



Flower Pollen Extract and its Effect on the Prostate

A multicenter, Placebo-controlled Study on the Efficacy and Tolerability of Adenoprostal in Patients with Benign Prostatic Hyperplasia (BPH)

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For the Adenoprostal Study Group*

Abstract

Prostatectomy is considered as the gold standard treatment for BPH and some 400,000 men undergo the procedure each year in the US alone. Several new pharmacological products for the treatment of BPH have been developed over the last few years but have given unconvincing results and a side effect profile which included impotence. Phytotherapeutic treatments are therefore of particular interest especially due to the low incidence of side effects.

Methods

A multicenter, double-blind, placebo-controlled study was carried out to evaluate the therapeutic activity and tolerability of Adenoprostal in the treatment of BPH. Patients suffering from benign prostatic hyperplasia with sporadic disturbances of micturition and residual urine < 100 ml (Grade I) or persistent disturbances of micturition and residual urine \geq 100 ml (Grade II) were recruited into this study and randomly assigned to 2 treatment groups. Patients received 1 capsule of Adenoprostal (containing 189 mg pollen extracts) or placebo per day for 8 weeks. At the end of the treatment period there was an 8-week follow-up period; another examination was carried out at Week 24 to evaluate how long the improvement lasted after treatment was stopped.

Benign prostatic hyperplasia (BPH) of the periurethral prostate gland is commonly seen in men over 50 years of age and causes varying degrees of bladder outlet obstruction. The etiology of this disease is unknown but may involve alterations in hormonal balance associated with aging.

As life expectancy has risen significantly over the last decade more than 15% of the population is now over 60 years of age. About 50-60% of 60 year old males suffer from benign prostatic hyperplasia and these increases in men over 70 years of age.

Given the incidence of the disease and the resulting functional disturbances, treatment of BPH becomes more important in order to improve the quality of life of the affected patients and perhaps avoid prostatic surgery.

Prostatectomy is widely used for the treatment of BPH. Some 400,000 men undergo the procedure each year in the USA for an estimated expenditure of \$3.5 billion.

Quality of life improves after surgery only for patients with severe symptoms. Yet most surgery is carried out in patients with mild or moderate symptoms which mean that for the majority of men this treatment will not have a great impact.

Several new products for the treatment of BPH have been introduced in the pharmaceutical market over the last few years. In a 1645-patient double-blind, placebo-controlled study, finasteride (Proscar, Merck Sharp, and Dohme), a 5- α reductase inhibitor that blocks the conversion of testosterone to dihydrotestosterone, which promotes prostate growth, gave unconvincing results. In addition, its side effects may include impotence, decrease libido and decrease ejaculate.

Hence phytotherapeutic treatments are of particular interest due to the low incidence of side effects.

*Adenoprostal is a novel phytotherapeutic treatment for benign prostatic hyperplasia. It contains selected rye pollen extracts which have been shown to be effective in the symptomatic treatment of BPH and the resultant functional disturbances.

Several studies have been published on the efficacy of pollen extract (Cernilton®) in the symptomatic treatment of BPH.

*Adenoprostal is marked by I.B.S.A., Lugano, Switzerland

Most of these studies used subjective parameters to assess efficacy and the evolution of BPH after treatment.

A more reliable objective marker that enables the diagnosis and evolution of the BPH to be assessed more accurately has recently been discovered. This marker, which is called prostate specific antigen (PSA), is a serine proteinase produced in the epithelial cells of the prostate. PSA levels are measurable in the serum of almost all men who have prostatic tissue present. While PSA is specific for prostatic tissue, its levels can be elevated in benign prostatic hyperplasia (BPH), adenocarcinoma of the prostate, prostatitis and after prostate biopsy or cytoscopy. Therefore, if patients with BPH only are selected, this parameter, together with echography, would enable the evolution of the disease to be assessed more accurately.

On this basis we carried out a multicenter, double-blind, placebo-controlled study to evaluate the therapeutic activity and tolerability of Adenoprostal in the treatment of BPH using both objective (PSA measurement and echography) and subjective parameters to assess efficacy.

Treatment

Patients received 1 capsule of Adenoprostal (containing 189 mg pollen extracts) or placebo per day for 8 weeks. At the end of the treatment period there was an 8-week follow-up period; another end point of this study was to evaluate how long the improvement lasted after treatment was stopped. Therefore a further examination was undertaken 16 weeks after the end of treatment (week 24).

Efficacy

The following were evaluated to assess treatment efficacy:

Symptoms

The parameters diurnal and nocturnal micturition, desire to urinate, difficulty or delay in initiating urination and prolonged micturition were individually assessed at baseline and 4, 8, and 24 weeks after the start of the study:

The parameters sensation of incomplete emptying, decreased force of the urinary stream, stranguria, terminal dribbling, incontinence, perineal disturbances, problems involving the testes were evaluated globally.

Ultrasonic examination

An echography of the prostate was carried out at baseline, after 8 weeks of treatment and at Week 24 as a post-treatment clinical control. This examination enables the width, height and length of the prostate to be measured to calculate the volume of the prostate. In addition, it also allowed the post-micturition residue to be measured on the basis of a normogram.

Prostate specific antigen

The prostate specific antigen was determined at baseline, after 8 weeks of treatment and at week 24. The PSA determination was carried out at an external laboratory (Anamedica SA, Giubiasco) using a RIA kit from Yang Laboratories INC, USA.

Global efficacy judgment

At week 8 and week 24, the doctors and patients expressed a global judgment on the efficacy of the treatments using a 4-point verbal scale (0=nil, 1=poor, 2=good, 3=excellent).

Secondary Effects

All secondary effects observed during the study were recorded in the individual patient case report forms including the type of effect, its duration and intensity.

Statistical methods

Parametric and non-parametric tests were used to analyze the data including the level of statistical significance within groups and

between groups. The following tests were used: Chi-square test, analysis of variance (ANOVA), paired t-test, Mann-Whitney test, and the two sample t-test.

Results

A total of 55 patients were recruited into this study and randomly divided into 2 treatment groups: the Adenoprostal group (32 patients) and the Placebo group (23 patients).

Of these, only 44 were assessable at the end of the study and their data were subjected to statistical analysis.

The characteristics of these 44 patients are reported in Table 1 below:

Table 1. Demographic characteristics of the patients

Patients' characteristics	Adenoprostal (N = 25)	Placebo (N = 19)
Average age ± S.D.	63.42 ± 7.407	62.11 ± 6.249
Age range	48 - 83 years	50 - 74 years
Height ± S.D.	169.60 ± 5.489	170.10 ± 5.089
Weight ± S.D.	76.84 ± 11.1	72.58 ± 8.79

The two groups were homogeneous for age, height and weight (two sample t-test: p = n.s.)

Eleven patients (7 from the Adenoprostal group and 4 from the Placebo group) were excluded from the analysis for the following reasons:

- Missing controls: 4 from Adenoprostal group, 1 from the placebo group.
- Death: 1 from the placebo group.
- Protocol violations: 3 patients from the Adenoprostal group and 2 from the placebo group: 2 patients from the Adenoprostal group were hospitalized for tumor removal and prostatectomy: 1 patient from the Adenoprostal group and 2 from the placebo group were excluded for use of diuretics.

The concomitant medications used were mostly psychoactive and cardioactive drugs. Three patients (2 from the Adenoprostal group and 1 from the placebo group), had taken non-steroidal anti-inflammatory drugs during the study.

Efficacy

Symptoms

Diurnal and nocturnal micturition:

Table 2 below shows that there was a reduction in the mean number of both diurnal and nocturnal micturitions in patients treated with Adenoprostal (p<0.05), two sample t-test).

Table 2. Diurnal and nocturnal micturition

Treatments	MICTURITION			
	DIURNAL		NOCTURNAL	
	START	COMPLETION	START	COMPLETION
ADENOPROSTAL (N = 25)	6	4	2	0
PLACEBO (N = 19)	6	6	2	2

Desire to urinate, difficult or delay in initiating urination, prolonged micturition

At the end of the study an improvement, even though at the limit of statistical significance, was observed in these symptoms only in the patients treated with Adenoprostal (p<0.05, Chi-squared test).

Global evaluation of the following symptoms which could not be assessed individually:

Sensation of incomplete emptying, decreased force of the urinary stream, stranguria, terminal dribbling, incontinence, perineal disturbances, and problems involving the testes.

The distribution of these judgments were very similar in the two treatment groups and were therefore non-significant (Chi-squared test, p=n.s.).

Ultrasonic examination

This test enabled the volume (ml) of the prostate to be assessed before (t = week 0) and at the end of the study (t = week 24).

The ecographic examinations were always carried out by the same investigator and the following formula was used to calculate the

volume of the prostate [23]: $V(\text{ml}) = (4/3)\pi(\text{axial value}/2) (\text{transversal value}/2) (\text{sagittal value}/2)$

Table 3 reports the mean values for the volumes of the prostate in both treatment groups at baseline (t = week 0) and at week 24 (t = week 24). The mean volume of the prostate had decreased progressively in both treatment groups. However the reduction was significantly greater ($p < 0.05$: two sample t-test) in the Adenoprostal group (-29%) than in the placebo group (-8.8%).

Table 3. Volume of the prostate (ML)

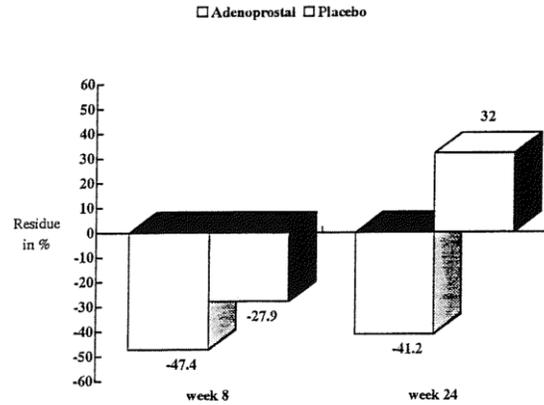
Treatments	t = 0 weeks	t = 24 weeks
ADENOPROSTAL		
(N = 21)	44.61 ± 23.25	31.66 ± 14.63* (-29%)
PLACEBO		
(N = 17)	46.63 ± 42.50	42.50 ± 20.87* (-8.8%)

difference between t = 24 / t = 0 (100) - 100

Measurement of post-micturition residue

The post-micturition residue in the patients treated with Adenoprostal decreased from 90.59 ml to 47.64 ml after 8 weeks of treatment ($p < 0.01$: paired t-test) and increased to 53.27 ml at the Week 24 examination ($p < 0.01$: paired t-test). In the placebo-treated patients, the decrease in post-micturition residue was not significant: the baseline value of 60.07 ml decreased to 43.94 ml after 8 weeks of treatment and increased to 80.4 ml at Week 24.

It is important to stress that if these results are expressed as a percent reduction of the post-micturition residue, a 47.4% reduction is observed after 8 weeks of treatment in the Adenoprostal group compared to a 27.9% reduction in the placebo group after the same period of treatment; at the end of the study (Week 24), the post-micturition residue remained at nearly the same levels (-41.2%) in the Adenoprostal group while it increased in the placebo group (+32%) compared to baseline values. The between-groups comparison was significant only at week 24 ($p < 0.01$: two-sample t-test).



Determination of PSA

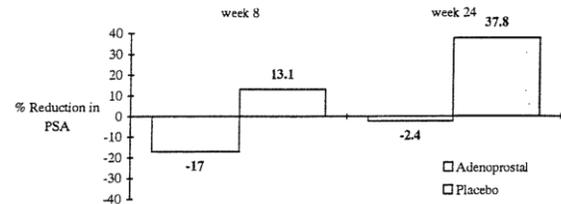
The serum levels* of the PSA in the two treatment groups were particularly interesting.

(*PSA: normal up to 4 ng/ml)

In the Adenoprostal group, the PSA levels decreased from baseline value of 5.5 ng/ml to 4.6 ng/ml after 8 weeks of treatment. This decrease was significant ($p < 0.05$: paired t-test). At the week 24 control, the value increased to 5.4 ng/ml ($p = \text{n.s.}$: paired t-test).

On the other hand there was a constant increase in serum levels of PSA after 8 weeks of treatment and at the final control (Week 24). The baseline value of 5.2 ng/ml increased to 5.9 ng/ml at week 8 and to 7.2 ng/ml at week 24.

The difference between the groups was statistically significant in favor of Adenoprostal ($p < 0.05$ at week 8 and at week 24: two-sample t-test).



Results

Adenoprostal significantly reduced the mean number of both nocturnal and diurnal micturitions ($p < 0.05$) compared to placebo. The echography examination showed that both the volume of the prostate and the post-micturition residue decreased after treatment with Adenoprostal compared to placebo. Statistically, the prostatic specific antigen levels at the end of

the study showed a significant decrease, compared to baseline values, in patients treated with Adenoprostal. Tolerability was excellent in nearly all the patients.

Conclusions

Patients treated with Adenoprostal showed a greater overall benefit, compared to those treated with placebo, with a marked reduction in the intensity of symptoms at all the evaluation periods.

Key words: BPH – benign prostatic hyperplasia, phytotherapy, rye pollen extract, PSA – prostate specific antigen

Appendix

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Global judgements on Efficacy

The global judgments on the therapeutic activity of the two treatments were calculated on the basis of the judgments expressed by the investigators and the patients who used a verbal score (0=no efficacy, 1=poor, 2=good, 3=excellent).

The mean score in the group of patients treated with Adenoprostal was 1.4 at the week 4 control; this improved to 1.7 at week 8 and 1.8 at the end of the study (Week 24).

The analyses showed statistically significant differences from week 8 onwards ($p < 0.05$: Wilcoxon test).

No statistically significant differences were seen in the scores from the placebo-treated group.

Even though a more favorable improvement was observed in the Adenoprostal group both at week 8 and at week 24, the analyses showed a statistically significant difference between treatments only at the end of the study (Mann-Whitney test: $p < 0.05$).

Global judgments on Tolerability

The majority of the tolerability judgments were "excellent" or "good" in both study groups (95% in the placebo group and 96% in the Adenoprostal group) at week 4 and week 8 of treatment.

The incidence of secondary effects was low: one case of anxiety was reported at week 8 in the Adenoprostal group and another at week 4 in the placebo group; one patient in the placebo group presented orthostasis at week 4. These secondary effects were of slight severity, transient and did not require treatment suspension.

The laboratory parameters analyzed did not show any clinically important changes in the two treatment groups.

Table 4. Global efficacy judgements

VARIABLE	ADENOPROSTAL	PLACEBO
Excellent	4%	0%
Good	64%	56%
Poor	32%	17%
Nil	0%	27%

Discussion

Most of the clinical studies that have been performed to evaluate the efficacy and tolerability of phytotherapeutic treatment in benign prostatic hyperplasia (BPH) have used subjective assessment parameters.

The aim of this double-blind, placebo-controlled study was to assess the validity of treatment with Adenoprostal using both subjective and objective parameters. In addition to the questionnaire that the patients were supposed to complete, objective parameters such as echography and the laboratory evaluation of PSA have been used. These objective examinations enabled the evolution of BPH in patients under treatment with Adenoprostal or placebo to be followed.

The three methods used (questionnaire, echography and laboratory analysis of PSA) demonstrated the clear benefits of Adenoprostal compared to placebo.

Patients treated with Adenoprostal showed an overall benefit with a marked reduction in the intensity of symptoms at the pre-fixed evaluation periods. Of particular importance was the favorable improvement of the following symptoms: frequency of diurnal and nocturnal micturition, desire to urinate, difficulty or delay in initiating urination and prolonged micturition.

Nearly all investigators participating in this study had carried out the sonography examinations in a standardized manner using the suprapubic position [18] for the measurement of the prostate and for the calculation of the post-micturition residue. The post-micturition volume [19, 20, 21], showed a good correlation between the

result obtained using the formula $(0.7 [x.y.z] = \text{ml})$ and the result obtained with the normogram [21].

The echography examination demonstrated that Adenoprostal was effective in the treatment of benign prostatic hyperplasia. At the end of the study it was observed that both the volume of the prostate, measured echographically [22, 23, 24], and the post-micturition residue had shown a definite decrease following treatment with Adenoprostal compared to the results obtained in the patients treated with placebo. Although there was a significant disappearance of symptoms and a significant reduction in post-micturition residue, the fact that this was not accompanied by a striking reduction in prostate volume probably has a two-fold explanation. In our opinion, the first is due to the limitations of trans-abdominal sonography: the posterior parts of the prostate are often difficult to delimit and hence an exact measurement is rather difficult; in addition it is practically impossible to evaluate the exact prostatic volume when there are irregular protrusions inside the vesicle.

Finally, in the early stages, benign prostatic hyperplasia is often characterized by an increase in the central hypoechogenicity without significant alterations of the total diameter [25].

As a result, the measurement of post-micturition residue was shown to be the most reliable parameter for the evaluation of efficacy in our patients, compared to the measurement of the prostate volume which should be evaluation using more accurate instrumental parameters.

The laboratory parameters did not undergo any noteworthy variations. However, the prostatic antigen levels at the end of the study showed a significant decrease, compared to baseline values, in patients treated with Adenoprostal. This decrease was not seen in the placebo-treated patients. The difference between the groups was statistically significant in favor of Adenoprostal at week 8 and week 24 ($p < 0.05$: two-sample t-test).

Tolerability was excellent in nearly all patients (95% favorable results in the Adenoprostal group; 96% favorable results in the placebo group). Secondary effects were seen only in three cases (one patient treated with Adenoprostal, two with placebo). However these were of slight severity and did not require treatment interruption.