



Phytotherapy of BPH with Cernilton® N

Results of a controlled clinical study

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Introduction

In a controlled clinical study in patients suffering from benign prostatic hyperplasia (BPH) the efficacy and the benefit/risk ratio of Cernilton® N is documented and its importance for the (long-term) treatment of this condition is discussed.

Treatment with phytopharmalogical preparations is well established in the therapeutic spectrum of benign prostatic hyperplasia and, on the basis of its high benefit/risk ratio, is recognized as a possible symptomatically oriented medication. Follow-up controls carried out within the framework of phytotherapy ensure that the indication for conservative treatment is regularly checked and, if necessary, revised. In view of the epidemiological knowledge concerning the comparatively rare indication of surgical intervention [2, 11] and the differentiated evaluation of TUR [7, 13], phytotherapeutic agents are used in BHP, preferably in the initial stages of the disease [2, 15, 18].

Based on the positive therapeutic experience with Cernilton N in benign prostatic diseases [6], we performed a clinical study in BHP patients in Stages II and III of the disease over a treatment period of 24 weeks, in which the standardized pollen-extract preparation Cernilton N¹ was investigated, according to a double-blind trial design, versus placebo, with separate follow-up phases for the two groups. The results of the double-blind phase have already been published [3].

This study, carried out in collaboration with 6 practising urologists in a representative patient population, documents the therapeutic efficacy of Cernilton N, which is attributed to the

anticongestive and antiinflammatory effects of the pollen extract.

Patients and method

With regard to the basic characterization of this clinical trial [3] it has to be established that the results of the double-blind study are confirmed in the trial population evaluated, and are therefore presented in the summarized pre/post comparison of Phase I. As an extension to the biometric methods, the variance analysis for the split-plot design of the time-points before the treatment, after Phase I and after Phase II is used.

The breakdown of BPH into Stages II and III was classified according to Vahlensieck [18] and the intensity of the disorders of miction according to the FDA recommendation [4]; the measurements of urinary flow are represented with reference to the urine volume, by means of the Uroflow Index [14].

Following the double-blind phase the active-drug and placebo groups were treated with Cernilton N, according to an open trial design, whereby this follow-up phase also covers a 12-week study period. Due to discontinuation of the treatment (urine retention/TUR, lost capsules), premature withdrawal of the treatment (freedom from symptoms) in Phase I and non-inclusion of 7 patients in the follow-up phase, a total of 92 patients could be included in the biometric analysis. Of these, 45 patients were treated first with active drug and then with Cernilton N, and 47 patients first with placebo and then with Cernilton N.

During Phase II neither the physicians nor the patients were informed which medication

(placebo or active drug) had been given during Phase I, or with what general result, in order to avoid any subsequent effect on the trial results at the final control examination after 24 weeks. Deviations from the treatment plan occurred due to discontinuation or interruption of the treatment in three cases. The medication for concomitant diseases was changed in Phase II, in comparison with Phase 1, in one case.

Results

The comparative groups are homogeneous and their inclusion data correspond to those for the double-blind study [3]. The clinical symptomatology of BPH patients is determined by the leading symptom, nycturia, which was reported by almost all the patients. Concomitant diseases, mainly diseases of the cardiovascular system and metabolic diseases were present in 54.3%, and concomitant medication, principally cardiovascular preparations and antidiabetics, was reported in 41.3% of the patients.

In the double-blind phase, statistically significant differences are documented in regard to nycturia, diuria (frequent urination during the day; pathological: >4 times a day), feeling of residual urine, volume of residual urine and overall assessment by the physician and the patient (Table 1).

Follow-up phase: Placebo - Cernilton N

In comparison with the findings at the end of the double-blind and follow-up phases, after the change-over from the 12-week placebo medication to the also 12-week Cernilton N therapy the following changes were observed.

The response, defined as asymptomatic or improved status following initially pronounced symptoms or findings, shows, for all the parameters studied, a marked increase in the number of patients in whom a regression of the symptomatology was recorded (Tables 2 and 3).

In the urodynamic parameters, a significant reduction of the residual urine volume (Fig. 1) and a further increase in the Uroflow Index values, from 0.79 ± 0.27 to 0.97 ± 0.25 (under placebo: from 0.70 ± 0.31 to 0.79 ± 0.27) were observed. Correspondingly, the overall assessment of the treatment as "very good" or "good", by the physician and by the patient, is documented more frequently after the follow-up

phase: in 63.8% and 66.0% of the cases, respectively (after the double-blind phase: 13.6% and 27.3%, respectively).

Follow-up phase: Active drug -Cernilton N

In the patients treated firstly with active drug (Cernilton N), the positive changes in the clinical symptoms, palpation findings and urodynamic test parameters observed after the subsequent 12 weeks' treatment with Cernilton N (Phase II), in comparison with the findings after Phase I, are slight when compared with the corresponding results in the placebo-Cernilton N group (Fig. 1).

In the overall assessment of the treatment, after the active drug phase (Phase I) "very good" or "good" assessments by the physician and the patient were made in 58.1% and 72.1% of the cases, respectively, and after the subsequent Cernilton N medication (Phase II) in 62.2% and 62.2% of the cases, respectively. The results after the total 24-week treatment period were assessed as poor by the patient in 4.4% of the cases and by the investigating physician in 13.3% of the cases.

Comparison of the treatment-groups

The findings concerning nocturia and volume of residual urine demonstrate that the therapeutic results under Cernilton N in the placebo-Cernilton N group correspond to those obtained under active drug (Fig. 1). In regard to the time-point of the effect on the following clinical symptoms and parameters, considerable differences were observed between the two treatment-groups: nycturia ($P = 0.051$), diuria ($P = 0.039$), feeling of residual urine ($P = 0.013$), enlargement of the prostate ($P = 0.046$) and congestion of the prostate ($P = 0.030$). In each case the earlier time-point was observed in the active drug-Cernilton N group.

In Phase I the residual urine volume decreases significantly more markedly under active drug ($P = 0.001$); in Phase II there is a marked reduction ($P = 0.002$) in the placebo-Cernilton N group. After Phase II the tolerability of Cernilton N is assessed as "good" in 86 cases (93.5%) and as "satisfactory" in 6 cases (6.5%). Unwanted effects, given as pressure over the stomach and nausea, are recorded in 3 cases.

Discussion

The results of this controlled clinical study confirm the effectiveness of the pollen-extract preparation Cernilton N in benign prostatic hyperplasia (BPH). Clear differences are demonstrated in favour of Cernilton N for nycturia, diuria, feeling of residual urine and residual-urine volume and, in the comparison between the treatment-groups, also for enlargement of the prostate and congestion of the prostate. Also, in the comparison of the therapeutic results under active drug with those under Cernilton N following initial placebo medication, an almost parallel course is to be observed. In regard to dysuria, pathological urge to urinate, malaise and the uroflow parameters, no statistically significant differences are to be observed.

In the patients treated with placebo in Phase I, marked improvement of miction is observed in the follow-up phase. In regard to certain of the parameters investigated, in particular diuria and feeling of residual urine, the continuous treatment with Cernilton N leads to freedom from symptoms. For the leading symptom, nycturia, improvement is obtained in three-quarters of all the patients.

In regard to the urodynamic test parameters, the findings for the residual-urine volume show a stable course in the follow-up phase, after an initially marked reduction under active drug. The Uroflow Index also shows a continuous increase whereby, in spite of increased miction volume [8, 9, 14], the flow time and flow-increase time are reduced.

The continuous therapeutic efficacy of Cernilton N in regard to the clinical symptomatology and the urodynamics, which also concurs with the results of a six-month, placebo-controlled, double-blind study with pollen extract in patients with comparatively advanced BPH [5], is reflected by the positive assessment of the treatment by the investigating physician and by the patient in over 80% and 90% of the cases, respectively.

The clinical relevance of changes in the congestion and inflammation of the prostate in BPH [2, 3, 12, 17, 18] is confirmed by the results of this clinical study, if a causal relationship with the irritative symptoms, and partly also with the obstructive symptoms, is assumed. In this respect the differential diagnosis based on the

urodynamics refers to the importance of the hyperactivity of the detrusor muscle, whereby the residual urine is also considered as a parameter of the performance of this muscle [9]. Assuming that the action of Cernilton N is based on anti-oedematous effects, which lead to normalization of pathological changes in the neural supply, this is also suggested by the parallel improvements in the irritative symptoms and the residual-urine volume. Furthermore, an inhibitory effect of orally administered Cernilton N on the hormonally stimulated growth of heterotransplants of BPH can be demonstrated in the nude-mouse model [19]. For a definitive evaluation of its clinical, human pharmacological relevance, more extensive studies are necessary.

Phytotherapy in BPH is characterized by a high benefit-risk ratio whereby, especially in disorders of frequency of miction, controlled long-term treatment is justified in view of the restrictive surgical indication [2, 7, 9, 11, 13, 18]. Although the clinical relevance of the treatment as an alternative to surgical intervention is not demonstrated [10], the main benefit is rather the improvement obtained in the subjectively experienced disturbance of miction. Therefore new drug developments [1, 16] need to be equally as effective as surgical intervention, unless tolerability equivalent to that of the phytotherapeutic agents is guaranteed.

Summary

In a controlled clinical study the efficacy and tolerability of the pollen-extract preparation, Cernilton N, were studied in patients with BPH in Stages II and III (according to Vahlensieck) in 6 urology practices. In the 12-week Phase I of the trial Cernilton N was studied according to a double-blind design versus placebo, and in the subsequent Phase II (follow-up), also of 12 weeks, according to an open trial design in the two comparative groups. The evaluation, carried out in 92 patients, shows significant differences between active drug and placebo after the end of the double-blind phase, which level out at the end of the follow-up phase after the change-over to Cernilton N in the group which received placebo during Phase I. The tolerability of Cernilton N is assessed as "good" in 93.5% of the cases and as "satisfactory" in 6.5%. These results of a study in a representative patient population demonstrate the good efficacy of Cernilton N in BPH in Stages II and III of the

disease over a period of 24 weeks and documents the continuous therapeutic benefit of the pollen extract, which makes possible an effective long-term treatment of BPH.

Conclusions for medical practice

The continuous therapeutic efficacy of Cernilton N makes low-risk long-term therapy possible. Antihormonally acting drugs have an equivalent benefit-risk ratio. Anticongestive therapy will continue to be the principal approach in the conservative treatment of BPH.

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Table 1. Results of a double-blind study: significant differences in favour of Cernilton N in clinical symptomatology, urodynamics and overall assessment of the therapy

Parameter	Active drug	Placebo	Significance (<i>P</i> value)
<i>Clinical symptomatology</i>			
	Response (%)		
Nycturia	66.7	37.2	0.011
Diuria	61.9	37.0	0.023
	Freedom from symptoms (%)		
Diuria	45.2	15.2	0.003
Feeling of residual urine	38.2	3.8	0.005
<i>Urodynamics</i>			
	Volume		
Residual urine			
- before Phase I (ml; $\bar{x} \pm s$)	54.5 \pm 24.9	51.9 \pm 32.0	
- after Phase I (ml; $\bar{x} \pm s$)	28.9 \pm 19.7	44.9 \pm 28.6	0.001
- reduction (%)	47.0	13.5	
<i>Overall assessment</i>			
	Proportion of patients (%)		
Investigating physician			
- very good	20.9	2.3	
- good	37.2	11.4	0.001
Patient			
- very good	25.6	2.3	
- good	46.5	25.0	0.001

Table 2: Response of the symptoms and improvement of the palpation findings under placebo and subsequent Cernilton N therapy

Response (%)

Symptom	Phase I (placebo)	Phase II (Cernilton N)
- Nycturia	37.2	68.2
- Diuria	37.0	60.9
- Feeling of residual urine	46.2	65.4
- Dysuria	52.0	76.0
- Urge to urinate	62.2	84.2
- Malaise	44.4	74.1

Palpation findings, improved (%)

Prostate	Phase I (placebo)	Phase II (Cernilton N)
- Enlargement	12.1	40.4
- Congestion	62.1	72.4

Table 3: Freedom from symptoms and negative palpation findings under placebo and subsequent Cernilton N therapy

Freedom from symptoms (%)

Symptom	Phase I (placebo)	Phase II (Cernilton [®] N)
- Nycturia	14.0	38.6
- Diuria	15.2	50.0
- Feeling of residual urine	3.8	42.3
- Dysuria	36.0	60.0
- Urge to urinate	32.4	60.5
- Malaise	33.3	74.1

Palpation findings, negative (%)

Prostate	Phase I (placebo)	Phase II (Cernilton [®] N)
- Enlargement	2.1	14.9
- Congestion	37.9	62.1

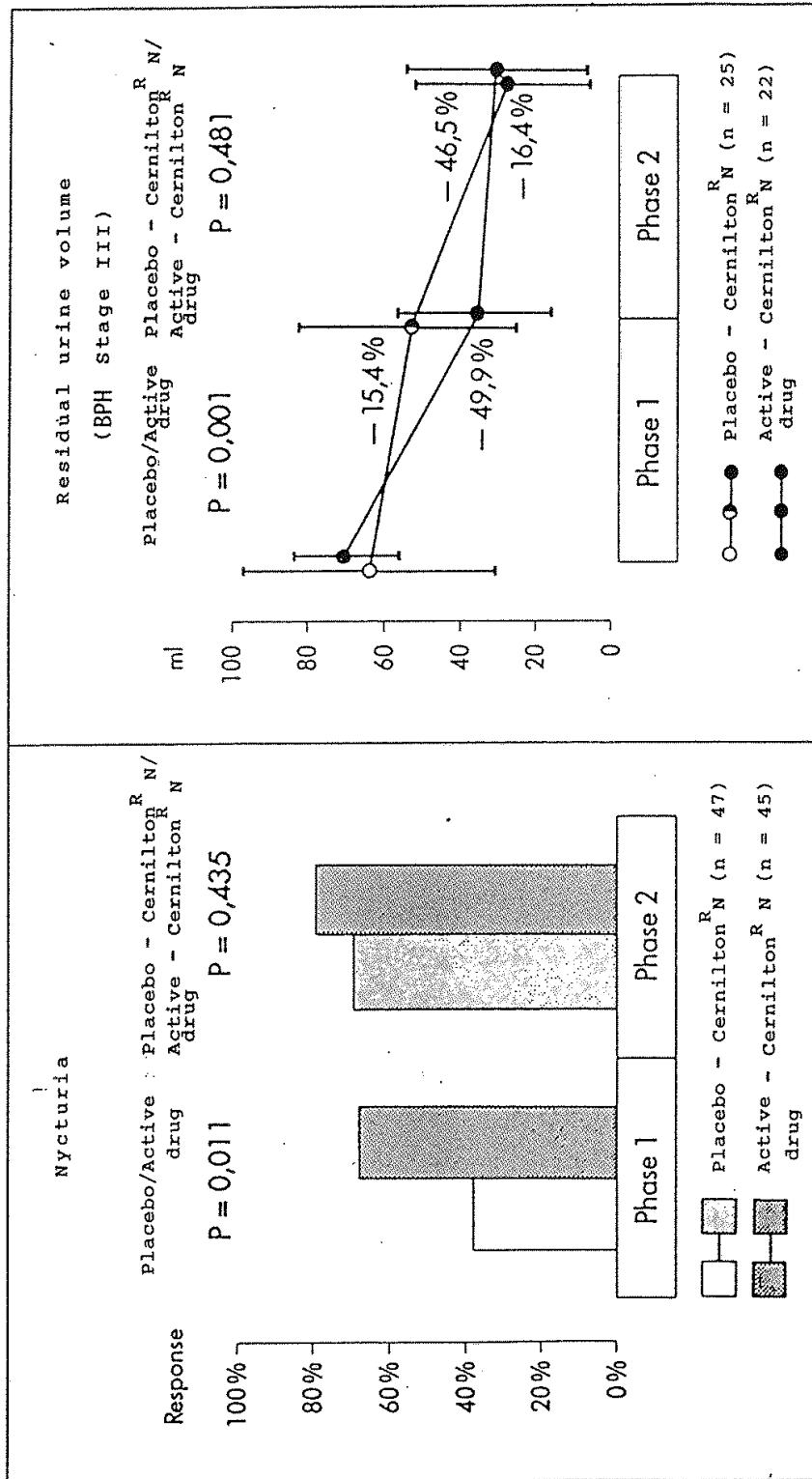


Fig.1: Comparison of the treatment-groups, placebo-Cernilton N and active drug-Cernilton N. Significant differences in the double-blind phase level out after subsequent Cernilton N therapy in the follow-up phase. Parallel course under active drug in comparison with Cernilton N with initial placebo medication in the double-blind phase. Significantly different ($P = 0.008$) course of the residual-urine volume over both phases in the two treatment-arms.