



PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Results of Treatment with Pollen Extract (Cernilton® N) in Chronic Prostatitis and Prostatodynia

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Summary— We report the results of a prospective study with the pollen extract, Cernilton® N, in a dose of 1 tablet *tid* for 6 months for the treatment of chronic prostatitis syndrome in 90 patients. The factors documented before and after 3 and 6 months' treatment were digital rectal examination (DRE) of the prostate, uroflowmetry, bacterial studies, leucocyte counts in urine and measurement of complement C3/coeruloplasmin in the seminal fluid.

The patients were divided into 2 groups: those without associated complicating factors (CFs) (n=72) and those with complicating factors, i.e. urethral strictures, prostatic calculi, bladder neck sclerosis (n=18). In the group without CFs, 56 (78%) had a favourable response; 26 (36%) were cured of their symptoms and signs and 30 (42%) improved significantly with an increase in flow rate, a reduction in leukocyturia in post-prostate massage urine (VB3) and a decrease in complement C3/coeruloplasmin in the ejaculate. In the patients with CFs only 1 patient showed a response. Complicating factors should be considered in patients who fail to respond to treatment within 3 months. Cernilton® N was well tolerated by 97% of patients.

Controversy surrounds the aetiology and clinical significance of the painful prostate and the diagnosis of chronic prostatitis and prostatodynia is seldom based on sound diagnostic criteria (Drach, 1980). Even when the diagnosis of chronic bacterial or non-bacterial prostatitis and prostatodynia has been reached, the results of treatment are often disappointing (Pfau, 1986).

Clinical studies with the pollen extract, Cernilton® N (A.B. Cernelle, Sweden), have revealed symptomatic improvement in prostatic inflammatory disease and benign prostatic hyperplasia (Denis, 1966; Ebeling, 1986; Becker and Ebeling, 1988, 1991; Buck *et. al.*, 1989, 1990). We present the results of a prospective study on the efficacy of Cernilton® N in the treatment of chronic non-bacterial prostatitis and prostatodynia.

Patients and Methods

Ninety patients aged from 19 to 90 years (mean 47.2±SD 17.6) with symptoms of prostatitis of at least 1 year's duration, in whom bacterial localization studies were negative, were entered

into the study. Thirty patients had had at least 2 previous episodes of bacterial prostatitis and/or urinary tract infection treated with antibiotics, but were entered into the study during an infection-free period.

The diagnosis was based upon bacterial localization studies of pre- and post-massage urine samples and expressed prostatic secretion (EPS) (Meares and Stamey, 1968). Leucocyte counts in the sediment from the first voided 10 ml of urine (VB1), mid-stream urine (VB2) and first voided 10 ml of after massage (VB3) were performed using a counting chamber and calculating the number of leucocytes/μl (MD-Kova-system^R) Sieck, 1983).

Additional investigation (ultrasonography, voiding and/or retrograde cystourethrography and endoscopy) revealed other pathology in 18 patients. These complicating factors were bladder neck sclerosis (10), urethral strictures (5) and extensive prostatic calcification (3). Eight patients had undergone a previous transurethral or open prostatectomy (7 for benign prostatic hyperplasia (BPH) and 1 for chronic prostatitis).

Forty-four patients (49%) had received treatment with various drugs, including antibiotics, anti-inflammatory agents and other empirical remedies, during the 3 months prior to entering the trial; 37 patients had improved.

Cernilton® N (Pharma Stroschein (licensed by Cernitin SA, Lugano, Switzerland; Hamburg, Germany) was given in a dose of 1 tablet *tid* and in most cases treatment was continued for 6 months. The following factors were recorded before treatment and after 3 and 6 months' therapy: (i) symptoms of discomfort and pain were graded as absent, mild, moderate and severe; (ii) nocturia, frequency and dysuria were scored according to Boyarsky *et al.* (1977); (iii) the findings of rectal palpation of the prostate; (iv) uroflowmetry; (v) leucocyturia in VB2 and VB3; (vi) bacteriuria; (vii) complement C3 and coeruloplasmin in the ejaculate (scored semi-quantitatively combining the values of complement C3/coeruloplasmin/dl according to a modified scheme of Blenk and Hofstetter (1975) as follows; 1 =<1.5 mg/negative; 2=1.5- <2 mg/ <0.5 mg; 3=2-4 mg/ 0.5-1 mg; 4=3-8 mg/>1-3 mg).

Complement C3 and coeruloplasmin were determined after the ejaculate had been liquefied and centrifuged for 5 min at 11,266 U/min resp. at 10,500 g. The radial immunodiffusion of the supernatant sample was performed with LC-Partigen® C 3c and LC-Partigen® plates (Behringwerke AG, Marburg, Germany). In addition to the sample, a control from calibrated standard serum was placed on the plates (dilution 1:20 for complement C3, dilution 1:11 for coeruloplasmin). The amount of complement C3 and coeruloplasmin was calculated from the diameter of the same precipitate according to the calibration curve from calibrated standard serum of complement C3 and coeruloplasmin (Behringwerke AG, Marburg, Germany).

A "cure" was defined as a complete response with a return to normal of all factors, an "improvement" as a partial symptomatic and objective response and "no improvement" as persistence of symptoms or signs or deterioration. The biometrical evaluation was performed by descriptive analysis of the factors before and after treatment as well as a comparison of changes at 3 months and 6 months. The following tests were used: (i) the *t* test for related samples for a comparison of

uroflow measurements; (ii) the Wilcoxon matched-pairs signed-rank test using χ^2 approximation for comparison of the leucocytes in VB3; (iii) the sign test for the scored complement C3/coeruloplasmin in the ejaculate; (iv) the Pawlik corrected contingency coefficient for qualitative and the Spearman rank correlation coefficient for quantitative correspondence between the changes of leucocyturia in VB3 and the peak urine flow rate.

Results

At the commencement of the study the patients' clinical symptoms were mainly moderate or mild; the prostate was enlarged in 56% and tender in 94%. On the basis of significant differences at initial presentation and the response to treatment the patients were separated into 2 groups: those without (n=72) and those with (n=18) complicating factors. Complement C3 in the ejaculate was >1.5 mg/dl in all cases.

Symptoms

Almost all of the patients complained of frequency and dysuria, while pain was present in about two-thirds. Patients with associated CFs responded poorly to treatment, whereas in those without CFs the symptoms were markedly reduced after 6 months' treatment (Table 1).

In patients without CFs the prostate reverted to a normal size in 15/39 cases; its consistency improved in 37/68 cases and it was no longer tender on palpation in 47/71 cases after treatment. These signs worsened in 5 patients. The findings on palpation of the prostate in the group with associated CFs were either unchanged or had deteriorated.

Table 1 Response to Treatment in 72 Patients without Complicating Factors

Symptom	Cured (%)	Improved (%)	No.
Discomfort	68	9	53
Pain	69	12	49
Nocturia	56	30	54
Frequency	49	26	72
Dysuria	52	12	69

Uroflowmetry

In contrast to the patients with CFs, where all uroflow parameters became worse, there was a significant improvement in the time to peak flow and increased voided volume in the patients without CFs ($P < 0.05$). Micturition and flow time remained unchanged. In patients with CFs the peak urine flow rate showed a slight decrease from 11.9 ± 3.9 to 10.5 ± 2.6 ($\bar{x} \pm SD$). In patients without CFs the mean peak flow rate before treatment was $15.9 \pm SD 5.2$ ml/s; this increased to $19.0 \pm SD 7.2$ ml/s at 3 months ($P < 0.001$) and to $23.9 \pm SD 10.6$ ml/s at 6 months ($P < 0.001$; comparing 6 with 3 months: $P < 0.001$).

Leucocyturia in VB3 (L-VB3)

In patients with CFs the L-VB3 increased from a median of 80 to 185 leucocytes/ μ l ($P < 0.001$). Comparing the number of leucocytes before and after treatment in patients without CFs the L-VB3 decreased from a median of 50 to 20 leucocytes/ μ l ($P < 0.001$). In these patients the pre-treatment mean leucocyte count fell from $85 \pm SD 89.9$ leucocytes/ μ l to $69.1 \pm SD 121.8$ at 3 months and to $42.2 \pm SD 62.6$ leucocytes/ μ l at 6 months (control vs 3 vs 6 months $P < 0.001$; comparing 6 with 3 months: $P < 0.001$). The individual changes documented separately as pre and post values at different baseline levels of leucocyturia, *i.e.* < 50 , 50-99, 100-1000 leucocytes/ μ l, are shown in Figure 1.

L-VB3 and PUFRR (peak urine flow rate)

Correlation of the changes in L-VB3 with the PUFRR in patients without CFs showed that the leucocyte count decreased in 52 cases while the PUFRR increased, but the PUFRR fell in 3 patients. An increase in L-VB3 occurred together with a decrease in PUFRR in 8 cases and an increase in PUFRR in 9 cases. There was a highly significant negative correlation between L-VB3 and PUFRR (CC corr= 0.720; $r = -0.56$). Because of the wide distribution pattern of the leucocytes in VB3, individual differences between the baseline values and the control after treatment were ranked separately for L-VB3 and PUFRR according to the definition of rank 1 as the strongest increase plotted as the combined ranks of the individual changes for both parameters (Fig.2).

Complement C3/coeruloplsmn

Patients without CFs showed a decrease in complement C3/coeruloplasmin in the ejaculate after 3 months ($P < 0.001$) and a further decrease after 6 months ($P < 0.001$; comparing 6 with 3 months: $P = 0.005$). Patients with CFs showed an increase in these indices of inflammation ($P = 0.07$) (Table 2).

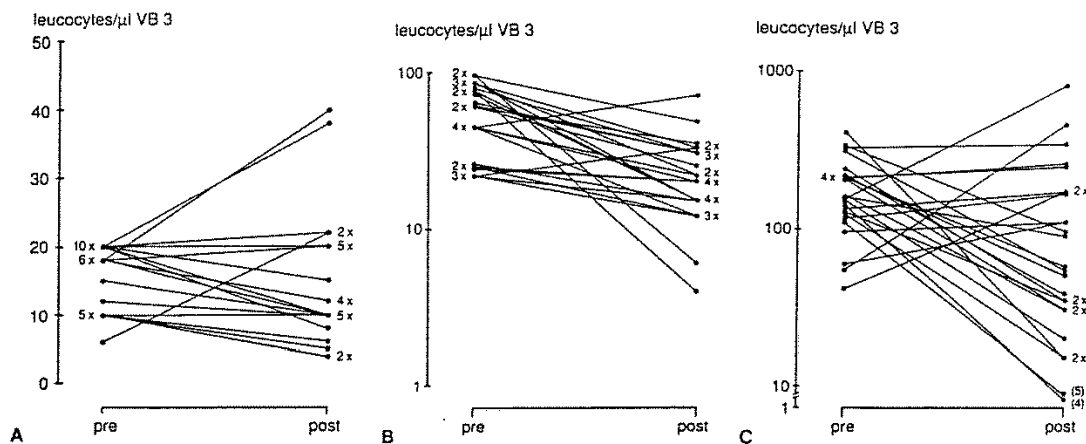


Fig. 1 Individual courses of leucocyturia in VB3 in 72 patients without complicating factors, plotted separately according to baseline values (pre: < 50 , 50-99, 100-1000 leucocytes/ μ l) or control (post) values. The numbers on the left and right sides of the lines refer to the number of patients with the corresponding baseline or post-treatment value, *e.g.* 10 \times in Figure 1A represents 10 patients with the same baseline value of 20 leucocytes/ μ l VB3. The numbers (5) and (4) in Figure 1C represent the post-treatment values of leucocytes/ μ l VB3 in 2 patients which are not assessable from the Figure owing to the broken axis of ordinate.

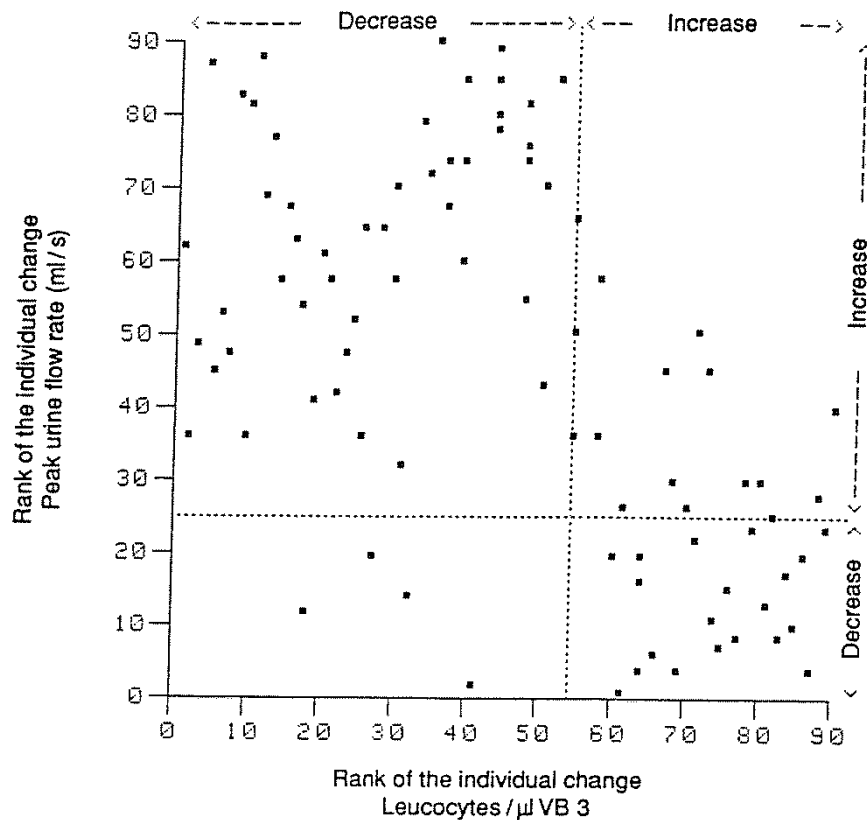


Fig. 2 Scattergram of the combined ranked individual changes in leucocyturia in VB3 (L-VB3) and peak urine flow rate (PUFR) in 90 patients with chronic prostatitis syndrome comparing the values before and after treatment. High inverse qualitative ($CC_{corr} = 0.720$) and quantitative ($r_s = 0.565$) correlation between the changes of L-VB3 and PUFR. Rank 1 = strongest decrease, rank 90 = strongest increase, parallel lines to ordinates = no change (conversion point).

Table 2 Complement C3/coeruloplasmin/dl Ejaculate before and after 3 ($P < 0.001$) resp. 6 Months ($P < 0.001$; $P = 0.005$ comparing 6 with 3 months) of Treatment in Patients without Complicating Factors and before and after Treatment in Patients with Complicating Factors (CF) ($P = 0.07$)

Complement C3/coeruloplasmin	No CF			With CF	
	Pre No.	3 months No.	6 months No.	Pre No.	Post No.
< 1.5 mg/negative	—	3	11	—	—
1.5–<2.0 mg/<0.5 mg	8	36	40	4	—
2.0–<4.0 mg/<0.5–1 mg	46	30	13	11	9
3.0–<8.0 mg/<1–3 mg	17	2	5	1	7
Missing values	1	1	3	2	2

Assessment of efficacy

There was an overall clinical response in 56/72 patients (78%) without CFs; 26 of these (36%) were cured of symptoms and signs and the

remainder (42%) were improved. In 16 patients (22%) there was no response. In patients with CFs only 1 improved and the remaining 17 showed no response. Treatment was discontinued in 12 patients because of an ineffective response or clinical deterioration. The most frequent cause of deterioration was symptomatic bacteriuria (83%) and these

patients were treated with antibacterial therapy. CFs were present in 67% of all patients in whom treatment was discontinued.

Treatment was well tolerated by 97% of patients. Three complained of a mild to moderate degree of meteorism, heartburn or nausea which did not require discontinuation of treatment.

Discussion

Cernilton[®] N was found to be effective in the treatment of patients with chronic non-bacterial prostatitis and prostatodynia. Patients with complicating factors due to incidental lower urinary tract pathology (e.g. bladder neck sclerosis, urethral stricture or extensive prostatic calcification) failed to respond and a high percentage of these developed bacteriuria.

Complement C3 in the ejaculate is regarded as an extremely sensitive index of an inflammatory process in the prostate or adnexae (Blenk and Hofstetter, 1991), even in patients with minor and/ or focal pathological changes within the gland that do not necessarily lead to an increase in the number of leucocytes in the expressed prostatic secretion or the VB3. Comparison of the baseline values of complement C3/coeruloplasmin and L-VB3 showed a high concentration of complement C3 in the ejaculate even in patients with a low leucocyte count in VB3 (i.e. prostatodynia). The decline in the complement C3/coeruloplasmin values with pollen extract in these patients suggests that inflammation of oedema may also be a feature of prostatodynia (di Trapani et al., 1988; Vahlensieck and Dworak, 1988).

Barbalias (1992) reported an increase in the maximum urethral closure pressure (MUCP) in patients with the prostatitis syndrome resulting in a simultaneous diminution in urinary flow rates. It is suggested that local inflammation may irritate adrenergic endings and cause a high MUCP. Our finding of an inverse correlation between inflammation and uroflow supports this hypothesis and the decrease in complement C3 leads us to speculate that local irritation may also be responsible in patients with prostatodynia. Takeuchi et al. (1981) reported a significant decrease in the MUCP from $92 \pm SD 23$ to $58 \pm SD 19$ cm H₂O with a reduction in the prostatic profile length and prostatic urethral resistance with pollen extract in patients with BPH. They concluded that this finding may be

related to the eradication of oedema and inflammation in the periurethral area.

Cernilton[®] N is an extract from several pollens. Its pharmacological action could be ascribed to inhibition of the cyclo-oxygenase and 5-lipoxygenase enzyme in the biosynthesis of prostaglandins and leucotrienes as demonstrated by the *in vitro* studies of Loschen and Ebeling (1991). A dose-related inhibition of noradrenaline-induced contractions of the rat and mouse urethra with pollen extract has been observed (Kimura et al., 1986; Nakase et al., 1988). In addition, extract of pollen was shown to inhibit the growth of the rat prostate and immortal prostate cancer cell lines in culture (Ito et al., 1986; Habib et al., 1990). From this broad spectrum of pharmacodynamic activity it is difficult at the present time to define a precise mode of action.

This study has shown a progressive improvement in the clinical course of patients with chronic prostatitis and prostatodynia over a 6-month period. This confirms the observation of Buck et al. (1989) that a 3-month period treatment with pollen extract is required before significant improvement occurs. This favourable response indicates that Cernilton[®] N has an important therapeutic role in the treatment of these conditions. Further studies are necessary to elucidate its precise mode of action.

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