

## Treatment of Outflow Tract Obstruction Due To Benign Prostatic Hyperplasia with the Pollen Extract, Cernilton® - A Double-Blind, Placebo-Controlled Study

A. C. Buck, R. W. M. Rees, L. Ebeling, A. John

From numerous experimental studies in animals and clinical studies in man there is unequivocal evidence for the role of androgens in the development of benign prostatic hyperplasia, but the precise hormonal interactions which initiate or, indeed, sustain these changes in the prostate gland are unknown (Wilson, 1980; Habib et al., 1981; Stone et al., 1986). The symptoms that ensue from BPH are variable and bear little relation to the size of the gland. They can be either obstructive or functional and irritative, owing to concomitant detrusor instability and alpha-adrenergic overactivity of the sympathetic innervation of the bladder neck and prostatic musculature. The medical approach to the treatment of symptomatic BPH has been both endocrine and neuropharmacological.

More than 30,000 prostatectomies are performed in the UK every year and approximately 10 times that number in the USA. Because of the large number of patients with moderate or mild symptoms of prostatic outflow obstruction awaiting surgery and a clearer insight into the pathophysiology of "prostatism", interest has been rekindled in the medical management of BPH with either hormonal manipulation or adrenergic blockade (Lancet, 1988). Reports of the efficacy of the pollen extract, Cernilton, in the symptomatic relief of BPH (Takeuchi et al., 1981; Becker and Ebeling, 1988) prompted us to carry out a placebo-controlled, doubleblind study to evaluate its effect in patients with outflow obstruction due to BPH.

### Patients and Methods

Sixty patients awaiting operative treatment for outflow obstruction due to benign enlargement of the prostate were entered into a double-blind, placebo-controlled study. Their ages ranged from 56 to 89 years (mean  $68.6 \pm SD 7.7$ ). The patients consented to enter the study and their family doctors were informed. Cernilton and a placebo were administered in a dose of 2 capsules bd over a 6-month period.

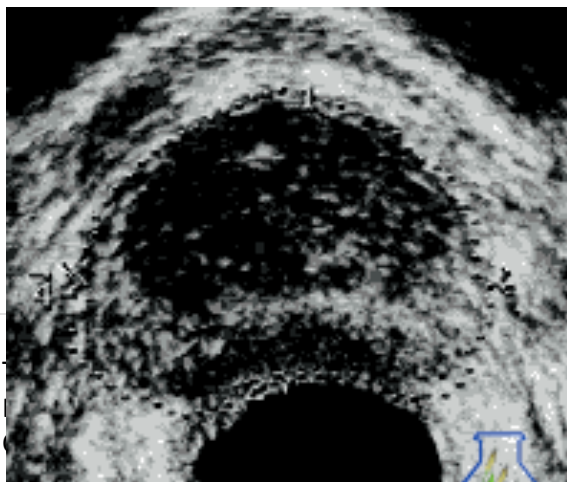
The objective criteria for the evaluation of outflow obstruction were (i) the urine flow rate (an accurate measurement of flow rate required a minimum voided volume of 150 ml. With volumes < 150 ml the flow rate was repeated twice with the sensation of a full bladder and the mean of 3 readings taken as representative of the flow rate); (ii) the voided volume; (iii) an ultrasound measurement of residual urine; (iv) ultrasound measurement of prostate size by transrectal ultrasound probe using the Kretz ultrasound equipment. The prostate was

scanned from the level of the seminal vesicles at the base of the prostate to its apex. An image of the prostate at its largest dimension was frozen on the screen and the outline of the prostatic image was circumscribed and measured in mm; the antero-posterior and transverse diameters were recorded (Fig. 1).

Subjective assessment was based on a modified "Boyarsky" scoring scale, as recommended by the Food and Drug Administration, for the symptoms of frequency, hesitancy, urgency, intermittency, incomplete emptying, terminal dribbling and dysuria, with a score of 0-3 for each of these symptoms (0 being an absence of symptoms and 3 being the most severe; see Appendix) (Boyarsky et al., 1977).

In addition, a full haematological and biochemical profile was performed, including liver function tests and serum cholesterol, triglycerides, high and low density lipo-proteins. All blood samples were obtained between 09.00 and 10.00 h, following an overnight fast. The investigations were performed before the patients began treatment with either active compound or placebo, again at 3 months and finally at the conclusion of the study. The study was commenced and completed within a 7-month period, from October 1987 to April 1988. All urodynamic and ultrasound measurements were performed by one observer (A.C.B.) but the subjective evaluation was done by 2 clinicians independently.

### Statistical Method and Analysis



The statistical analysis was divided into 5 sections dealing with (i) the homogeneity of demographic distribution and clinical presentation, (ii) the homogeneity of baseline findings, (iii) therapeutic measurements and trial course, (iv) assessment of efficacy and (v) assessment of safety and tolerance.

The tests for comparability of the trial groups were carried out by means of X2 tests for categorical data, X2 test with Yates' correction (4-fold tables) and Student's t test for continuous data. The comparison of trial groups with regard to symptoms was carried out by means of the X2 test. The changes in urodynamic and ultrasound data, and in laboratory and clinical parameters in both groups, were compared using analysis of variance. All tests were performed using the 5% level of significance.

### Results

Of the 60 patients entered into the study, 3 were excluded after the initial assessment: the first had an iron deficiency anaemia caused by gastrointestinal bleeding that required further investigation and treatment; the second patient had undergone an abdominoperineal resection for carcinoma of the rectum which precluded objective evaluation of the prostate and the third patient decided against continuing in the study. Thus 57 patients took part. There were 31 patients in the Cernilton arm and 26 in the placebo arm. During the course of the study a further 4 patients were excluded: 2 in the placebo arm were admitted with acute retention of urine and underwent transurethral resection of the prostate (TURP); 1 patient in the Cernilton arm was admitted with acute epididymitis that was considered to be unrelated to the trial procedure and another patient was admitted with acute retention of urine and underwent a TURP. Fifty-three patients were fully evaluable at the end of 6 months, 29 in the Cernilton arm and 24 in the placebo arm.

With regard to the stratification of patients, the 2 groups were evenly matched with respect to demographic data, clinical presentation, symptoms, laboratory investigations and objective evaluation with the exception that the patients in the Cernilton arm had a higher mean body weight (P0.05).

### Subjective Evaluation

There was no statistical difference in the symptoms of diurnal frequency between the 2 groups (P = 0.66), but 60 % of patients on Cernilton were improved or symptom-free as regards nocturia compared with 30 % of patients on placebo (P < 0.063). On Cernilton, 57% of patients showed improvement in bladder emptying compared with only 10 % in the placebo group (P < 0.004). There were no significant differences in hesitancy (P= 0.48), urgency (P=0.157), intermittency (P= 0.5), terminal dribbling (P = 0.9) or dysuria (P = 1.0). There was a statistically significant overall improvement in subjective symptoms in the Cernilton group (69 % of patients) compared with patients in the placebo group (29 %) (P < 0.009) (Table 1).

Tab. 1 Frequency of Symptom-free Findings following C and Placebo at 6

Symptom	Response Rate (%)		P value
	Cernilton	Placebo	
Frequency	37	47	0.664
Daytime	60	30.4	0.063*
Nocturia	47	29	0.480
Hesitancy	71	45	0.157
Urgency	52	33	0.505
Intermittency	57	10	0.004*
Incomplete emptying	61	56	0.59
Terminal dribble	62	71	1.0
Dysuria			

\*Statistically significant. Some test results remained non-sig because of the small number of positive findings before the treatment.

### Objective Evaluation

The results of peak urine flow rate, voided volume and residual urine in the 2 groups of patients before and after treatment are shown in Table 2. There was no significant change in peak urine flow rate (both groups showed a slight increase) or voided volume (slight decrease after Cernilton and a slight increase with placebo) before and after treatment in the 2 groups. However, residual urine volume decreased significantly in the patients receiving

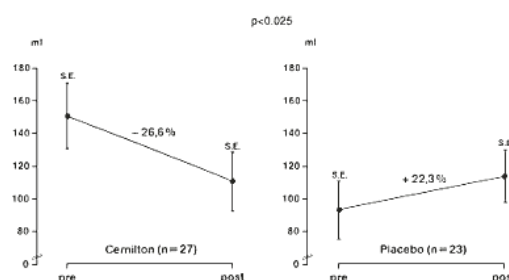


Fig.2 Residual urine volume.

Cernilton compared with the placebo group, in whom it increased (P < 0.025) (Fig. 2)

The results of ultrasound measurement of the parameters for prostate volume are shown in Table3. The A-P diameter was found to be significantly reduced after treatment with Cernilton at 6 months (P<0.025) (Fig. 3).

There were no significant changes in the haematological or biochemical measurements in either group. No significant changes in serum cholesterol, triglyceride or lipoprotein values were observed with Cernilton and no adverse side effects were reported.

### Discussion

Transurethral resection or open prostatectomy undoubtedly remains the most effective treatment for BPH but is not without complications in both the short and longer term,



decrease in the size of the ventral and dorsal lobes of the prostate gland accompanied by histological evidence of epithelial cell atrophy, a significant fall in total and prostatic acid phosphatase, with a significant increase in the zinc concentration in the dorsal lobe of the prostate and in blood in mature Wistar rats compared with the control animals (Ito et al., 1986). Habib et al. (1990) reported the inhibition of immortal human cell line growth in culture derived from prostate carcinoma in the presence of T-60. The hormone-stimulated growth of BPH tissue transplanted into nude mice is significantly inhibited by Cernilton extract but no histological differences were observed between the treated and untreated groups (Otto, et al., 1990). Despite the results of these experimental studies there have been no clinical studies to indicate that Cernilton has any influence on hormonal metabolism in man. In the present investigation the levels of LH, FSH, testosterone and DHT were unchanged, but the possibility that it acts on hormone-dependent target organs cannot be ruled out. The significant decrease in the A-P diameter of the prostate in patients treated with Cernilton suggests that prostate size was reduced with treatment, even within the short time of the trial period. Adenomatous hyperplasia takes several years to develop and a dramatic regression could be expected only with total androgen deprivation. In a placebo controlled study, Cernilton was reported to lower the levels of serum cholesterol and low density lipoprotein (LDL) (Ockerman, personal communication) but we were unable to show any difference in these lipid fractions between the 2 groups in this study, carried out under strict fasting conditions.

Kimura et al. (1986) observed that T-60 and GBX produced relaxation of the smooth muscle of the mouse and pig urethra and increased the contraction of the bladder muscle in a concentration-dependent manner. These studies were confirmed by Nakase et al. (1988), using rat vesicourethral and external urethral muscle strips; they showed that T-60 and GBX inhibited the contraction of muscle induced by noradrenaline bitartrate, with evidence for competitive antagonism of noradrenalin at the site of adrenergic receptors. Thus the subjective improvement in symptoms of nocturia and bladder emptying could be due to the effect of Cernilton on the rich adrenergic innervation of the bladder neck and prostate.

The precise mode of action of Cernilton in BPH is not known and further studies to determine its pharmacological action are in progress. However, this double-blind placebo-controlled study has shown distinct subjective and objective improvement with a positive response in the Cernilton group. As with other studies to evaluate the effect of drugs in BPH, there was a 30% subjective improvement in patients in the placebo arm of the study, which highlights the need for placebo control. In addition, we studied all of the patients together within a 7-month period in order to synchronise the times of serial evaluation and thus to eliminate the marked effect that seasonal variation can have on the symptomatology of this condition. A longer duration of treatment or a larger dosage may produce a more pronounced benefit and Cernilton, which appears to have no untoward side effects, may prove to be a useful agent in alleviating the early symptoms of outflow tract obstruction due to BPH.

### Acknowledgements

We thank Mr. Golding of Kretztechnik (UK) for his generous help in supplying the ultrasound equipment. Our thanks are also due to Dr. J. Schnitker and Dr. H.-F. Koch, of the Institut fir

Tab. 3 Measurements of Prostate Volume

Prostate size	Time of examination	Cernilton		Placebo		Analysis of variance (P value)
		$\bar{X}$	SE	$\bar{X}$	SE	
Circumference (mm)	Before treatment	(n = 29) 169.6	26.3	(n = 17) 163.2	16.2	0.446
	After treatment	153.4	27.5	150.5	21.6	
Transverse diameter (mm)	Before treatment	(n = 29) 56.4	8.3	(n = 24) 53.8	8.1	0.753
	After treatment	52.2	9.7	50.3	8.1	
Anteroposterior diameter (mm)	Before treatment	(n = 29) 29.1	5.3	(n = 24) 28.3	7.4	0.025*
	After treatment	23.8	7.0	26.7	9.1	

\* Benign Prostatic Hyperplasia with the Pollen Extract, Cernilton – A double blind placebo Controlled study

Angewandte Statistik Dr. Jörg Schnitker GmbH,  
for statistical analysis of this work.

## Summary

Whilst prostatectomy remains the "gold standard" for the treatment of outflow tract obstruction due to benign prostatic hyperplasia, medical treatment - if only for symptomatic relief - appears to be an attractive alternative. Most of the pharmacological agents in use block the hormonal or the sympathetic neurological pathways that influence prostate growth and function. All of these drugs are known to have side effects.

Sixty patients with outflow obstruction due to benign prostatic hyperplasia (BPH) were entered into a double-blind, placebo controlled study to evaluate the effect of a 6-month course of the pollen extract, Cernilton. There was a statistically significant subjective improvement with Cernilton (69 % of the patients) compared with placebo (30 %). There was a significant decrease in residual urine in the patients treated with Cernilton and in the antero-posterior (A-P) diameter of the prostate on ultrasound. However, differences in respect of flow rate and voided volume were not statistically significant. It is concluded that Cernilton has a beneficial effect in BPH and may have a place in the treatment of patients with mild or moderate symptoms of outflow obstruction.

## Appendix

### Daytime Frequency

- 0- 1 to 4 times daily
- 1- 5 to 7 times daily
- 2- 8 to 12 times daily
- 3-13 or > times daily

### Nocturia

- 0 - absence of symptoms
- 1 - subject awakened once each night because of the need to urinate
- 2 - subject awakened 2 to 3 times each night
- 3 - subject awakened 4 or > times each night

### Hesitancy

- 0 -occasional hesitancy (occurs in 20 % or fewer of subject's attempts to void)
- 1 - moderate hesitancy (occurs during 20 to 50 % of subject's attempts to void)
- 2 - frequent hesitancy (occurs more than 50 % of subject's attempts to void)
- 3 - symptoms always present, lasts for 1 minute or longer

### Urgency

- 0 - absence of symptoms
- 1 - occasionally difficult for subject to postpone urination
- 2 - frequently difficult (more than 50 % of the time) to postpone urination and may rarely loose urine
- 3 - always difficult to postpone urination and subject sometimes loses urine.

### Intermittency

- 0 - occasional intermittency (occurs in 20 % or fewer of subject's attempts to void)
- 1 - moderate interm-dttency (occurs during 20 to 50 % of subject's attempts to void)
- 2 - frequent intermittency (occurs more than 50 % of the time, but not always, and may last up to 1 n-dnute)
- 3 - symptoms always present, lasts for 1 minute or longer

#### Incomplete Emptying

0 - absence of symptoms

1 - occasional sensation of incomplete emptying of bladder after voiding

2 - frequent (more than 50 % of the time) sensation of incomplete voiding

3 - constant and urgent sensation and no relief upon voiding

#### Terminal Dribbling

0 - occasional terminal dribble (occurs in 20 % or less of the subject's attempts at voiding)

1 - moderate terminal dribble (occurs in 20 to 50 % of subject's voiding)

2 - frequent terminal dribble (occurs in more than 50 % of the time but not always)

3 - symptom always present, dribbling lasts for 1 minute or more, or wets clothes

#### Dysuria

0 - absence of symptoms

1 - occasional burning sensation during urination

2 - frequent (more than 50 % of the time) burning sensation during urination

3 - frequent and painful burning sensation during urination

\* Published in Brit.J. Urol. 66 (1990) 398-404

