Biometric Analysis of a Retrospective Documentation Study of Cernilton®N in the Treatment of Patients with Chronic Symptomatic Prostatitis

Schnitker J., Koch H.-F., Pall O.:

Study Director: Dr. Dr. med Erwin W. Rugendorff, Urologist
Ludwigsplatz 11, W-6300 GieBen 1, Germany

Coordinator: Leonardo Ebeling, Head of the Medical Dept./Clinical Research, Pharma Stroschein GmbH
Sellhopsweg 1, W-2000 Hamburg 61, Germany

Summary

A retrospective documentation study of the efficacy and tolerability of Cernilton®N in the treatment of chronic bacterial prostatitis was conducted by Dr.Dr.med. Erwin W. Rugendorff (Study Director), Giessen, Germany, between January and October 1988. The study included 40 patients between 23 and 69 years of age who were started on treatment with Cernilton®N between January and April 1988. The following parameters were determined before the start and at the end of Cernilton N therapy:

Clinical Features

- Discomfort
- Pain
- Nocturia
- Pollakiuria
- Dysuria

Uroflometry

- Micturition volume
- Peak urine flow
- Mean urine flow
- Flow time
- Micturition time
- Flow rise time
- Uroflow index

Findings on palpation

- Size of the prostate
- Consistency of the prostate
- Tenderness
- Tenderness of the prostate

Leukocyturia

- Leukocytes in midstream urine
- Leukocytes in post-massage urine

Bacteriuria

Ejaculate findings:

- C_{3c}/ ceruloplasmin
- IgG
- Antichlamydia IgA

Adverse drug reactions

Reasons for premature discontinuation of therapy

Assessment of tolerability and efficacy

Results

1. History

   - Acute bacterial infection: *n* = 32
   - TUR-P: *n* = 3
   - Prostatectomy: *n* = 0
   - Previous therapy in the preceeding 3 month: *n* = 15
   - Complicating factors: *n* = 14
     [1. Urethrostenosis: *n* = 4]
     [2. Prostatic calculi: *n* = 3]
     [3. Sclerosis of the bladder neck: *n* = 7]
   - Concomitant diseases: *n* = 8

2. Clinical features and laboratory parameters on admission:

   The patients complained of mild-to-moderate symptoms on admission. Uroflometry detected abnormalities (mean uroflow index = 0.91); the white cell count in the postmassage urine was significantly increased (range 45-610, median 128 WBC/ml); and the C_{3c}/ ceruloplasmin and IgG concentrations in the ejaculate were elevated.

3. Complicating factors:

   The clinical features were, to a large extent, influenced by the presence of complicating factors. While the incidence of manifest symptoms was lower before treatment, the impairment of urine flow was more pronounced.

4. Cernilton®N therapy:
   Cernilton®N therapy was provided on a fixed dosing regimen: 1 tablet t.i.d. The duration of therapy varied between 25 and 196 days; the median duration was 146 days. Treatment was discontinued prematurely in 24 cases for the following reasons:

   - Freedom from symptoms: *n* = 3
   - Marked improvement: *n* = 6

- Ineffectiveness: *n* = 1
- Exacerbation: *n* = 13
- Dropout for personal reasons: *n* = 1

Early dropout reasons are primarily ineffectiveness of therapy/ exacerbation of the disease, while the majority of the patients who discontinued therapy prematurely in the second quarter of the study had achieved either freedom from or a marked improvement in their complaints.

5. Changes in clinical features on Cernilton® N therapy:

In the absence of complicating factors, the following percentages achieved freedom from the following complaints on Cernilton® N therapy:

- Discomfort: 89.5%
- Pain: 83.3%
- Nocturia: 53.8%
- Pollakiuria: 56.0%
- Dysuria: 86.4%

In the presence of complicating factors, however, the response rates to Cernilton® N therapy was significantly lower.

6. Uroflometry:

In the absence of complicating factors, the urine flow parameters showed the following average improvements

- Micturition volume: - 6.1 ml
- Peak urine flow: + 3.0 ml/sec
- Mean urine flow: + 2.7 ml/sec
- Flow time: - 7.1 sec
- Micturition time: - 7.3 sec
- Flow rise time: - 3.0 sec
- Uroflow index: + 0.22

In the presence of complicating factors, uroflometry showed a slight tendency for deterioration. The between-subset (without vs. with complicating factors) differences proved to be significant for peak urine flow, mean urine flow, and uroflow index.

Thus, an increase in the uroflow index was reported for 92.0 percent of patients without complicating factors, while as few as 36.4 percent of those with complications achieved such an improvement.

7. Findings on palpation:
The subset of patients without complicating factors experienced marked improvements in the findings on palpation. Thus, 75.0 percent had nontender prostates after Cernilton® N therapy, while as few as 33 percent of the complicated cases were asymptomatic in this respect.

8. Leukocyturia:

Lower white cell counts in the urine were recorded for the following percentages of patients:

Midstream urine:

- Without complicating factors: 73.1%
- With complicating factors: 28.6%

Post-massage urine:

- Without complicating factors: 80.8%
- With complicating factors: 28.6%

9. Bacteriuria:

Bacteria were again found in the urine in the following percentages of patients:

- Without complicating factors: 15.4%
- With complicating factors: 49.9%

10. Ejaculate findings:

Reductions in the C_{3c}/ ceruloplasmin concentrations were determined for the following percentages of patients:

- Without complicating factors: 80.8%
- With complicating factors: 28.6%

IgG was elevated in

- 7.7% of the patients without complications
- 50.0% of the patients with complications

The majority of patients without complicating factors were either unchanged or achieved improvement.

12 . Antichlamydial IgA:

No change.

13. Adverse drug reactions:

There was no report of an adverse drug reaction.

14. Assessment of tolerability:

Tolerability was rated as good in 35 patients and as fair in 5.

15. Assessment of efficacy:

Efficacy was judged as follows:

Judgment	Without complications	With complications
Normalization	3 (11.5 %)	1 (7.1 %)
Improvement	18 (69.2 %)	3 (21.4 %)
No improvement	5 (19.2 %	10 (71.4 %)
Comparison	p = 0.005 (chi-square test)	

The response was

- 80.8% without complicating factors
- 28.6% with complicating factors

Table of Contents

1. Study Objective

A retrospective documentation study of the efficacy and tolerability of Cernilton® N in the treatment of chronic bacterial prostatitis was conducted.

The present exposé reports about the biometric analysis of the clinical data.

2. Methods

The present retrospective documentation study includes patients with chronic bacterial prostatitis started on Cernilton® N therapy between January and April 1988. The study parameters were determined at baseline (before the start of the study) and at the end of therapy. The study period was > = 6 months for non-dropouts.

Enclosed CRF shows the scope of the clinical and laboratory workup done in the individual patients.

Outcome is assessed by comparing the results obtained for the study parameters before and after treatment. In addition, a comparison is made between

- The patients without complicating factors
  and
- Those with complicating factors (urethrostenosis, prostatic calculi, sclerosis of the bladder neck).

These two subsets are compared by

- The chi-square test for frequency distributions;
- Student's t-test for baseline means and mean pre-post differences (parametric test); and
- The U-test for baseline medians and median pre-post differences (non-parametric test).

The nonparametric statistic is used for testing the white cell count per ml urine.

Both documented parameters and selected derived parameters are included in the statistical analysis.

- *Normal range of peak urine flow:*

  The reference value + -20% range is used as the normal range. The micturition volume-dependent reference values are as follows:

Micturition volume	Reference value
"200 ml" = < 250 ml	22.5 ml/sec
"300 ml" = 250 - < 350 ml	26 ml/sec
"400 ml" = 350 - < 450 ml	28 ml/sec
"500 ml" = > = 450 ml	30 ml/sec

- *Normal range of mean urine flow:*

  The reference value + -20% range is used as the normal range. The micturition volume-dependent reference values are as follows:

Micturition volume	Reference value
"200 ml" = < 250 ml	15 ml/sec
"300 ml" = 250 - < 350 ml	17 ml/sec
"400 ml" = 350 - < 450 ml	20 ml/sec
"500 ml" = > = 450 ml	23 ml/sec

- *Assessment of uroflow index:*

Normal:	> = 1.2
Reduced:	0.8 - < 1.2
Markedly reduced:	< 0.8

The uroflow index I is calculated from the following formula:

$$I = \frac{\text{peak urine flow + Mean urine flow}}{[(\text{micturition volume}/400) + 0.75] * 20}$$

- *Normal range of white cells in the urine:*

Normal:	< = 20 ml urine*
Elevated:	> 20 ml urine

*Urine: Midstream urine
Postmassage urine

- *Ejaculate IgG determination:*

Normal:	0 mg/dl
Elevated:	1 - 20 mg/dl
Markedly elevated:	> 20 mg/dl

3. Patients

The retrospective documentation study included 40 patients with chronic bacterial prostatitis. Their age ranged between 23 and 69 years (median 42 yrs); their mean height was 176 cm, and their mean weight, 75.4 kg (Table 1). Three patients with concomitant BPH, whom we did not exclude from analysis, will be dealt with specifically in Section 6. Prominent history features include (Table 1):

- Acute bacterial infection: *n* = 32
  [bacterial prostatitis: *n* = 32; bacterial urethritis: *n* = 14]
- Previous therapy in the preceding 3 months: *n* = 15
- Complicating factors: *n* = 14
  [1. Urethrostenosis: *n* = 4]
  [2. Prostatic calculi: *n* = 3]
  [3. Sclerosis of the bladder neck: *n* = 7]
- Concomitant diseases: *n* = 8

The patients typically complained of mild-to-moderate symptoms on admission (Table 2). The following mean values were obtained for the uroflow parameters*:

- Micturition volume: 277 ml
- Peak urine flow: 17.7 ml/sec
- Mean urine flow: 9.5 ml/sec
- Flow time: 31.7 sec
- Micturition time: 33.2 sec
- Flow rise time: 10.2 sec
- Uroflow index: 0.91

The prostate was enlarged in 52.5 percent and tender in 85.0 percent of patients. Merely one patient showed a WBC count > 20/ml in the midstream urine. However, all patients had elevated WBC counts in postmassage urine (range: 45-610/ml; median: 128/ml). The C_{3c}/ ceruloplasmin and IgG concentrations in the ejaculate were elevated in all patients; 25.0 percent tested positive for antichlamydial IgA (Table 2).

Documented patients with complicating factors differed markedly from those without complications

- By a reduced incidence of the cardinal clinical features.
- By a more pronounced impairment of urine flow.
  (Table 3)

4. Cernilton® N Therapy

Cernilton® N was prescribed at a dosage of 1 tablet t.i.d. None of the patients included in this retrospective documentation study had his dose modified or his therapy suspended.

The treatment was continued for 25-196 days (median 146 days). Twenty-nine patients discontinued therapy prematurely (< 180 days). Five patients who had almost completed the “180-day minimum” (duration of therapy: 144, 158, 162, 163, 177 days) and another 4 patients who had achieved improvement in their signs and symptoms were obviously not classified as *dropouts*.

Early discontinuation of therapy was primarily due to exacerbation of the disease/ ineffectiveness of treatment (Table 4). Premature termination as a consequence of improvement occurred no earlier than after 3 months’ treatment in the present study cohort.

Treatment was discontinued prematurely in 24 cases for the following reasons:

- Freedom from symptoms: n = 3
- Marked improvement: n = 6
- Ineffectiveness: n = 1
- Exacerbation of the disease: n = 13
- Dropout for personal reasons: n = 1

5. Results

5.1 **Clinical Features**

The percentages of patients with the various clinical features before and after Cernilton® N therapy are shown in Table 5 and Figures 1 through 5:

- Discomfort (Figure 1)
- Pain (Figure 2)
- Nocturia (Figure 3)
- Pollakiuria (Figure 4)
- Dysuria (Figure 5)

The patients of the subset without complicating factors experienced marked improvements. The following percentages of patients achieved freedom from complaints:

- Discomfort 89.5%
- Pain 83.3%
- Nocturia 53.8%
- Pollakiuria 56.0%
- Dysuria 86.4%

The presence of complicating factors results in lower response rates (cf. Figure 6); in particular, there is a comparatively elevated incidence of deterioration. Estimative chi-square tests revealed parallel differences between the subsets “without” and “with” risk factors for the five cardinal features, the differences being marginal, as emerges from the p-values.

5.2 Uroflometry

Table 6 shows the distribution of the uroflometry parameters. The pre-post difference in micturition volume is small. Also, the difference between patients without and those with complicating factors is a minor one. Differences are, however, noted for the following parameters:

Peak urine flow (p = 0.020):
- Without complicating factors: +3.0 ml/sec
- With complicating factors: -1.7 ml/sec

Mean urine flow (p = 0.004):
- Without complicating factors: +2.7 ml/sec
- With complicating factors: -0.8 ml/sec

Flow time (p = 0.013):
- Without complicating factors: -7.1 sec
- With complicating factors: +1.3 sec

Uroflow index (p = 0.006):
- Without complicating factors: +0.22
- With complicating factors: -0.03

For the latter parameter, the overall change results from an average increase from 0.97 to 1.20 for uncomplicated patients and an essentially unchanged result for “high risk” patients (mean change from 0.77 to 0.75). While consistent influences of complicating factors emerge for the other parameters, these fail to attain the level of statistical significance also for high-risk patients, although there is a tendency for improvement. Figures 7 through 13 visualize the average values of the uroflometry parameters before and after Cernilton® N therapy:

- Micturition volume (Figure 7)
- Peak urine flow (Figure 8)
- Mean urine flow (Figure 9)
- Flow time (Figure 10)
- Micturition time (Figure 11)
- Flow rise time (Figure 12)
- Uroflow index (Figure 13)

The tables that follow complement the quantitative analysis of uroflometry by providing a qualitative pre-post comparison of urine flow and uroflow index:

Pre-post comparison of **peak urine flow** (qualitative)						
Post / Pre	Without complications			Complications		
	Below normal	Normal	Above normal	Below normal	Normal	Above normal
Below normal	12	2	1	11	-	-
Normal	-	6	3	2	1	-
Above normal	-	1	-	-	-	-

Pre-post comparison of **mean urine flow** (qualitative)						
Post / Pre	Without complications			Complications		
	Below normal	Normal	Above normal	Below normal	Normal	Above normal
Below normal	16	5	1	12	-	-
Normal	1	2	-	2	-	-
Above normal	-	-	-	-	-	-

Pre-post comparison of **uroflow index** (qualitative)						
Post / Pre	Without complications			Complications		
	< 0.8	0.8 to <1.2	> =1.2	< 0.8	0.8 to <1.2	> =1.2
<0.8	2	2	2	6	1	-
0.8 to <1.2	-	8	6	1	2	-
> =1.2	-	-	5	-	-	1

Marked gradual effects on the uroflow index emerged for the subset without complicating factors. These are particularly prominent for the individual tendency of the uroflow index:

Change	Without complications		Complications	
Increase	23	(92.0 %)	4	(36.4 %)
No change	--	(0.0 %)	1	(2.8 %)
Decrease	2	(8.0 %)	6	(54.5 %)

The differences between the subsets without and with complications are statistically significant (p = 0.002). The trend in the uncomplicated subset (23:2) is quite obvious (p < 0.001 in the signed rank test).

5.3 Findings on Palpation

Normalization of the enlarged prostate at baseline is achieved in 6/12 uncomplicated patients but in none of those with complicating factors. In fact, two patients of the latter group experienced deterioration (Table 7). As regards the consistency of the prostate, 16/26 patients without complications showed improvement while merely 2/14 of those with complications did so (Table 7). Similar results are obtained for tenderness (2 consistently negative cases of both subsets are not included).

Change	Complications NO	YES
Deteriorated	3	8
Unchanged	2	-
Improved	1	-
Asymptomatic	18	4
% asymptomatic	75.0	33.3
Comparison	p = 0.016 (chi-square test)	

The presence of complicating factors also proved to be a limiting factor for the response of the parameter tenderness of the prostate.

For graphic representations of tenderness please refer to Figures 14 and 15:

- Intensity of tenderness (Figure 14)
- Change in tenderness (Figure 15)

5.4 Leukocyturia

While the majority of the patients of the uncomplicated subset showed reductions in their white cell counts in the midstream urine in the course of therapy, the high-risk patients predominantly had higher WBC counts (Table 8; p < .001 for the between-subset comparison of the median change in white cell count). The within-patient pre-post comparison demonstrates reductions in the WBC count

- In 73.1% of the subset without complications, and
- In 28.6% of the subset with complications

(p = 0.005 for the between-subset comparison of the within-patient pre-post change).

Change	Without complications		Complications	
Decrease	19	(73.1 %)	4	(28.6 %)
No change	2	(7.7 %)	-	(0.0 %)
Increase	5	(19.2 %)	10	(71.4 %)

The 19:5 trend (decrease:increase) for uncomplicated cases attains the level of statistical significance (p = 0.007) in the signed rank test.

The increase in the white cell count was beyond the upper limit of normal

- In *n* = 1 patient in the subset without complications, and
- In *n* = 5 patients in the subset with complications

Pre-post comparison of **midstream urine WBC count** (qualitative)				
Post / Pre	Without complications		Complications	
	< = 20	> 20	< = 20	> 20
< = 20	24	1	9	5
> 20	1	-	-	-

The white cell count in postmassage urine decreased in the majority of patients without complications, but tended to increase in most of the high-risk patients (Table 8; p = 0.002 for the U-test subset comparison). The whitin-patient pre-post comparison demonstrates reductions in the WBC count.

- In 80.8% of the subset without complications, and
- In 28.6% of the subset with complications

(p = 0.001 for the between-subset comparison of the within-patient pre-post change).

Change	Without complications		Complications	
Decrease	21	(80.8 %)	4	(28.6 %)
Increase	5	(19.2 %)	10	(71.4 %)

The 21:5 trend (decrease/increase) for uncomplicated cases attains the level of statistical significance (p = 0.002) in the signed rank test.

The reductions in the white cell count was tantamount to normalization

- In *n* = 3 patients of the subset without complications, and
- In *n* = 1 patient of the subset with complications.

Pre-post comparison of postmassage urine WBC count (qualitative)				
Post / Pre	Without complications		Complications	
	< = 20	> 20	< = 20	> 20
< = 20	-	-	-	-
> 20	3	23	1	13

Figure 16 visualizes the leukocyturia findings.

5.5 Bacteriuria

Ten patients again had bacteria detected in their urine in the course of CERNILTON® N therapy, namely

- 4/26 (15.4%) of the patients without complications, and
- 6/14 (49.9%) of the high-risk patients.

5.6 Ejaculate Findings

The pre-post comparison of the ejaculate findings yields the following results (Table 9):

C3c/ceruloplasmin		
Change	Without complications	Complications
Improvement	21 (80.8 %)	4 (28.6 %)
No change	1 (3.8 %)	1 (7.1 %)
Deterioration	4 (15.4 %)	9 (64.3 %)
Comparison	*p* = 0.004 (chi-square test)	

IgG		
Change	Without complications	Complications
Improvement	8 (30.8 %)	3 (21.4 %)
No change	16 (61.5 %)	4 (28.6 %)
Deterioration	2 (7.7 %)	7 (50.0 %)
Comparison	*p* = 0.009 (chi-square test)	

The tendencies for improvement in the subset of uncomplicated cases are quantified by p = 0.001 (21:4) and p = 0.109 (8:2), respectively.

Figure 17 visualizes the ejaculate findings.

5.7 Antichlamydial IgA

No changes were seen on CERNILTON® N therapy.

5.8 Adverse Drug Reactions

There were no adverse drug reactions.

5.9 Assessment of Tolerability and Efficacy

Tolerability was rated as good in 35 patients and as fair in 5 (Table 10). The judgment of efficacy was significantly affected by the presence of complicating factors (urethrostenosis, prostatic calculi, sclerosis of the bladder neck; Table 10). The response rate was

- 80.8% in the subset without complicating factors, and
- 28.6% in the subset with complicating factors.

6. Specific Cases

6.1 Concomitant BPH

Three patients with existing prostatic hyperplasia (BPH) were included in the retrospective documentation study. The following therapeutic responses were obtained:

Pat #1 (absence of complicating factors):

- Improvement in all clinical symptoms;
- Increase in peak and mean urine flow;
- Reduction in flow time, micturition time, and flow rise time;
- Increase in uroflow index from 0.63 to 0.74;
- Normalization of the consistency of the prostate;
- Decrease in tenderness;
- Reduction in white cell count in the urine;
- Decrease in C_{3c}/ ceruloplasmin levels;
- Judgment of efficacy: Improvement.

Pat #12 (sclerosis of the bladder neck):

- No change in clinical features;
- No improvement in urine flow; decrease in uroflow index from 1.07 to 0.94;
- Palpation findings unchaged ;
- Increase in WBC count in postmassage urine;
- Ejaculate unchanged;
- Judgment of efficacy: No improvement.

Pat #14 (sclerosis of the bladder neck):

- Improvement in all clinical symptoms other than dysuria;
- No improvement in urine flow; uroflow index unchaged (0.66);
- Tenderness on palpation improved;
- Decrease in WBC count in post-massage urine from 312 to 92/ ml;
- Decrease in C_{3c}/ ceruloplasmin levels;
- Decrease in IgG;
- Judgment of efficacy: Improvement.

Given the impact of complicating factors on therapeutic effects, the presence of BPH does not cause an additional impairment.

6.2 Patient #26 (absence of complicating factors)

Patient #26 had been admitted to the study with a significantly elevated micturition volume.

- Improvement in all clinical symptoms;
- Normalization of urine flow;
- Tenderness on palpation improved;
- Decrease in WBC count in postmassage urine from 315 to 52/ ml;
- Decrease in C_{3c}/ ceruloplasmin levels;
- Judgment of efficacy: Improvement.

Given the overall consistent pattern of changes in the clinical features on Cernilton® N therapy, exclusion of patient #26 from analysis should be limited to the uroflometry parameters.

7. Data Listings

The individual data are collated in 4 lists:

- Demographics & History (List 1)
- Concomitant diseases/ therapy/ comedications (List 2)
- Clinical features & lab tests (List 3)
- ADR/ dropouts/ judgments (List 4)

Appendices

1 CRF	(6 pages)
10 tablets	(18 pages)
17 figures	(17 pages)
4 data listings	(21 pages)