PENTOSAN POLYSULFATE SODIUM FOR THERAPY OF INTERSTITIAL CYSTITIS

A Double-Blind Placebo-Controlled Clinical Study

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ABSTRACT—Pentosan polysulfate sodium (PPS) was compared with placebo for the symptomatic therapy of interstitial cystitis in a double-blind, multicenter study. A total of 110 patients were enrolled and treated for three months. In this study, overall improvement of greater than 25 percent was reported by 28 percent of the PPS-treated patients and by 13 percent of the placebo-treated patients ($p = 0.03$). The investigators' overall evaluation provided similar results, 26 percent vs 11 percent in favor of PPS ($p = 0.04$). Improvement in pain and pressure to urinate also favored PPS over placebo and approached statistical significance ($p = 0.07$ and 0.08). The incidence of adverse reactions was 6 percent in the PPS-treated group and 13 percent in the placebo-treated group. All adverse reactions were minor, and treatment was discontinued by 1 patient in the PPS group and 2 in the placebo group. In this study, PPS was found to be significantly more effective than, and equally as safe as, placebo.

Interstitial cystitis is a syndrome characterized by the symptoms of urinary urgency, urinary frequency, nocturia, and lower abdominal and perineal pain and/or discomfort. It occurs in the absence of infection or other known pathologic processes such as carcinoma in situ, radiation, or chemical cystitis. Although its etiology has not been definitely established,[1] it has been postulated that interstitial cystitis is caused by a dysfunctional epithelium which becomes permeable and allows the leak of urinary solutes across the transitional cells.[2] In both animals and humans, it has been shown that the principal barrier to permeability is the surface glycosaminoglycans.[3-7] A permeable bladder epithelium can result in diffusion of irritating components from normal urine through to the bladder wall to set up a chronic inflammatory condition initiating the symptoms of pain, urgency, and frequency.[5] Based on the possibility that there is a deficiency of the surface glycosaminoglycans in patients with interstitial cystitis, patients were treated with a synthetic sulfated polysaccharide, pentosan polysulfate sodium (PPS), in an attempt to ameliorate their symptoms.

This hypothesis has been tested in three published clinical studies using PPS (Elmiron). In two studies, one double-blind, placebo-controlled,[7] and one open-controlled,[8] PPS was shown to be effective in relieving the symptomatology of interstitial cystitis in a significant number of patients. In a third study,[9] the authors concluded that there were no significant differences between the PPS and placebo-treated groups. However, in the group of

patients with clinically and patho-anatomically verified interstitial cystitis, the reduction in pain was greater for the PPS-treated group than for the placebo-treated group, although no p values were given by the authors. In addition, the PPS-treated patients with verified disease were shown to have a statistically significant increase in bladder capacity measured under anesthesia, as well as a statistically significant improved cystoscopic appearance of the bladder.

Because of the existing evidence indicating that PPS may have efficacy in this disorder, the current study was undertaken with a greater degree of control and a larger population of patients with well-defined disease.

Material and Methods

This study was conducted in a double-blind manner, and a placebo concurrent control group was used as a comparison for the efficacy and safety of PPS. The three-month double-blind period with the placebo control made it possible to study the true extent to which PPS modulated the symptoms of disease in these patients. The study was multicentered with five participating centers.

Patients were categorized in terms of the severity of their disease. Patients with a moderate degree of disease were defined as having an anesthetic bladder capacity over 400 mL, 18 or fewer voids per day, and an average voided volume of 75 mL or more. Patients were considered to have a severe degree of disease if they had a bladder capacity under anesthesia of less than 400 mL, or more than 18 voids per day, or an average voided volume of less than 75 mL. A patient with any one of these three criteria was included in the severe group. Anesthetic bladder capacity was measured under 80 cm of water pressure held for one minute in all patients under general or spinal anesthesia.

To be included in the study, all patients had to have the following examination requirements and symtom complex:

Urgency expressed as "moderate" on a 5-point analog scale
Frequency of at least 10 voids per day
Nocturia of at least 2 voids per night
Pain as recorded on a 5-point analog scale
Continuous duration of symptoms of at least one year
Failed previous conventional therapy such as chlorpactin, hydrodilatation, or DMSO
Average voided volume of 200 mL or less measured over a three-day period
Negative urine culture and cytology
Cystoscopic examination under anesthesia (80 cm of water and 1 minute distention) showing petechial hemorrhages or ulcers with gross blood in the fluid return and a bladder capacity of 800 mL or less

Patients were excluded from participation in the study for any of these conditions:

Age less than eighteen years
Pregnancy
Premenopausal and not practicing effective means of birth control
Evidence of active bleeding peptic ulcer disease
Bleeding diathesis
Anticoagulant therapy
Chronic use of narcotics
Known allergy to pentosan polysulfate sodium
Lack of availability for the duration of the study or inability to follow instructions
Use of artificial sweeteners
Lactating mothers
Signs of:
- recurrent bacteriuria
- obvious neurologic impairment
- history of pelvic irradiation
- previous treatment with known bladder irritants
- bladder carcinoma
- urinary tuberculosis
- shistosomiasis

Treatment with Elmiron within six weeks of study

Patients were randomly assigned to PPS or placebo group in accordance with a computer-generated random code providing two parallel groups of patients for comparison. All investigators were blinded during the study with the code established and maintained by a separate center.

The dose of PPS was 300 mg daily given orally in divided doses of 100 mg three times a day one hour before meals or two hours after meals. Identically-appearing placebo capsules were given in the same manner. All patients were seen at zero time before start of treatment for evaluation of baseline symptoms and laboratory values and at twelve weeks after start of treatment for measurement of these same variables.

The primary instrument used for evaluation was a follow-up questionnaire completed by the patient at the end of the double-blind treatment period. The patients were asked if they felt improved overall since the start of treatment, and

if so, was the improvement "slight" 25 percent, "moderate" 50 percent, "great" 75 percent, or "complete cure" 100 percent. This instrument also allowed the patient to evaluate the changes, if any, they perceived in urgency and pain using the same definitions for overall improvement.

An investigator's evaluation form for overall improvement was completed by the investigator after examining the patient and reviewing the data provided in voiding profiles and the pain and urgency scales while maintaining the double-blind. The scale used by the investigator contained categories of "worse," "no change," "fair," "good," "very good," and "excellent."

A volume-voiding profile measuring the time and quantity of all voids during waking hours as well as the number of voids during sleeping hours over three consecutive days was completed by the patient before treatment, and at the end of the first, second, and third months of treatment. This provided information concerning changes in average voided volume, frequency, and nocturia during the three-month treatment period.

Pain and urgency scales were included on one sheet and were completed before start of treatment and at the end of one, two, and three months of treatment. Both scales allowed the patient to express the degree of pain and urgency on a scale of 0 to 5: 0 = none, 1 = mild, 3 = moderate, and 5 = severe.

Routine laboratory examinations were conducted before treatment and at the end of the three-month treatment period. This included urinalysis, complete blood counts, blood chemistries including prothrombin time and partial thromboplastin time, and liver function tests.

Adverse reaction report forms provided space for recording the type of reaction, treatment, outcome, comment, and relation to treatment as possible, probable, not likely, or other cause. Reports of side effects were volunteered. This was considered appropriate for these patients because interstitial cystitis patients are known to be exquisitely aware of any changes in their condition and prone to discuss them with their physicians.

At the end of the three-month double-blind period, the patients were offered the opportunity to continue taking PPS as long as they continued to experience relief of their symptoms, or to start taking PPS if they had been assigned to the placebo group. Variables for the determination of PPS efficacy in order of relevancy were the patient's assessment of overall improvement, the investigator's assessment of overall improvement, the changes in pain and urgency, the change in nocturia, and the change in frequency and average voided volume. In each case the change from the baseline values at the end of the double-blind period was used as the basis for determining the efficacy of Elmiron.

Statistical Treatment of Data

The treatment groups were compared both within each study center and across all study centers, with respect to the response variables recorded at the pretreatment visit. For the quantitative variables such as age, bladder capacity, pain, urgency, frequency of urination, and total urine volume, a t-test was used. The analysis of the qualitative variables such as sex, race, and severity of variables associated with the cystoscopic evaluation were analyzed with a chi-square contingency table analysis. Additionally, for those response variables scored with a severity rating, a Mantel-Haenszel test was used to compare the treatment groups with respect to a linear association between severity and response rate.

The treatment groups were compared for changes in the response variables of pain, urgency, frequency of urination, and the total urine volume, both within each study center and across all study centers. The analysis of these changes from baseline variables was with an analysis of variance, using a general linear models procedure. For each treatment group, the significance of the mean change was determined with a t-test.

With respect to the pain and urgency scales, treatment was considered to be successful if there was a 1-point or greater reduction on the severity scale or unsuccessful if there was less than a 1-point reduction on the severity scale. A decrease of 3 or more per day in frequency of urination, and an increase in urine volume of 20 mL or more per void were also used as indications of improvement. For each of these criteria, treatment groups were compared using Fisher's exact test within each study center, and the Mantel-Haenszel test was used to compare treatment groups after collapsing data across study centers.

For the investigator and patient evaluations made at the completion of the three-month double-blind phase, treatment group comparisons were made with chi-square contingency

TABLE I. *Patient characteristics at baseline*

Parameter	PPS	Placebo
Patients		
Mean age (yrs.)	43.3	45.3
Females (%)	91	87
White race (%)	100	95
Mean duration of disease (yrs.)	7.4	5.8
Cystoscopic findings		
Bloody fluid return (%)		
Mild	31	27
Moderate	39	46
Severe	30	27
Fissures (%)		
None	6	7
Few	28	29
Moderate	40	35
Many	26	29
Petechial hemorrhages (%)		
Few	26	27
Moderate	46	48
Many	28	25
Hunner's ulcer present (%)	8	4
Other abnormalities present (%)	4	11
Mean bladder capacity (cc)	569	585
Patients with severe disease (%)	59	59

table analysis for qualitative variables. For those response variables recorded on a severity scale, the treatment groups were compared using a Mantel-Haenszel test with respect to linear association. In addition, a blocked Wilcoxon test was used to compare the treatment groups after adjustment for study center differences.

All adverse experiences were recorded and their frequency determined for each treatment group. For each type of adverse experience, the treatment groups were compared with respect to the percent of patients experiencing the adverse effect, using Fisher's exact test.

All computations were performed using the Statistical Analysis System (SAS). Statistical significance was declared if the p-value was equal to or less than 0.05.

Results

There were 110 patients with documented interstitial cystitis with a duration of one year or more enrolled in the study. Of these, 56 patients were treated with placebo, and 54 were treated with PPS. There were no significant differences between the treatment groups at the beginning of the study in terms of age, sex distribution, race, cystoscopic findings, duration of disease, bladder capacity, or severity of disease. These data are summarized in Table I.

Twelve patients, 3 treated with PPS and 9 treated with placebo, failed to complete the three month study. Of these 12, 8 were in the group of patients classified as having severe disease, 1 (3%) receiving PPS and 7 (21%) receiving placebo. Most of these patients were lost to follow-up, and it is likely that lack of efficacy was responsible for the patients dropping out. The difference in the drop-out rate between the treatment groups in these patients with severe disease was statistically significant ($p = 0.05$).

At the end of the three-month treatment period, 28 percent of the PPS patients versus 13 percent of the placebo patients evaluated themselves as more than slightly improved relative to their condition at the beginning of the study on the 5-point scale from "no change" to "complete cure" ($p = 0.04$).

In terms of reduced pain, 27 percent of the PPS patients evaluated themselves as improved compared with 14 percent of the placebo patients ($p = 0.08$). This was confirmed by the pain scale data where 46 percent of the PPS patients and 29 percent of the placebo patients recorded a decrease in pain of 1 or more ($p = 0.07$). The mean reduction in pain from baseline as measured by the pain scale was 0.5 for the PPS-treated patients compared with 0.2 for the placebo patients at three months. This difference between the treatment groups was not statistically significant, but the difference from baseline was significantly different from zero ($p = 0.05$) for the PPS-treated group but not for the placebo-treated group. The latter held true with $p = 0.01$ to 0.05 for the end of months 1 and 2 as well.

At the three-month self-evaluation, 22 percent of the PPS patients and 11 percent of the placebo patients expressed an improvement in pressure to urinate ($p = 0.08$). This was not confirmed by the urgency scale data which revealed a slight margin of 39 percent to 46 percent in favor of placebo. By the investigator's evaluation of overall improvement, 26 percent of the PPS-treated patients and 11 percent of the placebo patients had an improvement of at least good or better on the 6-point scale from "worse" to "excellent" ($p = 0.03$).

There was a mean increase in volume per void of 9.8 cc for the PPS-treated patients, and 7.6 cc per void for placebo patients. Among the PPS patients, 30 percent had an increase of 20 cc or more compared with 20 percent of the placebo patients. The PPS group had a mean increase in total daytime volume of urine at the

TABLE II. *Efficacy data (% of patients improved in terms of pain, urgency) and overall improvement*

Parameter	PPS	Placebo	p
Overall improvement three months			
Investigator evaluation	26	11	0.03
Patient self-evaluation			
Overall improved	28	13	0.04
Pain follow-up questionnaire	27	14	0.08
Pain scale	46	29	0.07
Pressure to urinate	22	11	0.08
Urgency scale	39	46	ns
Mean reduction in pain score from baseline	0.5*	0.2	ns
Changes from baseline, voided volume			
Mean volume per void (cc)	9.8	7.6	ns
Increase of ≥20 cc (% pts.)	30	20	ns
Total daily urine volume (cc)	+60	−20	ns

*Significantly different from 0 (p = 0.05).

endpoint of 60 cc compared with a mean decrease of 20 cc for the placebo group. These differences were not statistically significant. The efficacy data as measured by these parameters in this study are summarized in Table II. The changes from baseline at the endpoint in the remaining parameters studied were not different between treatments. These were voids per day (−1 for both treatments), percent of patients having 3 less voids per day (32% PPS, 24% placebo), and nocturia (−0.8 PPS, −0.5 placebo).

The incidence of adverse reactions in this study was low in both treatment groups. Among the PPS-treated patients, 3 (6%) reported a total of 6 adverse reactions, and 7 (13%) placebo patients reported a total of 8 adverse reactions. The observed reactions were not different from reactions that might be observed in any random population over a three-month period and were not serious. Only 1 PPS and 2 placebo patients discontinued treatment due to adverse reactions. Only diarrhea was observed in more than 1 patient. These data are summarized in Table III.

There were no differences between the treatment groups in terms of clinically significant changes in any of the laboratory data. One patient in the PPS-treated group had SGOT and SGPT values of 118 and 133 at three months compared with 56 and 115 at baseline, respectively, at each time. There were no other remarkable changes.

Of the patients who completed the three-month double-blind period, 44 percent were continuing therapy with PPS one and a half years after the start of the study. These patients, therefore, had been on therapy for periods ranging from six months to one and a half years.

TABLE III. *Incidence of adverse reactions*

Reaction	PPS (%)	Placebo (%)
Headache	1 (1.9)	2 (3.6)
Nausea	1 (1.9)	0
Indigestion	1 (1.9)	0
Increased perspiration	1 (1.9)	0
Severe mood swings	1 (1.9)	0
Suicidal ideation	1 (1.9)	0
Diarrhea	0	2 (3.6)
Explosive diarrhea	0	1 (1.8)
Severe joint pain	0	1 (1.8)
Skin rash on arms	0	1 (1.8)
Itching	0	1 (1.8)
Total reactions	6	8
Total patients	3 (6)	7 (13)

Comment

The primary measurement used to determine effectiveness of PPS was the patient evaluation of overall improvement. The investigator's assessment of overall improvement was also a measure of efficacy, second only to the patient's self-evaluation.

The measure of overall improvement was considered to be the most appropriate measure of treatment efficacy because the individual symptoms of interstitial cystitis—frequency, urgency, pain, and nocturia—vary widely within and among patients in terms of occurrence, severity, and the importance that patients attach to individual symptoms.

Patients are not at all alike in the manner in which they evaluate and report individual symptoms. Some patients report a decrease in urgency, or perhaps pain, when the number of days that these symptoms are present is significantly reduced, while other patients with a similar reduction will not report a decrease because the urgency or pain is still severe on the days that either one is present. Frequency and urine volume also can be misleading symptoms. Some patients restrict fluid intake during particularly painful periods and increase fluid intake when pain is ameliorated. In these patients, when treatment produces a decrease in pain, frequency may increase while urine volume per void may remain the same or show a small increase, or frequency may remain the same with an increase in volume per void.

The symptom complex varies among patients in terms of which of the symptoms is most prominent and/or is perceived as most bothersome or disabling. While any given treatment may provide some relief for most or all of a patient's symptoms, it may not provide enough relief of the particular symptom or symptoms that the patient perceives as most important. Guiding the patient to think in terms of overall relief, helps to overcome the dilution that can result from too sharp a focus on individual symptoms.

For these reasons emphasis in this study was placed on overall improvement as expressed by the patient and investigator, while the changes in specific symptomatology were considered as supportive data. In this respect, the results of this study confirm the observations made in previous studies of PPS for the treatment on interstitial cystitis. On the self evaluation by the patient, 28 percent of the patients who received PPS felt that they experienced significant overall improvement in their disease compared with their condition at the beginning of treatment. This differed significantly ($p = 0.04$) from the placebo-treated patients, 13 percent of whom reported a similar result. The investigators' overall evaluation at the end of the double-blind period agreed with the patients' self-evaluation with 26 percent of the PPS patients evaluated as significantly improved compared with 11 percent of the placebo patients. This difference was significant at the 0.03 level. In the self-evaluation of overall improvement, patients who reported only slight improvement on the scale of "no change," "slight," "moderate," "great," or "complete" were not included in the group considered to have been significantly improved. In the evaluation by the investigator, overall improvement that was rated as "fair" on the scale of "worse," "no change," "fair," "good," "very good," or "excellent" was not included in the group of patients considered to have had significant overall improvement.

Improvement in pain approached significance on both the pain scale and in terms of the patient's perception of pain improvement as expressed on the follow-up questionnaire ($p = 0.07$ and 0.08, respectively). Also at each of the periods of measurement from the end of one month to the end of treatment, the decrease in pain as measured on the pain scale was significantly different from 0 ($p = 0.01$ to 0.05) for the PPS-treated group but not for the placebo group, although the degree of change between the groups was not significant. Pain as a symptom may improve first, representing a decrease in inflammatory response. On the other hand, refunctionalization of the bladder appears to be a much slower response.

The results from the urgency scale and the follow-up questionnaire were disparate. On the urgency scale, the difference between the groups was slightly in favor of placebo (46% to 39%) but not statistically significant. On the follow-up questionnaire where the question was framed in terms of pressure-to-urinate rather than urgency, the difference between the groups in favor of PPS (22% to 11%) approached significance at 0.08. The reason for the disparity is unknown, except that patients may interpret the terms differently.

The data relating to the changes in voided volume were in favor of the PPS-treated group although not significantly different from placebo. There was a mean increase of 9.8 cc in volume per void, a mean increase of 60 cc in total daily volume, and an increase of 20 cc or more in volume per void by 30 percent of the patients who received PPS. The comparable figures for the patients who received placebo were 7.6 cc, mean decrease of 20 cc, and 20 percent, respectively.

The changes in frequency noted in this study did not differ significantly between the groups in terms of daytime voids where there was a reduction of 1 void per day for both groups, for nocturia where there was a reduction of 0.8 voids for PPS and 0.5 voids for placebo, and for percent of patients having a reduction of 3 or more voids per day with 32 percent for PPS and 34 percent for placebo.

It is noteworthy that at one and a half years after the start of the study, 44 percent of the patients who completed the three-month treatment period have continued treatment with PPS for ongoing periods ranging from six months to one and a half years. This indicates that this proportion of patients considers PPS to be effective enough to continue its use on a long-term basis and attests to the efficacy of this medication for the relief of the symptoms of interstitial cystitis.

It is important to note that these positive results for PPS were achieved in a selected population of patients who had previously failed to experience satisfactory relief with conventional treatments such as DMSO, chlorpactin, and others. It is not unlikely that in a group of newly diagnosed patients who have not been found to be refractory to treatment, the proportion of patients responding to treatment would be greater.

The incidence of adverse reactions was higher among the placebo-treated patients than the PPS-treated group, but the difference was not significant. There were no adverse reactions considered to be serious. Treatment was discontinued because of adverse reactions in 2 patients receiving placebo and in 1 patient receiving PPS.

Conclusions

In this double-blind, placebo-controlled study, both efficacy and safety of PPS for the relief of the symptoms of interstitial cystitis have been confirmed. Both patients and investigators evaluated PPS as significantly more effective than placebo overall. For pain and urgency, the improvements due to PPS compared with placebo were statistically significant or approached significance. In terms of the voided volume parameters, the improvements favored PPS over placebo, although the differences were not statistically significant. The changes in frequency were similar in both groups, as were adverse reactions and changes in laboratory values.

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