

Possibilities and Limitations of Phytotherapy for Benign Prostatic Hyperplasia (BPH) Results of Treatment with Cernilton® for Stages 1-3 according to Alken

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Introduction

Surgical treatment (transurethral resection or open surgical enucleation of the adenoma) of benign prostatic hyperplasia (BPH) is still the only curative therapy and therefore the "gold standard" for the treatment of BPH. Other treatment modalities have to be judged according to this standard. Despite all improvements in surgical technique and modern anesthesiology, a perioperative mortality rate of 0.2% and an increased delayed mortality due to cardiovascular diseases remains a significant risk factor (19). Furthermore, other possible complications of surgery such as urinary incontinence, erectile impotence, or retrograde ejaculation are not acceptable to some patients.

Despite extensive investigation into the endocrinological control of the growth of the prostate, the etiology of the pathological enlargement of this gland has not yet been definitely resolved. As a target organ for male steroid hormones, the prostate is under the influence of dihydrotestosterone and 17- β -estradiol, which act in particular synergistically on the growth of the fibromuscular stroma. This explains why antiandrogens may be useful in the treatment of BPH (4,20). Because of the adverse effects of antiandrogens such as disturbances of libido and erectile function as well as gynecomastia, this therapeutic principle has thus far not been utilized widely, and is only used for certain patients such as those at prohibitive surgical risk. Other treatment attempts such as the inhibition of the enzyme 5 α -Reductase require further studies concerning efficacy and adverse effects (14).

The importance of phytotherapeutic drugs with a low side effect profile has consequently increased in regard to the conservative treatment of BPH, which at least in Germany is mainly the responsibility of nonhospital-affiliated physicians. In recent years a standardized pollen extract (Cernilton®¹) has been investigated (5,6,9) and utilized. This pollen extract has also been utilized to treat prostatic congestion and/or prostatodynia and non-bacterial prostatitis without proven pathogens (8). The anticongestive effect of the pollen extract in the treatment of BPH should be considered as a clinically relevant therapeutic principle.

To examine the value of treatment of BPH with phytotherapeutic drugs in clinical practice, a study was conducted in BPH patients to determine efficacy and tolerance of the pollen extract in the various stages of the disease.

Patients and Methods

Patients

Over the course of one year, 208 practicing physicians documented their treatment experiences using Cernilton® in 1,933 patients with BPH. Because of missing follow-up examinations or premature termination of either treatment or documentation not related to the treatment with Cernilton®, data on only 1,894 patients were available for analysis. An additional 96 cases which were not classified in regard to the stage of the disease were also excluded from the analysis. In seven of these patients treatment was terminated after the 12th week.

The patient material included therefore 1,798 patients with consecutive treatment over 24 weeks (**2 tablets orally 3 times daily**). In 1,661 patients pretreatment evaluations and evaluations after 12 and 24 weeks of treatment were available, while in 29 patients data were available for the pretreatment evaluation and after 24 weeks of treatment with Cernilton®. In 51 patients the treatment was terminated because of symptomatic improvement (N = 11), lack of efficacy (N = 7), surgery (N = 27), untoward side effects (N = 4) or urinary tract infections (N = 2). In 57 cases treatment was terminated without a specified reason. Overall, therefore, 108/1,798 (6%) of the patients terminated treatment prematurely in the study population, as opposed to 115 / 1,894 (6.1 %) in the entire patient population.

The patients were staged according to *Alken*. Nine hundred and ten patients (50.6 %) were in stage 1, 770 patients (42.8 %) in stage 2, and 118 patients (6.6 %) in stage 3. The average age for these three groups was 60.0, 67.6, and 71.6 years, respectively. Overall, 59.1 % of patients had been pretreated, usually with other phytotherapeutic drugs used in BPH over an average duration of 21.2 (stage 1), 32.5 (stage 2), and 46.8 months (stage 3). This pretreatment was judged as "successful" in 52.0 % of stage 1 patients, 42.6 % of stage 2 patients and 30.4 % of stage 3 patients. Concomitant diseases existed in 812 (45.2 %) of the patients. Cardiovascular diseases (57.4%) endocrine and metabolic diseases (22.8%) and urological diseases (11.0 %) were most common. Among the urological diseases, prostatitis and bladder cancer were the most common.

To further describe the voiding disturbances, data such as age at the first manifestation, specific symptoms (irritative versus obstructive), intensity of the symptoms over time (constant versus variable, either increasing or decreasing), and incidence of episodes of acute urinary retention were documented.

Methods

Clinical evaluation was conducted prior to initiation of therapy as well as after 12 and 24 weeks of treatment. Irritative and obstructive symptoms (nocturia, frequency, feeling of incomplete emptying, urgency, delayed voiding, prolonged voiding time, weak urinary stream, and post-void dribbling) were classified as either mild, moderate, or severe.

Size and congestion of the prostate were evaluated by digital rectal examination (DRE).

Residual urine volume was determined by ultrasonography. The documentation of residual urine was optional, and flow rate parameters were not documented at all since several of the participating physicians were family physicians and general practitioners who often did not have the means to perform residual urine or, in particular, flow rate measurements.

According to the design of the study, a statistical analysis was conducted using minimum, maximum, median, and mean values, standard deviation (STD), and frequency distributions. To compare frequency distribution across the various stages of BPH, the X² test was used. For the comparison of means, a simple analysis of variance was employed, and for the comparison of mean time effectiveness profiles, split plot variance analysis was utilized.

Results

Voiding Disturbances and Findings on DRE

Tab. 1 Moderate to severe intensity of voiding symptoms and findings at digital rectal examination (DRE) in 1,798 patients with BPH. [The frequency of symptoms and DRE findings differ significantly between the three stages. (p<0.001).]

Parameter	BPH 1 (N = 910)	BPH 2 (N = 770)	BPH 3 (N = 118)
Nocturia	43.6%	65.2%	79.8%
Frequency	53.8%	60.3%	77.9%
Feeling of incomplete emptying	20.9%	45.2%	69.8%
Urgency	26.4%	30.3%	49.5%
Delayed voiding	31.1%	62.3%	85.3%
Prolonged voiding	34.2%	70.1%	90.5%
Weak stream	38.7%	74.3%	88.8%
Postvoid dribbling	26.3%	44.0%	74.6%
Prostate enlargement	32.1%	86.1%	89.5%
Prostate congestion	28.1%	43.2%	63.0%

The distribution of obstructive and irritative voiding symptoms at the time of entry into the study is tabularized in Table 1. Data concerning age at first manifestation and type of voiding symptoms as well as their course are listed in Table 2. While in stage 1 BPH nocturia and frequency are the dominating symptoms, prolonged voiding time and a weak urinary stream are most common in stage 2, and in particular in stage 3 BPH.

Post-void dribbling was of particular importance in patients with stage 3 BPH. Prostatic congestion increased significantly with increasing stages. As expected, a more pronounced enlargement of the prostate was found in patients with stages 2 and 3.

Of interest was the significantly different average age at the first manifestation of the voiding symptoms. In patients with stage 1, it was eight years earlier than in stage 3. If one takes the average age of the patient into account, symptoms have been present prior to treatment for 3.5 years in stage 1 patients, for 5.7 years in stage 2 patients, and for 7.1 years in stage 3 patients. If one excludes the possibility that the data obtained from older patients become relatively imprecise, these results can only be explained by an age-dependent dynamic course of progression of the disease process of BPH.

Irritative symptoms dominated in patients with stage 1, while in stages 2 and 3 obstructive symptoms were more common. However, in the advanced stages, often both irritative and

obstructive symptoms were found equally common. Fluctuation of the intensity of the symptoms was particularly characteristic for patients with stage I BPH, while in patients with stages 2 and 3 a progression of the symptoms and a higher incidence of episodes of acute urinary retention was evident.

In regard to the findings on DRE and the voiding symptoms, the treatment with Cernilton® did not yield a significant difference in the response rates (range from 68% - 83%) between stages 1 and 2 (Table 3).

Tab. 2 Characteristic of voiding symptoms in the three stages of BPH.

Parameter	BPH 1	BPH 2	BPH 3	Comparison of Stages
Age at first manifestation (years)	\bar{x} 56.5	61.9	64.5	$p < 0.001$
	SD 10.2	8.7	8.0	
o not available	35	26	4	
Type of complaints				$p < 0.001$
o Mainly irritative	58.5%	29.7%	14.8%	
o Mainly obstructive	29.4%	42.5%	55.7%	
o Irritative and obstructive	11.8%	27.1%	28.7%	
o not available	8	10	3	
Clinical course (multiple listings)				$p < 0.001$
o Sometimes more, sometimes less	51.0%	32.5%	23.7%	
o Variable symptoms	47.8%	37.9%	22.0%	
o Increasing symptoms	31.9%	54.3%	73.7%	
o Episodes of retention	4.1%	9.9%	38.1%	
o not available	10	7	2	

However, if one compares the therapeutic efficacy in stages 1 and 2 with respect to the symptom-free status concerning nocturia and the obstructive voiding symptoms as well as the DRE concerning the prostatic size, a significant difference in favor of stage I was found (Table3). For patients with stage 3 BPH, a response rate between 28% and 63% was found, while a symptom-free status was found in 0 - 15% of patients (Table 3).

Unchanged positive symptoms and/or prostatic congestions (Non-responder) were found between 16.8% and 28.7% for patients with stage 1, 19.8% and 31.2% for patients with stage 2, and between 33.3% and 52.7% for patients with stage 3 BPH. Unchanged positive symptoms were found more commonly in the obstructive symptom category. Considering these findings, the comparison between the different stages yielded significant differences ($p < 0.001$) for all parameters, with a weaker effect in particular for stage 3 patients and in comparing stage I with stage 2. Worsening of the status in up to 6.4% of the patients was found particularly in patients with stage 3 BPH.

Tab. 3 Overall treatment response rates (R) and symptom-free or negative DRE status (S) after treatment with Cernilton® in percent (rounded) of patients who initially had symptoms or findings on DRE.

Parameter	Patients (N) Stage 1/2/3	BPH 1		BPH 2		BPH 3	
		R (%)	S (%)	R (%)	S (%)	R (%)	S (%)
Nocturia	727/719/111	76	43	73	21	57	5
Frequency	746/693/108	82	48	89	34	63	12
Feeling of incomplete emptying	469/605/101	83	64	79	47	56	15
Urgency	449/454/ 83	79	60	79	56	59	33
Delayed voiding	645/701/111	72	46	73	27	54	5
Prolonged voiding	629/711/113	72	40	70	20	47	2
Weak stream	736/737/112	71	37	70	17	46	4
Postvoid dribbling	592/651/109	72	49	68	37	55	15
Prostatic enlargement	802/746/111	29	13	33	3	28	–
Prostatic congestion	504/495/ 74	75	55	68	38	51	16

An analysis of the time course showed for all parameters - with the exception of the size of the prostate - an increase in the rate of patients with a symptom-free status in regard to voiding symptoms and prostatic congestions at

24-week evaluation in comparison with the 12-week evaluation. The incremental rate of improvement between 12 and 24 weeks of treatment was 13 % to 24 % for stage 1, 10 % to 25 % for stage 2, and 1 % to 17 % for stage 3. There was no principle difference detected between stages 1 and 2. Fig. 1 illustrates the time course of one of the symptoms (nocturia) for the different stages of the disease throughout the treatment period. The mean severity index for this symptom is shown.

Residual Urine

Significant improvements in the amount of residual urine were noted under treatment with Cernilton® in patients with stages I and 2. A comparison between pre-treatment and post-treatment values in patients who had initially at least 20ml of residual urine revealed a mean decrease of 32.7ml (51 %) for stage 1, 43.1 ml (45 %) for stage 2, and 18.5 ml (13 %) for stage 3.

A time-course analysis in these patients showed for stages 1 and 2 a continuing decrease of the amount of residual urine under treatment. However, in patients with stage 3 BPH a worsening was noted at 24 weeks after an initial improvement (Fig.2). Analysis of variance revealed a significant difference when comparing the different stages of the disease ($p=0.016$). In patients with stage 2 BPH in comparison with stage 1, a more significant decrease of the residual urine volume was achieved after 24 weeks of treatment. In stage 1, 39.6 % of the patients with an initial residual urine volume of >20 ml had a residual urine volume of <20 ml at 24 weeks, while 25.0 % of patients with stage 2 achieved the same result. In patients with stage 3 BPH the residual urine volume was at the end of the treatment still significantly elevated. The degree of obstruction in this stage apparently does not allow a significant quantitative change of residual urine volume during treatment.

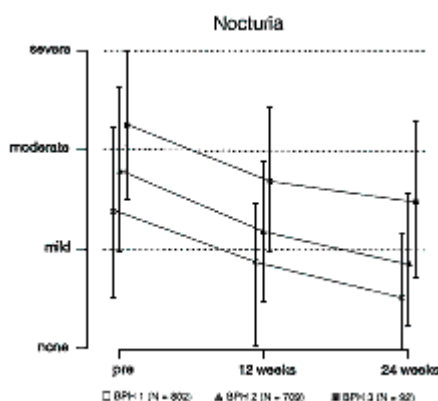


Fig.1 Nocturia (average intensity, $X \pm SA$) during 24 weeks of treatment in patients with stages 1, 2 and 3 BPH with Cernilton®. The intensity of the symptom decreases throughout the treatment in all three stages.

Adverse Effects

Adverse effects were noted in 15 patients for an incidence of 0.8 %. Except for two cases without specific documentation, the adverse effects were mainly gastrointestinal symptoms (stomach pain, pressure sensation, nausea, diarrhea, and indigestion). Treatment was terminated because of adverse effects after 12 weeks in four patients.

Global Assessment of Efficacy and Tolerance

Independent of the stage of the disease, tolerance was judged to be good in over 99 % of patients. There were statistically significant differences in the judgment of the treating physicians concerning the efficacy across the three stages (Fig. 3). The subjective assessment of the patients showed in principal a similar distribution of the results, but was overall somewhat more favorable when compared to the physicians' judgment. While the treatment result in patients with stages 1 and 2 BPH was judged as positive in over 90 %, it was judged as poor in 35 % of patients with stage 3. The main reasons for the treatment failure were advanced stage of the disease, need for surgery, psychogenic problems, bacterial prostatitis, and non-compliance of the patient.

Discussion

Reports in the urological literature document that several so-called conservative treatment options for BPH compete for both physicians and patients with BPH. Results following balloon dilation of the prostate, insertion of urethral spirals or stents made of surgical steel mesh in the prostatic urethra, thermotherapy, and drug treatment have been reported. Balloon dilation (15), insertion of spirals (11,18), or stents, (24), improved micturition only temporarily. Thermotherapy has apparently not yet reached practical applicability in the treatment of BPH (7,13,16,21).

If all these methods fail, oftentimes transurethral or suprapubic catheterization is a method of last resort. However, patients usually do not tolerate a permanent catheter over a long duration. This leaves the different drug treatments amongst which the low-risk phytotherapeutic drugs have a permanent place (2).

The use of these drugs is justified by good treatment results documented in case reports, open-label clinical studies, or prospective placebo-controlled double-blind studies. Criticism has been raised stating that the number of placebo-controlled studies is too low to prove the efficacy of the treatment (10). The placebo effect, which has to be taken into account with all drug treatments, is superimposed over the actual drug effect, and therefore no clear determination as to the efficacy of these drugs can be made.

However, concerning the pollen extract preparation, Cernilton®, experimental *in vitro* and *in vivo* data, and clinical documentation of effectiveness are available. An inhibition of the prostaglandin and leukotrien synthesis (17), an inhibition of the enzymes 5 α -Reductase, 3 α - and 3 β -Hydroxysteroid-dihydroxygenase (22), an anti-proliferative effect on BPH cells (12), as well as on BPH heterotransplants (23), and a significantly better efficacy of verum as compared to placebo in regard to nocturia, residual urine, and the global assessment of the treatment results have been reported (5,9). The following discussion therefore aims at the question of the clinical relevance and the indication for the use of phytopharmaca in the treatment of BPH.

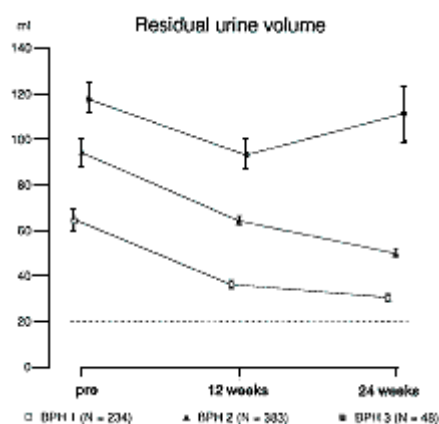


Fig.2 Residual urine volume ($X \pm SEM$) during 24 weeks of treatment in patients with stages 1, 2, and 3 BPH with Cernilton®. Continuing decrease of residual urine volume in stages 1 and 2, and a worsening after initial improvement during the first 12 weeks in stage 3 patients are observed.

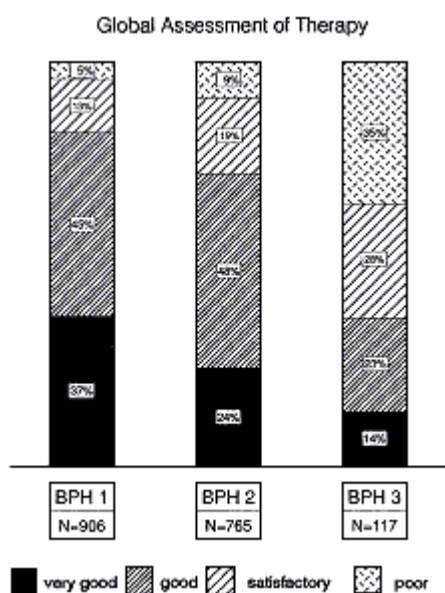


Fig. 3 Overall assessment of the efficacy of Cernilton® in 1,788 patients with BPH by physicians stratified by stage.

The present report details the observation made by 208 practicing physicians during the treatment of 1,933 BPH patients with Cernilton®. Under the conditions of routine clinical practice, it can be shown that irritative and obstructive voiding symptoms, prostatic congestion, and the residual urine volume are significantly improved, depending on the stage of the disease.

When comparing the results with those of controlled clinical trials, the response rates and the percentage of patients who achieve a symptom-free status or whose clinical findings become negative are higher in the present report. This may be explainable by the patient selection necessary for clinical studies. However, except for the symptom of frequency, which may be judged differently because of inconsistencies in its definition, there are no principal differences and therefore the data of the present study remain valid.

Concerning the symptoms, it is noted that the irritative symptoms show the largest margin of improvement, and patients with stage 1 BPH obtain the most benefit. Since irritative and obstructive symptoms are often equally common in patients with stage 2 BPH, these subjective voiding symptoms also improve significantly in patients with stage 2 BPH.

The clinical course of the voiding symptoms indicates that with the progression of the disease, obstructive symptoms increase and become more important in comparison to irritative symptoms. In regard to the therapeutic effect, this results in a lower percentage of patients achieving a symptom-free status in those men with stage 2 disease. In this group, prostatic congestion is also usually more pronounced.

In contrast to this, the residual urine volume decreases both absolutely and relatively more in patients with stage 2 disease than in patients with stage 1 disease. This may explain the relatively small differences in the global assessment of the therapeutic results stratified by these stages of the disease. The course over 24 weeks of treatment indicates that the residual urine decreases in particular in patients with stage 2 BPH between week 12 and 24. The percentage of patients with improved or symptom-free status further increases during the second half of the treatment course. These results document therefore a relatively better efficacy of the treatment in stages 1 and 2 BPH during long-term therapy.

The clinical relevance of a therapeutic strategy is significantly impacted by the improvement of the quality of life as defined by the patient. The improvement of the voiding dysfunction is reflected in the overall global subjective assessment of the therapeutic result by the patient. If

curative surgery is not medically indicated - this has to be decided for each individual patient - and an immediate surgical intervention independent of the stage of the disease is not necessary given the availability of continued monitoring of the patient (3), the results of the present study indicate that patients with stage 1 and 2 BPH according to *Alken* represent a classical target group for the treatment with phytotherapeutic drugs. The impact of the treatment on prostatic congestion and associated inflammation is thereby the main focus of this treatment regimen (1).

The treatment of BPH with phytotherapeutic drugs is well tolerated and represents a treatment option with few risks. Therefore, a treatment trial may be justified even in patients with stage 3 BPH until the time of definite surgical treatment. In more than one-half of these patients some improvement in symptoms and a minor decrease in the amount of residual urine can be achieved. Phytotherapeutic drugs are not suitable for long-term treatment of patients at prohibitive surgical risk.

Summary

To examine the possibilities and limitations of phytotherapy for benign prostatic hyperplasia (BPH) a 24-week treatment trial using the pollen extract preparation Cernilton® was conducted. Based on 1,798 cases a significant improvement in voiding symptoms, palpable prostatic congestion, and residual urine could be documented in stages 1 and 2. In patients with stage 3, the improvement in voiding symptoms was rather limited, as expected. When comparing the results after 12 and 24 weeks of treatment, a continuing improvement of all parameters during the second 12 weeks of treatment was noted. The drug was tolerated well in over 99% of patients. The efficacy in stages 1 and 2 was judged to be satisfactory, good or very good by over 90% of the patients. Because of the lack of conservative treatment alternatives for patients with BPH, treatment with phytotherapeutic drugs with their associated minimal risks is recommended as one of the prime treatment modalities for patients with BPH who are under continued medical care and monitoring. Until surgery, a treatment trial is also justified in patients with stage 3.

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