (2.8)	64.6 (15.3)
After double-blind trial	6.4 (3.8)d	5.8 (3.6)c,d	1.5 (0.9)	12.4 (5.4)	25.6 (18.7)d
At 18-month follow-up	7.4 (4.3)	7.0 (4.1)d	1.8 (1.1)d	12.5 (4.1)	48.0 (35.2)
Group 4					
At randomization	13.6 (3.5)	14.1 (4.2)	3.0 (0.9)	10.8 (3.3)	66.6 (30.6)
After double-blind trial	10.9 (4.2)	11.3 (4.7)	2.4 (1.0)	12.2 (5.9)	47.3 (27.1)
At 18-month follow-up	8.1 (3.9)e	7.7 (4.6)e	1.5 (0.9)e	14.8 (6.7)	32.5 (27.9)
Group 5					
At randomization	13.1 (2.9)	13.2 (3.1)	2.6 (0.9)	9.3 (2.3)	71.6 (23.8)
After double-blind trial	11.9 (3.8)	12.3 (3.4)	2.9 (1.0)	10.9 (3.8)	71.9 (28.5)
At 18-month follow-up	12.4 (4.9)e	11.7 (4.6)e	2.8 (1.2)e	10.4 (3.2)	70.7 (59.8)

$P < 0.01$ comparing changes from baseline at given time points between: a, group 1 and group 4; b, group 1 and group 5; c, group 2 group 4; d, group 2 and group 5; e, group 4 and group 5.

stantial group of 83 patients who were excluded from the follow-up evaluation (41.5% of the original recruited 200 patients) were analysed for possible effects on the results. Three major indicators of treatment failure, e.g. surgical intervention, choice of α1-blocker or finasteride therapy, and discontinuation of medication during the randomized trial, were more prevalent in those receiving placebo. In addition, more patients were lost to follow-up in the placebo than in the β-sitosterol group. Results from the randomized study phase for the excluded patients showed no substantial differences in outcome compared with those not excluded. Therefore, no relevant factors appeared to affect the results of the 18-month follow-up caused by the exclusion of these patients.

The proportion of patients undergoing BPH-related surgical intervention (7.5%) was about half that reported in the recent PLESS study with finasteride [9]. Of these 15 interventions, 12 were in patients receiving placebo and in those who chose no further therapy in the open extension, with only two in those treated with β-sitosterol. These findings further support the beneficial effect of β-sitosterol therapy. However, as the study was not designed to assess this criterion it remains unclear whether other factors than β-sitosterol were responsible for this effect. Thus, as with many medical therapies for BPH, it is unclear if surgery is postponed rather than prevented in the long-term.

In the open-extension protocol each patient was free to chose their further treatment. When the outcome values for patients after unblinding were compared with their choice of further treatment, no significant factors, e.g. treatment outcome or treatment arm, were predictive in any of the follow-up groups. Therefore, it appears that additional factors other than treatment outcome, e.g. personal or doctor's preferences, may have also been involved in the choice. Of 32 patients who apparently required no further therapy, 18 were in the former placebo group and of 22 patients who changed to other phytotherapy, eight were former placebo patients. This reflects the typical wide spectrum of BPH symptom bother and the relative indications for therapy. Thus, as with other medical treatment for BPH, frequent monitoring of symptoms during therapy is advisable and therapy should be interrupted if the symptoms are relieved.

Together with other phytotherapy agents, β-sitosterol is often criticised because the mechanism of action is unknown. As prostatic size remains mostly unchanged during treatment, a substantial endocrine mechanism of action is unlikely. However, as shown in a recent study from our group [10], β-sitosterol has a significant effect on stromal TGFβ production within the prostate *in vitro*. Whether the induction of TGFβ is responsible for symptom relief in patients with BPH remains unclear.

As there are no known major side-effects of β-sitosterol therapy and the effects are maintained over at least 18 months, β-sitosterol should be considered with other medical therapies for patients with symptomatic BPH; however, it remains unclear which type of patient with BPH would benefit the most from this therapy. In addition, further randomized clinical trials should confirm the present data, as the relatively few patients and brief duration of the double-blind study limit the conclusions drawn about the long-term results. As there are no pressure flow data, this therapy should be considered as symptomatic relief rather than removing obstruction. This should always be considered when symptomatic BPH is treated conservatively with β-sitosterol.

Acknowledgements

This study was sponsored by Hoyer-Madaus GmbH & Co KG, Monheim, Germany.

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Urtica dioica for Treatment of Benign Prostatic Hyperplasia: A Prospective, Randomized, Double-Blind, Placebo-Controlled, Crossover Study

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ABSTRACT. *Purpose*: To determine the effects of therapy with *Urtica dioica* for symptomatic relief of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH).

Material and Methods: A 6-month, double-blind, placebo-controlled, randomized, partial crossover, comparative trial of *Urtica dioica* with placebo in 620 patients was conducted. Patients were evaluated using the International Prostate Symptom Score (IPSS), the maximum urinary flow rate (Qmax), postvoid residual urine volume (PVR), Serum Prostatic-Specific Antigen (PSA), testosterone levels, and prostate size. At the end of the 6-month trial, unblinding revealed that patients who initially received the placebo were switched to *Urtica dioica*. Both groups continued the medication up to 18 months.

Results: Five hundred fifty-eight patients (90%) completed the study (287/305, 91% in the *Urtica dioica* group, and 271/315, 86% in the placebo group). By intention-to-treat analysis, at the end of the 6-month trial, 232 (81%) of 287 patients in the *Urtica dioica* group reported improved LUTS compared with 43 (16%) of 271 patients in the placebo group ($P < 0.001$). Both IPSS and Qmax showed greater improvement with drugs than with placebo. The IPSS went from 19.8 down to 11.8 with *Urtica*

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Journal of Herbal Pharmacotherapy, Vol. 5(4) 2005
Available online at http://www.haworthpress.com/web/JHP

doi:10.1300/J157v05n04_01

dioica and from 19.2 to 17.7 with placebo ($P = 0.002$). Peak flow rates improved by 3.4 mL/s for placebo recipients and by 8.2 mL/s for treated patients ($P < 0.05$). In *Urtica dioica* group, PVR decreased from an initial value of 73 to 36 mL ($P < 0.05$). No appreciable change was seen in the placebo group. Serum PSA and testosterone levels were unchanged in both groups. A modest decrease in prostate size as measured by transrectal ultrasonography (TRUS) was seen in *Urtica dioica* group (from 40.1 cc initially, to 36.3 cc; $P < 0.001$). There was no change in the prostate volume at the end of study with placebo. At 18-month follow-up, only patients who continued therapy, had a favorable treatment variables value. No side effects were identified in either group.

Conclusion: In the present study, *Urtica dioica* has beneficial effects in the treatment of symptomatic BPH. Further clinical trials should be conducted to confirm these results before concluding that *Urtica dioica* is effective.

KEYWORDS. Benign prostatic hyperplasia, phytotherapy, stinging nettle, *Urtica dioica*, symptom score, and long-term outcome

INTRODUCTION

There is a general perception that herbal products are, at worst, harmless placebos, but this is not always true. As early as the 15th century BC, the use of plant extracts for the symptomatic treatment of BPH was described on Egyptian papyrus.[1] Unfortunately, many questions remain unanswered; therefore the scientific case for their use remains unproven. With the recent proliferation of nutrition and vitamin stores, use of these agents has greatly increased.[2] In some European countries, plant extracts are the most commonly recommended initial treatment for men with BPH, and patients are reimbursed for the cost of these agents by health insurance companies.[3] Numerous plant extracts have been used in the treatment of LUTS secondary to BPH. Some of these extracts are *Aletrius farinose* (Unicorn root), *Serenoa repens* (Saw palmetto), *Pygeum africanum* (African pulm), *Populus tremula* (Aspen), *Echinacea purpurea* (Purple cone flower), *Cucurbita pepo* (Pumpkin seeds), *Secale cereale* (Rye), and *Hipoxis roperi* (South African star grass). The most popular agent is Saw palmetto (*Serenoa repens,* Dwarf

palm), which is derived from the berry of the American dwarf palm tree.[4] In a variety of clinical trials, the use of Saw palmetto in men with lower urinary tract symptoms secondary to BPH has led to significant subjective and objective improvements.[5-10] Despite increased awareness and use, basic and clinical research with regard to the role and efficacy of natural remedies in men with BPH continue to lag.

Urtica dioica is extract from the root of a stinging nettle and it is widely used in Germany.[11] The extracts of the roots of the stinging nettle contain a complex mixture of water- and alcohol-soluble compounds such as fatty acids, sterols (β-sitosterol, campesterol, and stigmasterol), and flavonoids. There have been three studies that suggest different mechanisms of action for stinging nettle. These include inhibition of prostatic growth factor interaction,[12] inhibition of membrane sodium and potassium-adenosine triphosphate in the prostate, which results in the suppression of prostate cell metabolism and growth,[13] and modulation of binding of sex hormone-binding globulin to its receptor on prostate cell membranes.[14] These laboratory studies only suggest possible mechanisms of action.

Urtica dioica is widely used in Europe.[11] Stinging nettle is found in many areas of Iran. The raw plant is obtained from wastelands, woodlands, and gardens. Compared to other phytotherapeutic agents, *Urtica dioica* has not been extensively studied. Currently, there are no efficacy data on the effects of *Urtica dioica* for the treatment of LUTS secondary to BPH. Thus, we performed a randomized, double-blind, placebo-controlled study to assess the clinical effects and safety of *Urtica dioica* in patients with symptomatic BPH.

MATERIALS AND METHODS

A total of 620 patients, 55 to 72 years old (mean age 63 years), with lower urinary tract symptoms due to BPH 1 to 3 years in duration presenting to the outpatient urology clinic participated in this study. A detailed medical history was obtained from each patient and all patients completed an IPSS questionnaire. A physical examination and laboratory evaluation, including a complete blood count, urine analysis, serum chemistry study, testosterone and Prostatic Specific Antigen (PSA) determination, transrectal ultrasonography (TRUS), ultrasonography from urinary tract, postvoid residual volume (PVR) and maximum urinary flow (Qmax) measurement were performed.

To assess the volume of prostate accurately with TRUS, precise measurements were made in 3 dimensions: the anterior-posterior, the coronal, and the sagittal. The volume was determined using the formula of $4/3\ \pi\ r_1 \times r_2 \times r_3$, where r is the radius (each of the 3 radii represent a different dimension).

Serum PSA levels were measured using the Yang assay. Residual urine measurements were made by catheterization and Qmax were recorded electronically.

The following inclusion criteria were used: the patient had no cancer, the laboratory findings were normal; and the patient had no lower urinary tract problem other than BPH. Patients were excluded from analysis if there was: loss to follow-up, surgical intervention for BPH, discontinuation of study medication during the double-blind trial, α_1-blocker, 5-α-reductase inhibitor or other drug therapy during trial and follow-up, any combination of *Urtica dioica* with other phytotherapeutic agent, and insufficient follow-up. Patients meeting inclusion criteria had their medical histories and demographic information recorded and underwent a full physical examination by the author.

A table of random numbers was used to assign subjects at a 1:1 ratio to receive a sealed opaque bottle of *Urtica dioica* or inert placebo. The placebo was indistinguishable from the *Urtica dioica.* The fluid extract of *Urtica dioica* was synthesized from the roots via a fractional percolation process and standardization. The herbal blend contained a standard preparation of 100 mg of *Urtica dioica* root extract in 1 ml. Each preparation was ingested three times daily with meals. Each patient was given *Urtica dioica* (n = 305) 120 mg three times daily or placebo (n = 315) in a double-blind, randomized order for six months. At the end of the trial, patients were evaluated according to the original protocol. After completion of the 6-month trial, unblinding occurred, a compliance evaluation was carried out, and patients were asked what they thought they had received. Patients were free to choose further treatment with *Urtica dioica* or discontinue therapy of any kind. Patients who initially received placebo were crossed over to receive *Urtica dioica* for 18 months, and patients who had used the *Urtica dioica* continued their medication in the 18-month follow-up period. A complete crossover design was not used because we believed that patients who had responded to the *Urtica dioica* were deprived of an effective treatment. The patients came for monthly check-ups, and in each visit, they were re-evaluated using the IPSS, Qmax, and PVR.

All patients with a follow-up of > 16 months after recruitment for the double-blind trial were included. Only patients that had been continuously treated for at least 90% of the follow-ups and had no changes in the treatment were included in the analysis. Exclusion and inclusion criteria were also applied in these patients. In all, 340 patients who chose further treatment and 131 patients who discontinued therapy of any kind were eligible for analysis at the end of follow-up. At the 18-month follow-up, patients were re-evaluated using the initial protocol.

The unpaired *t*-test was used to assess differences between all the variables in the original double-blind trial protocol. *P* values reported (compared with placebo) were considered descriptive only, as are all *P* values reported in the follow-up program analysis. The level of significance was defined as $\alpha = 0.05$ (two-sided). Intention-to-treat analyses were performed on all efficacy variables and included the subjects who had a baseline measurement and at least one measurement after the start of treatment.

RESULTS

Six hundred twenty-one patients were recruited, only 558 (90%) completed the whole randomized trial study. The remaining 10% were excluded from the study for several reasons (Table 1). Overall patients' demographics are shown in Table 2. Comparison between the *Urtica dioica* group and the placebo group for IPSS, Qmax, PVR, prostate size, PSA, and testosterone serum levels at various times during the study are shown in Table 3.

Initial 6-month, double-blind, randomized trial: After six months of treatment, patients receiving *Urtica dioica* demonstrated significantly improved LUTS compared to those receiving placebo. The least square mean scores to the IPSS questions assessing the severity of bladder outlet obstruction demonstrated significant improvement among patients receiving *Urtica dioica* compared with placebo ($P < 0.001$, Table 3). In this study, greater improvements in the IPSS, Qmax, and PVR were seen in the treatment group then with the placebo group. The IPSS went from 19.8 to 11.8 with *Urtica dioica* and 19.2 to 17.7 with placebo ($P = 0.002$), which represent decreases from baseline of 40% and 9%, respectively. In terms of peak flow rate, the *Urtica dioica* treated patients improved by 8.2 mL/s and only by 3.4 mL/s for placebo recipients ($P < 0.05$). This is a 77% increase from baseline for the *Urtica dioica* group compared with a 31% increase from baseline for the placebo group.

TABLE 1. Reasons for exclusion from study

Reason for exclusion	*Urtica dioica*	Placebo
Lost to follow-up	25	36
Surgical intervention	5	14
Medication discontinued during		
randomized trial	2	10
α-blocker or finasteride therapy	4	9
Combination therapy	0	0
Follow up < 16 months	16	9
Total	65	84

TABLE 2. Baseline characteristics of participants in the 2 groups

Characteristic	*Urtica dioica*	Placebo
Patients number	305	315
Mean age, y (range)	64 (57-71)	62 (53-73)
Mean duration of LUTS	2.2 (1-3)	2.3 (1-3)
due to BPH, y (range)		
Education		
Did not complete high school	115	118
High school	155	159
Graduate/Professional	35	38
Mean IPSS ± SD	19.8 ± 4.9	19.2 ± 4.6
Mean Qmax ± SD, mL/s	10.7 ± 2.4	10.8 ± 2.8
Mean PVR ± SD, mL	73 ± 32.6	74 ± 29.6
Mean prostate volume ± SD, cc	40.1 ± 6.8	40.8 ± 6.2
Mean serum PSA ± SD, ng/mL	2.4 ± 1.4	2.7 ± 1.1
Mean serum testosterone ± SD, ng/dL	645 ± 31	651 ± 27

LUTS = Lower urinary tract symptoms, IPSS = International prostrate symptom score, Qmax = Maximum urinary flow rate, PVR = Postvoid residual urine volume, PSA = Prostatic specific antigen, SD = Standard deviation, y = year

Postvoid residual urine (PVR) was decreased in the treatment group (before treatment, 73 cc; after treatment, 36 cc; $P < 0.05$). The placebo group showed no significant change in residual urine volume (before treatment, 74; after treatment 71) ($P > 0.05$). Prostate size (as measured by TRUS) decreased from 40.1 cc to 36.3 cc in *Urtica dioica* group ($P <$

TABLE 3. Effect of *Urtica dioica* in men with symptomatic BPH

Mean ± SD	Baseline	Randomization	At 18-month follow-up	
			Urtica dioica continued at the end of 6-month trial	*Urtica dioica* discontinued at the end of 6-month trial
IPSS				
Urtica dioica	19.8 ± 4.9	11.8 ± 4 *	11.1 ± 4.8	19.1 ± 4.2
Placebo	19.2 ± 4.6	17.7 ± 3.1	12.1 ± 3.8	19.4 ± 3.9
Qmax (mL/s)				
Urtica dioica	10.7 ± 2.4	18.9 ± 4.7 **	16.2 ± 3.2	11 ± 3
Placebo	10.8 ± 2.8	14.2 ± 3.7	18.2 ± 3.4	10.2 ± 3.3
PVR (mL)				
Urtica dioica	73 ± 32.6	36 ± 25.5 ***	37 ± 28.2	70 ± 28
Placebo	74 ± 29.6	71 ± 24.4	38 ± 25.5	77 ± 22
Prostate volume (cc)				
Urtica dioica	40.1 ± 6.8	36.3 ± 4.2	36.1 ± 7.2	39.5 ± 6
Placebo	40.8 ± 6.2	40.6 ± 5.1	40.6 ± 4.1	42.4 ± 5.2
Serum PSA (ng/mL)				
Urtica dioica	2.4 ± 1.4	2.2 ± 1.2	2.3 ± 1.1	2.5 ± 1.1
Placebo	2.7 ± 1.1	2.6 ± 0.8	2.6 ± 1.2	2.7 ± 1.2
Serum testosterone (ng/dL)				
Urtica dioica	645 ± 31	649 ± 29	650 ± 34	650 ± 32
Placebo	651 ± 27	645 ± 30	649 ± 33	649 ± 29

LUTS = Lower urinary tract symptoms, IPSS = International prostrate symptom score, Qmax = Maximum urinary flow rate, PVR = Postvoid residual urine volume, PSA = Prostatic Specific antigen, SD = Standard deviation
*P = < 0.002 *v* placebo, **P = < 0.05 *v* placebo, ***P = < 0.001 *v* placebo

0.001), while no significant change was observed in the placebo group. Testosterone and PSA levels were unaffected in both groups.

Long term results: Those in the primary *Urtica dioica* group continued to have a favorable outcome, with all values remaining stable from the end of the double-blind study to the 18-month follow-up. There was no additional effect from the longer treatment period. All improvements at 18 months were significantly better than participants who never received active treatment ($P < 0.001$).

Of the former placebo group, those who received *Urtica dioica* improved to the same extent as the treated group in the double-blind trial for all variables.

Of the initial 620 patients, 27 (4.3%) reported undergoing surgery for BPH during the whole study schedule: 22 (3.5%) belonged to the placebo group and 5 (0.8%) to the patients who received *Urtica dioica*. The mean time to surgery was 210 days in the patients without active treatment and 448 in those taking *Urtica dioica*.

DISCUSSION

The widespread use of phytotherapeutic products necessitates our need to explore the true magnitude and level of efficacy of these products. Other than alpha-blockers or hormonal agents, medical treatments for BPH have included phytotherapeutic agents, cholesterol lowering agents, amino acid complexes, and organ extracts.[15] In the past decade, the use of phytotherapeutic agents has become particularly popular in men with lower urinary tract symptoms secondary to BPH.

There has only been one recent study on *Urtica dioica* that utilized a liquid dosage form.[16] The liquid preparation has subsequently been removed from the market because of its unacceptable taste.[11] In that study, 41 patients were randomized to receive either placebo or the stinging nettle preparation. They were treated for a period of three months. Treated patients had superior improvement compared with placebo recipients in terms of IPSS results.[16] The placebo was the same taste of the stinging nettle extract and was indistinguishable from active treatment.

The data that is available to date does not confirm its efficacy in the treatment of lower urinary tract symptoms secondary to BPH. From the 305 eligible patients taking *Urtica dioica* during randomized trial, only 52 (17%) chose to discontinue after unblinding while most remained on the *Urtica dioica* treatment. The reasons for discontinuation included lack of efficacy (n = 22), bothered by participation in study (n = 16), and achieved enough improvement (n = 14). In these patients, the results were stable over the 18-month follow-up. Of the 315 placebo patients, 236 (75%) subjects chose phytotherapy over the 18-month follow-up period. Interestingly, when starting *Urtica dioica* therapy, they had the same extent of symptom relief as had those taking *Urtica dioica* during the randomized study. Of all eligible patients, most [n = 340 (61%)] chose drug therapy post-unblinding in both *Urtica dioica* and placebo groups. Overall, patients had a substantial and lasting favorable effect compared with the symptom severity at randomization. Active treatment was generally better than watchful waiting.

To interpret the present results correctly, the substantial group of 149 patients who were excluded from the follow-up evaluation (24% of the original recruited 620 patients) were analyzed for possible effects on the results. Three major indicators of treatment failure were surgical intervention, choice of α_1-blocker or finasteride therapy, and discontinuation of medication during the randomized trial, which were more prevalent in those receiving placebo. In addition, more patients were lost to follow-up in the placebo than in the *Urtica dioica* group. Results from the randomized study phase for the excluded patients showed no substantial differences in outcome compared with those not excluded. Therefore, no relevant factors appeared to affect the results of the 18-month follow-up caused by the exclusion of these patients.

The proportion of patients who underwent BPH-related surgical intervention (4.3%) was about one-fourth to those that reported surgery in the study with finasteride.[17] Of these 27 interventions, 22 were patients who received placebo and also chose no further therapy post unblinding, with only five in the *Urtica dioica* group. These findings further support the beneficial effect of *Urtica dioica* therapy. Since the study was not designed to assess this criterion, it remains unclear whether *Urtica dioica* was solely responsible for this effect. Furthermore, as with many medical therapies for BPH, it is unclear if surgery is postponed rather than prevented in the long-term.

In the open-extension protocol, each patient was free to choose further treatment. When the outcome values for patients after unblinding were compared with their choice of further treatment, no significant factors, such as treatment outcome or treatment arm, were predicted in any of the follow-up groups. Therefore, it appears that additional factors such as personal or doctor preferences influenced the decision.

An unexplained finding in our study is the lack of a change in serum PSA despite decreased prostatic size. This apparent paradox may involve some novel mechanism of action. The results of these studies suggest a wide spectrum of activity. However, precise mechanism(s) of action remain obscure.

CONCLUSION

As there are no known major side-effects with *Urtica dioica* therapy in addition to the fact that the effects are maintained over at least 18 months, *Urtica dioica* may be considered along with other medical ther-

apies for patients with symptomatic BPH. However, it remains unclear which type of patient with symptomatic BPH will benefit the most from this therapy. Although several studies suggest some clinical efficacies with many phytotherapeutic agents, further randomized, placebo-controlled trials are needed to evaluate their efficacy in preventing progressions, such as urinary retention and need for surgery. Further study is also needed to ascertain the mechanism and reproducibility of these effects. More laboratory analyses are also required to determine the active ingredient or ingredients and their mechanism of action. Alpha-adrenergic blockers and 5-alpha-reductase inhibitors are among the most extensively evaluated drugs in urologic practice. It is imperative that phytotherapeutic agents be evaluated to an equal extent.

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