



### The Treatment of Benign Prostatic Hyperplasia with Phytopharmata

A comparative study of Cernilton<sup>R</sup> vs.  $\beta$ -sitosterol

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The conservative treatment of benign prostatic hyperplasia (BPH) has gained increasingly in significance in view of the increased life expectancy. In a controlled comparative study (n = 39) with Cernilton<sup>R</sup> and  $\beta$ -sitosterol the course of treatment was objectified by clinical-chemical findings. The results demonstrate the marked improvement of symptoms and signs, whereas the regression of complaints was more pronounced under Cernilton<sup>R</sup>. The significant decrease of PAP and PSA serum levels shows the reduction of cell lesions in BPH under the treatment with Cernilton<sup>R</sup>. A comparable effect of  $\beta$ -sitosterol could not be demonstrated. The relative lack of toxicity of both drugs can be confirmed by the biochemical data.

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In the second half of the normal life-span the physiological process of ageing leads to the appearance of an increasing number of diseases. One of these is benign prostatic hyperplasia (BPH), which sooner or later develops in practically all males. The data on the incidence of benign prostatic hyperplasia vary more than for almost any other condition.

Some authors assume that from the fourth decade of life almost 80%, and from the seventh decade almost 100% of all men show a more or less pronounced nodular hyperplasia of the prostate (2, 6). This means that the older a man becomes the more certain it is that he will be confronted with an alteration of his prostate and its consequences. The almost unbelievable increase in life expectancy which has been achieved through the diagnostic, therapeutic and prophylactic measures of modern medicine means that more and more men are reaching the critical age for prostate disease. In Sweden, the United Kingdom and Germany, for example more than 50% of the population is over the age of 65 years.

The figures published by the German Federal Statistics Office in Wiesbaden for 1983 show that 156,000 people in the Federal Republic were 90 years of age or over. Ten years earlier the corresponding figure was only 92,000. The trend is the same in all industrial countries and will continue. As a result, the incidence of the "old man's disease", prostatic hyperplasia, will also increase.

The aetiology and pathogenesis of benign prostatic hyperplasia are still unclear and are the subject of controversial discussion. Changes in enzyme activity in the prostate, shifts in various hormonal parameters (e.g. DHT) and, more recently, altered hormone-receptor conditions, are accepted as possible triggering factors (1, 2, 4, 6, 7). It is established that the endocrine system influences the development of a prostatic hyperplasia.

#### Rationale of Study

The fact that only relatively few men are not affected by benign prostatic hyperplasia makes it almost impossible to find a healthy control group in the same age-range, in order to obtain comparative clinico-chemical data, for reference. This is probably also the reason for the sometimes contradictory results reported in many publications.

In our study two phytopharmaca, Cernilton<sup>R</sup> (Stroschein, Hamburg) and  $\beta$ -sitosterol, were compared and the course of the treatment with each preparation objectified on the basis of clinico-chemical data.

#### Our Investigations

##### *Selection of Patients*

It was possible to carry out the study almost exclusively with trial subjects from a large old people's home, who always received food of the same type and composition, and to a certain extent the same amount. It was thus relatively easy to exclude changes attributable to nutritional factors in the parameters to be measured in the course of the study, in both groups.

With a predictable drop-out rate of 20%, 50 patients were taken into the study, in accordance with the defined criteria for exclusion and inclusion, in order to reach a total of at least 20 patients in each group, for the final evaluation. The patients were allocated to the two groups according to a strict randomization procedure. All the patients entered the study without any additional medication. In order to exclude possible uncheckable drug effects, a one-week wash-out period was included before the start of the treatment, in 4 cases. All the patients required treatment and had been receiving medical therapy for their prostatic symptomatology for more than 6 months. Because of unsatisfactory results of previous therapy they can be considered as a "simple negative" patient selection.

Two patients were excluded from the initial patient population because of extreme obesity and a further seven because of the results of diagnostic laboratory investigations (malignant tumors, severe alcoholic liver disease and extreme electrolyte imbalances). One patient had to discontinue the study for private reasons. At the final evaluation one patient of Group A with residual urine values of over 130 ml and who had to be operated for anuria before the end of the study period, was excluded. Table 1 shows the mean values for age, height, and weight in the two groups, A and B. Tables 2a and 2b provide information on concomitant diseases and the general condition of the patients of Groups A and B, respectively.

### *Methodology*

The patients of Group A (trial preparation: a specially prepared pollen extract (3). Cernilton<sup>R</sup> <sup>1)</sup> received, as did the patients of Group B (control preparation:  $\beta$ -sitosterol <sup>2)</sup>, 2 tablets/capsules 3 times a day for the first week, and then 1 tablet/capsule 3 times a day<sup>3)</sup> from the 8th to the 42nd day.

The blood samples were taken in the morning, between 8:00 and 9:00 a.m., in the fasting state, by the Vacutainer system (Becton & Dickinson), centrifuged after maturation of the fibrin (1 hour at room temperature), separated by means of Seraclear filters and deep-frozen at -25° C and kept constantly at this temperature until the analytical processing. The clinico-chemical and hematological parameters were analyzed on a Type 12/60,6/60, 9/60 and 7A Auto-analyzer on a Type determinations of prostatic acid phosphatase (PAP) and prostate-specific antigens (PSA) were carried out by radioimmunoassay (RIA), as double-blind determinations which were repeated if the results exceeded the normal values by more than 600 counts. The counting was carried out with a Y-counter system (MR-1032-W+W) of the Kontron Co.

The enzyme activities were measured at the normal physiological temperature of 37°C. The reproducibility for these values and for the hematology is  $\pm 3\%$ , and for the other clinico-chemical parameters  $\pm 1\%$ .

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- 1) One tablet contains: Stand. Extr. Pollin. sicc. (Cernitin T60) 60 mg; Stand. Extr. Pollin. dialys (Cernitin GBX) 3 mg.
  - 2) One capsule contains: 10 mg  $\beta$ -sitosterol.
  - 3) The manufacturer's recommendation of a dosage of 2 capsule 3 times a day was not followed, in order to be able to compare the therapeutic effects of the two preparations.

The data of the clinical investigations were classified according to symptoms and complaints and recorded according to the degree of change at each examination.

The residual urine was determined by catheterization, always performed by the same investigator. The bacterial examinations of the urine samples were performed by means of the classical culture methods.

All the data have been documented in accordance with GLP<sup>4)</sup> and processed according to standard biostatistical methods on an EDP unit (Olivetti L I M 40 ST).

## Results

### *Changes in the clinical symptomatology*

#### *Subjective Complaints*

Comparison of the initial findings with those at the end of the study shows improvement in the clinical symptoms with both preparations, which were clearly more pronounced with the pollen-extract preparation, according to both the investigating physician's impression and that of the patients themselves. This is true particularly for the patients with several concomitant symptoms. If the results are classified, then on the basis of the subjective findings of the patients and the observations of the treating physicians these data are supported, at least semi-quantitatively, by Table 3. This table shows a clinically relevant rate of improvement in the subjective symptoms, painful micturition, changes in the urinary stream and pollakisuria, for both preparations, with Cernilton<sup>R</sup> proving better than  $\beta$ -sitosterol. For vesicle tenesmus, polyuria, urinary dribbling, as well as for pain and a feeling of pressure there is also a marked regression of the symptomatology in both groups.

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4) GLP = Good Laboratory Practice: recommendations of the German GLP committee, according to the guidelines of the Food and Drug Administration.

#### *Determination of residual urine*

In the  $\beta$ -sitosterol group the residual urine volume was  $35 \pm 22.5$  ml and in the pollen-extract group  $28 \pm 16.6$  ml. In both groups the mean values had fallen to under 15 ml at the end of the treatment.

#### *Urine Examinations*

Table 4 gives an overview of the changes in the cell-counts and the bacterial status during the treatment. With the improvement in the symptomatology the pathomorphological picture also improved.

#### *Changes in biochemical parameters under the medication*

The parameters indicating disturbances of renal function, namely creatinine and blood urea nitrogen, showed a clear decrease under both

Cernilton<sup>R</sup> and  $\beta$ -sitosterol. The urea nitrogen fell from 19.5 mg/100 ml to below 18.5 mg/100ml and from 21.0 mg/100 ml to 20.2 mg/100 ml under the two medications, respectively. The creatinine also showed a trend towards a slight decrease in the plasma concentration, which can be interpreted as not statistically significant tendency to improvement. The uric acid concentration was not influenced by either of the two preparations. The electrolytes remained largely within the ranges of the baseline values. Only in the case of chloride was there slight regression, by about 1 mmol/l. Neither preparation has any effect on blood pressure.

Impressive are those enzyme values which indicate cellular lesions. The  $\gamma$ -GT, generally known as a cholestase-indicating enzyme in alcohol abuse, had its highest intracellular value in the renal parenchymal cells. The fall in the primarily intrarenal  $\gamma$ -GT was not only statistically significant but also clinically relevant, and was more pronounced in the Cernilton<sup>R</sup> group.

Although the alkaline phosphatase (AP) isoenzyme group is not particularly prostate-specific, an enzyme of this group is however to be found in a high concentration in the prostate tissue. During the course of the study there was a marked fall in the serum concentration of AP in both groups.

The PAP and PSA determinations in the serum show a clear difference in the effectiveness of the two preparations. Prostatic acid phosphatase (PAP) is a highly tissue-specific enzyme which is normally passed into the seminal fluid. All pathological changes of the prostate, whether carcinoma, benign hyperplasia or prostatitis, lead to an increase in the concentration of this enzyme in the peripheral blood. In Group A the PAP concentration fell, the decrease being not only clinically relevant but also statistically significant ( $p < 0.05$ ), from 3.5 to 2.7 ng/ml, i.e. the serum concentration reached the normal range, the upper limit of which, measured by the RIA method, is 2.8 ng/ml. Group B, with a high baseline value, showed a similar initial fall from 4.4 to 3.7 ng/ml, which remained at this level until the end of the study, and thus did not reach the normal range (Fig. 1).

The prostate-specific antigen (PSA) originates from the epithelium of the excretory ducts of the

glandular complex and shows a maximum physiological concentration in the serum of 2.3 ng/ml. In benign prostatic hyperplasia concentrations of up to 12 ng/ml are reached.  $\beta$ -sitosterol lowered the serum concentration from the start to the end of the study by only 0.5 ng/ml (from 12.9 to 12.4 ng/ml). This value is not statistically significant and also there is no detectable trend. Statistically significant and also there is no detectable trend. Statistically significant ( $p < 0.01$ ), and in our opinion clinically relevant, on the other hand, is the fall in the PSA value in the pollen-extract group. Here the value fell from 8.25 to 5.8 ng/ml, i.e. a decrease of 2.45 ng/ml was obtained (Fig. 2).

For the other clinico-chemical parameters, namely iron, total protein, albumin, calcium, anorganic phosphate, bilirubin, LDH, GPT (ALT), GOT (AST), triglycerides, cholesterol, cholinesterase, copper, magnesium and zinc, no significant changes were recorded, between the baseline and final values. Only in the values for leukocytes, erythrocytes, haematocrit, haemoglobin and CPK is there a trend towards a slight fall in both groups, so that on the basis of this spectrum of parameters the relative innocuity of both preparations can be confirmed.

## Discussion

Prostatic acid phosphatase (PAP) is a glycoprotein with a relatively low carbohydrate content of only 6%. Under normal physiological conditions this enzyme is passed from the prostate to the seminal fluid in which, together with hyaluronidase, it influences the fluidity of the semen (8). Because of secretory obstruction a benign prostatic hyperplasia is always accompanied by raised internal pressure in the glandular complex. This raised pressure leads to compressive cellular lesions and cytolysis, as a result of which the PAP concentration in the peripheral blood increases. During the course of the study the mean value of the PAP concentration in Group A fell below the upper limit of the normal range (Fig. 1), while in Group B there was an initial improvement, but then no further change in the mean value for the rest of the period of the study.

In healthy subjects the prostate-specific antigen (PSA) is to be found in high concentrations only in the semen. In the peripheral blood it is normally present only in a very low

concentration (up to 2.3 ng/ml) (5), but increases markedly (up to 12 ng/ml) in the presence of cellular lesions of the excretory ducts resulting from a benign prostatic hyperplasia. Like the PAP concentration, that of the PSA also shows a marked fall under pollen extract therapy, from 8.25 ng/ml (Day 0) to 5.8 ng/ml (Day 42), while under  $\beta$  sitosterol therapy the values fall only slightly (Fig. 2).

The fall in the serum concentrations of these two highly prostate-specific markers (PAP and PSA) permits the conclusion to be drawn that the cellular lesions of the glandular tissue resulting from prostatic changes show marked improvement under treatment with pollen extract. Presumably the internal pressure in the glandular complex due to the secretory obstruction also subsides. The concentrations of the mediators of inflammation, of the prostaglandin and leukotriene types, are certainly also reduced. In this way the vicious circle of a self-perpetuating inflammatory process can be broken, since the excessive secretion of prostaglandin is always set in motion by cellular lesions and persists for as long as these lesions are present. Thus with these values it can be confirmed that Cernilton<sup>R</sup> exerts an anti-inflammatory effect.

On the basis of the measurement values presented here the use of Cernilton<sup>R</sup> can be recommended for the indication, "benign prostatic hyperplasia in Stages I and II", provided the residual urinary volume is still under 100 ml. Cernilton<sup>R</sup> reduces the symptomatology of prostatic hyperplasia. The antiinflammatory and micturition-improving effects are confirmed by the various measurement data. We consider very important the fact that the preparation is extremely well tolerated.

The conservative drug therapy of benign prostatic hyperplasia is also of great significance, both in the hospital environment and in general practice, in view of the fact that the proportion of the general population over the age of 50 will in future be even greater than it is today.

**Keywords:** Prostatic hyperplasia, benign, Cernilton<sup>R</sup>,  $\beta$ -sitosterol, Prostatic acid phosphatase, Prostate-specific antigen.

## References

1. Alken, C.-E., J. Sokeland: Urologie, 9. Aufl. Thieme, Stuttgart 1983
2. Blacklock N.: Pathophysiology and Pathogenesis of Benign Prostatic Hyperplasia. Vortrag auf dem I. Symposium New Perspectives in the Treatment of Benign Prostate Disease, Edinburgh 21. 9. 1985
3. Cholcha W.: Cernitin T60 und Cernitin GBX – zwei Pollenextrakte: Struktur und Zusammensetzung. Vortrag auf dem I. Symposium New Perspectives in the Treatment of Benign Prostate Disease, Edinburgh 21.9. 1985
4. Djoseland D., K. J. Tveter, A. Attramadal, V. Hansson, H. N. Hangen, W. Mathisen: Metabolism of testosterone in the human prostate and seminal vesicles. Scand J Urol. Nephrol. 11, 1-6 (1977)
5. Myrtle J. F., W. Shackelford, R. M. Bartholomew, J. Wampler: Prostate-specific antigen: Quantitation in serum by immunoassay. Clin. Chem. 28, 1216(1983)
6. Pegel K. H., H. Walker: Neue Aspekte zur benignen Prostata-hyperplasie (BPH). Extracta urol. (Suppl. 1) 7, 91-96 (1984)
7. Tamm J.: Der Einflub von Pollen-Extrakten auf den Steroidmetabolismus in der Prostata vortrag auf dem 1. Symposium New Perspectives in the Treatment of Benign Prostate Disease, Edinburgh 21. 9. 1985
8. Thomas L.: Labor und Diagnose, 2. Aufl. Medizinische Verlagsges. Marburg 1984

Table 1: Statistical data (age, height, weight) in the two comparative groups ( $\bar{x} \pm s$ )

Group	n	Age (years)	Height (cm)	Weight (kg)
A (Cernilton <sup>R</sup> )	19	68.9 $\pm$ 15.13	171.5 $\pm$ 8.28	76.3 $\pm$ 10.32
B (B-sitosterol)	20	73.0 $\pm$ 10.9	171.1 $\pm$ 6.8	73.9 $\pm$ 9.9

Table 2a: Concomitant diseases and general condition of the patients of Group A

Patient No.	Concomitant diseases	General Condition
5	Arteriosclerosis, cerebral sclerosis	Poor
9	Moderate hypertension, diabetes mellitus	Good
12	Moderate hypertension, diabetes mellitus, cholelithiasis, coronary sclerosis	Satisfactory
13	Osteoarthritis of the hip, arteriosclerosis, hypertension, coronary sclerosis	Satisfactory
15	Hypertension, coronary sclerosis	Good
18	-	Good
19	-	Satisfactory
21	Nephrolithiasis	Satisfactory
23	Spondylarthrosis, arteriosclerosis	Satisfactory
24	Coronary sclerosis, angina pectoris	Poor
27	-	Good
30	Generalized osteoarthritis, diabetes mellitus	Poor
31	Coronary sclerosis	Satisfactory
32	Moderate hypertension, coronary sclerosis	Poor
33	-	Satisfactory
36	Arteriosclerosis, coronary sclerosis	Good
37	Duodenal ulcer	Good
38	Glaucoma, bronchial asthma, coronary sclerosis	Satisfactory

Table 2b: Concomitant diseases and general condition of the patients of Group B

Patient No.	Concomitant disease	General condition
1	Slight hypertension	Satisfactory
2	Slight hypertension	Satisfactory
3	Nephrolithiasis, diabetes mellitus, angina pectoris	Poor
4	Slight hypertension, varicose veins	Poor
6	Slight hypertension	Satisfactory
7	Moderate hypertension, spondylosis	Satisfactory
8	Spondylosis, spondylarthropathy	Good
10	Moderate hypertension	Good
11	Slight hypertension, coronary sclerosis	Satisfactory
14	Arteriosclerosis, Parkinson's disease	Satisfactory
16	Cerebral sclerosis	Satisfactory
17	Cor pulmonale	Satisfactory
20	-	Good
22	Generalized osteoarthritis	Satisfactory
25	Angina pectoris	Poor
26	Cor pulmonale, arteriosclerosis, chronic obstructive bronchitis	Satisfactory
28	Slight hypertension, angina pectoris	Good
29	Slight hypertension, cerebral sclerosis, cerebral insufficiency, coronary sclerosis	Satisfactory
34	Angina pectoris, coronary sclerosis	Satisfactory
36		Satisfactory

Table 3: Baseline status and course of the subjective complaints (A = Cernilton<sup>R</sup> group, B=B-sitosterol group)

Complaints	Group	n	Day 0	Day 14			Day 42		
				No change	Reduced	Absent	No change	Reduced	Absent
Painful micturition	A	19	13	7	6	0	1	7	5
	B	20	14	10	4	0	1	9	4
Changes in urinary stream	A	19	9	3	4	2	2	1	6
	B	20	16	12	4	0	1	9	6
Pollakisuria	A	19	15	10	5	0	1	6	8
	B	20	13	10	2	1	2	5	6
Vesical tenesmus	A	19	4	4	0	0	2	1	1
	B	20	5	3	1	1	0	4	1
Polyuria	A	19	1	1	0	0	0	1	0
	B	20	3	2	1	0	0	3	0
Incontinence	A	19	2	1	1	0	1	0	1
	B	20	0	0	0	0	0	0	0
Urinary dribbling	A	19	4	3	1	0	2	1	1
	B	20	5	3	2	0	2	1	1
Pain or feeling of pressure	A	19	7	5	2	0	0	5	2
	B	20	4	1	3	0	0	3	1

Table 4: baseline status and course of the urinary findings (A = Cernilton<sup>R</sup>, B =  $\beta$ -sitosterol group)

	Day 0		Day 14		Day 42	
	A n	B n	A n	B n	A n	B n
<b>Erythrocytes</b>						
None	15	14	17	14	18	13
Few	4	4	2	4	1	5
Moderately numerous	-	-	-	-	-	-
Numerous	-	-	-	-	-	-
<b>Leukocytes</b>						
None	3	1	3	2	5	4
Few	8	8	12	10	11	9
Moderately numerous	7	8	4	8	2	6
Numerous	1	3	-	-	1	1
<b>Epithelial cells</b>						
None						
Few	18	17	16	16	19	16
Moderately numerous	1	1	2	2	-	2
Numerous	-	-	-	-	-	-
<b>Bacteria</b>						
None	13	12	15	12	16	13
Few	3	5	3	8	3	7
Moderately numerous	2	3	1	-	-	-
Numerous	1	-	-	-	-	-

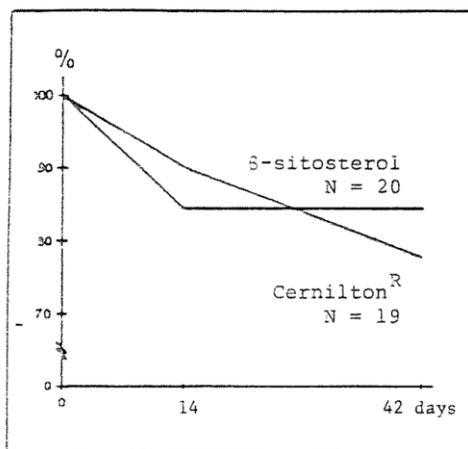


Fig. 1: Significant reduction ( $p < 0.05$ ) of the serum PAP in %, after 6 weeks Cernilton<sup>R</sup> therapy. A comparable effect with  $\beta$ -sitosterol cannot be demonstrated\*.

\*The absolute values before and after treatment are, in the Cernilton<sup>R</sup> group  $3.5 \pm 1.67$  ng/ml (Day 0) and  $2.7 \pm 1.11$  ng/ml (Day 42), and in the  $\beta$ -sitosterol group  $4.4 \pm 5.68$  ng/ml (Day 0) and  $3.7 \pm 4.42$  ng/ml (Day 42). Normal serum PAP value, by radioimmunoassay (RIA) =  $\geq 2.8$  ng/ml.

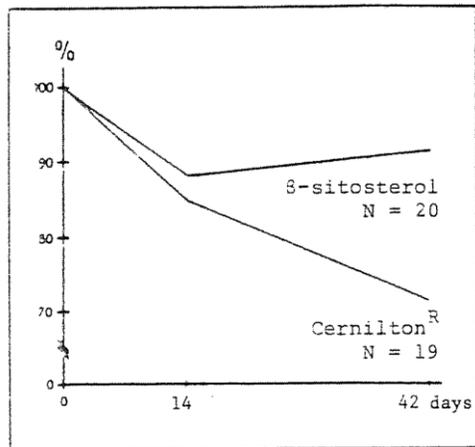


Fig. 2: Significant reduction ( $p < 0.01$ ) of the serum PSA in %, after 6 weeks Cernilton<sup>R</sup> therapy. A comparable effect with  $\beta$ -sitosterol cannot be demonstrated\*\*.

\*\*The absolute values before and after treatment are, in the Cernilton<sup>R</sup> group  $8.25 \pm 10.77$  ng/ml (Day 0) and  $5.8 \pm 6.56$  ng/ml (Day 42), and in the  $\beta$ -sitosterol group  $12.9 \pm 14.55$  ng/ml (Day 0) and  $12.4 \pm 13.57$  ng/ml (Day 42). Normal serum PSA value, by radioimmunoassay (RIA) =  $\geq 2.3$  ng/ml.