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A QUANTITATIVELY CONTROLLED METHOD TO STUDY PROSPECTIVELY INTERSTITIAL CYSTITIS AND DEMONSTRATE THE EFFICACY OF PENTOSANPOLYSULFATE

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ABSTRACT

A randomized, prospective, double-blind, placebo-controlled study was conducted at 7 clinical centers on 148 patients. Patients received orally either 100 mg. pentosanpolysulfate (a synthetic polysaccharide) 3 times per day or a placebo. Of the patients on drug therapy 32% showed significant improvement compared to 16% of those on placebo ($p = 0.01$). This study provides a model to assess this disease quantitatively in a prospective manner using a method whereby the patients globally assess their symptoms as either worse or improved by 0, 25, 50, 75 or 100%. Patients on drug therapy also experienced a significant decrease in pain and urgency ($p = 0.04$ and 0.01) on analogue scales when compared to placebo and also more drug patients showed an average increase of more than 20 ml. in voided volume than did placebo patients ($p = 0.02$).

All adverse effects were minor, with 7 in the drug group and 10 in the placebo group. The results support the concept that some patients with the interstitial cystitis syndrome may have abnormal bladder surface glycosaminoglycans.

KEY WORDS: bladder diseases, cystitis, pentosan sulfuric polyester

Interstitial cystitis is a disease that is manifested primarily by a symptom complex of significant urinary frequency, urgency and/or bladder or pelvic pain. The subjective nature of the disease has been believed by many to make it difficult to assess in a controlled perspective clinical trial. We present a 7-center randomized prospective double-blind study and evaluate the drug pentosanpolysulfate in interstitial cystitis. This study documents methods to track the disease course quantitatively to allow for straightforward statistical analysis.

There are 3 important aspects of this study. 1) It confirms earlier observations that the drug pentosanpolysulfate is active at ameliorating the symptoms of interstitial cystitis. 2) The study provides a model for a randomized prospective double-blind study for future investigators. 3) The global assessments reported allow for accurate and easy assessment of the symptoms of this disease, and make it possible to follow these symptoms quantitatively throughout the course of the study, and readily lend the data to statistical analysis.

PATIENTS AND METHODS

The efficacy and safety of pentosanpolysulfate were compared to those of placebo in a double-blind manner for a treatment period of 3 months. The study was multicentered with 7 participating centers. Patients were selected for enrollment into the study on the basis of anesthetic bladder capacity (350 to 1,000 cc), number of voids per day (8 or more), average voided volume (50 to 200 cc) and nocturia (at least 1 or 2). Patients lacking 1 or 2 of these criteria were entered into the study but they had to have pain and/or moderate urgency, negative urinary cytology studies and cultures, and cystoscopic findings of petechial hemorrhages and blood in the fluid return after bladder dilation. Patients were excluded from participation in the study for age less than 18 years, pregnancy or lactation, evidence of active bleeding peptic ulcer disease, bleeding diathesis, use of anticoagulant therapy, chronic use of narcotics, known allergy to pentosanpolysulfate sodium, use of artificial sweeteners or a history of treatment with Elmiron within 4 weeks of the study. Patients also were excluded if they were premenopausal and not practicing effective means of birth control, if they were not available for the duration of the study or were unable to follow instructions, and if they showed signs of recurrent bacteriuria, obvious neurological impairment, history of pelvic irradiation, previous treatment with known bladder irritants, bladder carcinoma, urinary tuberculosis or schistosomiasis.

Patients were randomly assigned to receive pentosanpolysulfate or placebo in accordance with a computer generated random code providing 2 parallel groups for comparison. All investigators were blinded during the study with the code established and maintained by a separate center. The dose of pentosanpolysulfate was 100 mg. 3 times daily given orally 1 hour before meals or 2 hours after meals. Identically appearing placebo capsules were given in the same manner. Symptomatology and laboratory values were obtained before and 3 months after the start of treatment.

The primary means of efficacy evaluation was a followup questionnaire completed by the patient at the end of the double-blind treatment period. The patients were asked to evaluate any overall change they perceived in their condition since the start of treatment as either worse, no better or improvement, with improvement rated as slight (25%), moderate (50%), great (75%) or symptoms gone (100%). The questionnaire also allowed the patients to evaluate the changes, if any, they perceived in urgency and pain using the same definitions as for overall improvement. Successful therapy was defined before the study as a report by the patient of at least a 50% overall improvement in the symptoms.

An investigator evaluation form for overall improvement was completed after examination of the patient and review of the data provided in voiding profiles, and the pain and urgency scales. The categories used were worse, no change, fair (25%), good (50%), very good (75%) and excellent (100%). A volume voiding profile that measured the time and quantity of all voids during waking hours, as well as the number of voids during

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sleeping hours during 3 consecutive days was completed by the patient before and after 3 months of treatment. This profile provided information concerning changes in average voided volume, frequency and nocturia during the treatment period. Pain and urgency scales were included on 1 sheet, and were completed before and after 3 months of treatment. Both scales allowed the patient to express the degree of pain and urgency on a scale of 0 to 5 in which 0 was equivalent to none, 1 was mild, 3 was moderate and 5 was severe.

Routine laboratory examinations were conducted before and at the end of the 3-month treatment period, including urinalysis, complete blood counts, blood chemistry studies including prothrombin time and partial thromboplastin time, and liver and renal function tests. Adverse reactions were documented with respect to the type of reaction, treatment, outcome and relationship to treatment as possible, probable, not likely or other cause. Predefined variables for the determination of pentosanpolysulfate efficacy were, in descending order of relevance, the assessment by the patient of overall improvement (global assessment at least 50% improved for successful therapy), the assessment by the investigator of overall improvement, changes in pain and urgency, change in nocturia, and 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 pentosanpolysulfate. It should be noted that before the start of the study a significant patient improvement was defined as the patient reporting at least a 50% decrease in symptoms on the global assessment.

Statistical treatment of data. Treatment groups were compared with respect to baseline demographic and disease status variables. Quantitative variables, except for duration of disease, were compared using a General Linear Models analysis of variance with the model including effects due to study site, treatment and their interaction. Duration of disease was analyzed with a blocked Wilcoxon test. The qualitative variables were analyzed with either a Cochran-Mantel-Haenszel test, pooling over study sites or Fisher's exact test.

The treatment groups were compared for changes in the response variables of pain, urgency, frequency of urination and the total urine volume, within each study center and across all study centers. The evaluation of these changes from baseline variables was made with an analysis of variance using a General Linear Models procedure. In addition, each of these variables was analyzed with respect to change from baseline to 3 months and end point. These data were analyzed using an analysis of covariance. For each treatment group the significance of the mean change was determined with a 1-tailed 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 or urination and an increase in urine volume of 20 ml. or more per void were also used as indications of improvement. Each of these outcomes was predefined and analyzed using a Mantel-Haenszel test, pooling over study sites.

For the investigator and patient evaluations made at the completion of the 3-month double-blind phase, each outcome was analyzed using a Mantel-Haenszel test. Treatment groups were compared with respect to the incidence of adverse experiences based on Fisher's exact test. All computations were performed using the Statistical Analysis System.

RESULTS

A total of 148 patients was enrolled in the study, 74 in each treatment group, all of whom had documented interstitial cystitis of at least 1 year in duration. There were no significant differences between the treatment groups at baseline in terms of age, sex distribution, race, duration of disease, cystoscopic findings or bladder capacity (table 1). A total of 18 patients, 9 in each treatment group, failed to complete the 3-month study. Of these patients 3 in the pentosanpolysulfate group and 5 in the placebo group dropped out because of adverse experiences and the remainder were lost to followup. It is likely that lack of efficacy was responsible for these latter dropouts.

TABLE 1. *Patient characteristics at baseline*

Parameter	Pentosanpoly-sulfate	Placebo
Mean age (yrs.)	42.7	45.5
% Women	100	93
% White pts.	97	96
Mean duration of disease (yrs.)	6.6	6.6
% Cystoscopic findings:		
Bloody fluid return:		
Mild	18	15
Moderate	36	37
Severe	46	47
Fissures:		
None	3	4
Few	7	8
Moderate	42	47
Many	49	41
Petechial hemorrhages:		
None	1	1
Few	9	8
Moderate	41	43
Many	49	47
Hunner's ulcer present	4	4
Other abnormalities present	11	8
Mean bladder capacity (cc under anesthesia)	656	601

At the end of the 3-month treatment period 24 of 74 pentosanpolysulfate patients (32%) versus 12 of 74 placebo patients (16%) evaluated themselves as 50% overall improved relative to the condition at the beginning of the study ($p = 0.01$). In terms of reduced pain, 38% of the pentosanpolysulfate patients evaluated themselves as 50% improved compared to 18% of the placebo patients ($p = 0.005$). This finding was confirmed by the pain scale data in which 66% of the pentosanpolysulfate patients and 51% of the placebo patients recorded a decrease in pain of 1 point or more ($p = 0.04$).

At the 3-month self-evaluation, 30% of the pentosanpolysulfate patients and 18% of the placebo patients reported an improvement of at least 50% in pressure to urinate ($p = 0.04$). This finding was confirmed by the urgency scale data, which revealed that 61% of the pentosanpolysulfate patients and 43% of the placebo patients experienced a decrease in urgency of 1 point or more on the 5-point scale ($p = 0.01$).

With respect to improved quality of life, the difference between the treatment groups was not statistically significant for improvement in sleep but approached significance for sexual intercourse. Of the patients who engaged in sexual intercourse, 15 of 49 (31%) in the pentosanpolysulfate group and 10 of 56 (18%) in the placebo group reported that they had enjoyed increased frequency of sexual intercourse after 3 months on treatment ($p = 0.06$).

Analysis of the investigator's evaluation of overall improvement indicated that 36% of the pentosanpolysulfate treated patients and 15% of the placebo patients had an improvement of at least good or better on the 6-point scale from worse to excellent ($p = 0.002$). These efficacy data are shown in table 2.

There was a mean increase in volume per void of 20.4 cc for the pentosanpolysulfate treated patients, and a decrease of 2.1 cc per void for placebo treated patients (not significant). Among the pentosanpolysulfate group 40% had an increase of 20 cc or more compared with 24% of the placebo group ($p = 0.02$). None of the remaining voiding profile data pertaining to frequency or nocturia revealed any significant differences between the treatment groups (table 3).

The incidence of adverse reactions in this study was low in both treatment groups. Among the pentosanpolysulfate treated patients 7 (9%) reported a total of 12 adverse reactions and 10

TABLE 2. *Efficacy data expressed as per cent of patients with 50% improvement in terms of pain, urgency and overall improvement*

Parameter	Pentosanpoly-sulfate	Placebo	P Value
Overall improvement 3 mos., investigator evaluation	36	15	0.002
Pt. self-evaluation:			
Overall improved	32	16	0.01
Pain followup questionnaire	38	18	0.005
Pain scale	66*	51*	0.04
Pressure to urinate	30	18	0.04
Urgency scale	61*	43*	0.01
Improved sexual intercourse	31	18	0.06

* Per cent of patients reporting a decrease of at least 1 point on analogue scale (0 to 5).

TABLE 3. *Changes from baseline in voided volume*

Parameter	Pentosanpoly-sulfate	Placebo	P Value
Mean vol./void (cc)	+20.4	−2.1	Not significant
Increase of 20 cc or more (% pts.)	40	24	0.02
Total daily urine vol. (cc)	+3	−42	Not significant

TABLE 4. *Incidence of adverse experiences*

Reaction	Pentosanpoly-sulfate No. (%)	Placebo No. (%)
Headache	0	1 (1.4)
Nausea	1 (1.4)	3 (4.1)
Diarrhea	2 (2.7)	2 (2.7)
Vomiting	0	2 (2.7)
Bowel obstruction	1 (1.4)	0
Jaundice	0	1 (1.4)
Suicide attempt	0	1 (1.4)
Felt high	1 (1.4)	1 (1.4)
Side-to-side eye movements	0	1 (1.4)
Insomnia	1 (1.4)	0
Rash	0	1 (1.4)
Pruritus	0	1 (1.4)
Increased mole size	1 (1.4)	0
Nocturia increased	1 (1.4)	0
Pain worse	0	1 (1.4)
Amenorrhea	0	1 (1.4)
Urgency post-dose	1 (1.4)	0
Vaginal pruritus	0	1 (1.4)
Vaginal yeast infection	1 (1.4)	0
Dry nasal mucosa	0	1 (1.4)
Rhinorrhea	1 (1.4)	0
Watery/runny eyes	1 (1.4)	1 (1.4)
Total No. experiences	12	19
Total No. pts. (%)	7 (9)	10 (14)

placebo patients (14%) reported a total of 19 adverse reactions. The observed reactions were not different from reactions that might be observed in any random population during a 3-month period and were not serious. Only 3 patients in the pentosanpolysulfate group and 5 in the placebo group discontinued treatment due to adverse reactions. Only digestive system events, diarrhea or nausea was observed in more than 1 patient, and occurred more often on placebo (8 events) than on pentosanpolysulfate (4 events). These data are summarized in table 4. There were no clinically significant differences between the treatment groups for any of the laboratory data, and there were no patients with laboratory findings critically outside the normal range for any of the parameters measured.

DISCUSSION

Interstitial cystitis has historically been a disease with a subjective symptom complex of pain, urgency and frequency but with not much data concerning the pathogenesis of this disease. More recent data have suggested that the disease represents an epithelial dysfunction such that the membrane becomes leaky and allows the passage of urinary solutes across the transitional cells to initiate the complex of pain, urgency and frequency.[1-3] It has been shown in animals and human subjects that establishment of such a leak will indeed set up this symptom complex.[1-3] These studies also demonstrated that polysaccharides (pentosanpolysulfate, heparin) reverse induced leaks. Our current study partly supports the theory that polysaccharides, which appear to be the primary permeability control of the bladder, may be dysfunctional in some individuals with the interstitial cystitis syndrome. The rationale for selecting pentosanpolysulfate to treat interstitial cystitis patients was based on the hypothesis that it could help protect the bladder surface, since it is a sulfated polysaccharide.[3, 4] Our study, in addition to supporting these concepts, provides a valuable model for future investigators to use as a method to perform prospectively controlled clinical trials on this disease. The study was designed to run for 3 months. A longer study (6 months) would probably be ideal in a chronic disease with perhaps slow and gradual response. However, it was not considered humane to ask patients in pain to endure 6 months on a placebo with no other therapy. A crossover design was also considered but rejected by the statistician as too complicated to evaluate.

Primary variables for following efficacy in this study were the self-evaluation by the patients of overall improvement, the data from the pain and urgency scales, and the assessment by the investigator of overall improvement as stated in the protocol before the study. Of course, all of these data were obtained in a randomized double-blind prospective manner. Based on our previous experience with controlled clinical trials with interstitial cystitis,[5, 6] the voided volume data (which tend to be widely variable between and within patients) were considered to be of secondary importance as a measure of efficacy. Data for efficacy were, therefore, subjective (patient self-evaluation), objective (pain and urgency scales) and subjective/objective (investigator evaluation based on all data). Interstitial cystitis is a disease particularly suited to this combination of efficacy variables because its symptom complex varies widely daily within and among patients in terms of presence and severity of symptoms and the importance that the patient has attached to such symptoms. Patient behavior, such as control of fluid and/or food consumption, may also influence results particularly with voided profiles.

For these reasons, in our study overall improvement as expressed by the patient and the investigator (global assessment) was the primary efficacy variable and these variables were so defined before the start of the study. Other data were considered as supportive. Results of this study confirmed the observations made in previous studies of pentosanpolysulfate for the treatment of interstitial cystitis. All of the primary variables showed statistically significant differences in favor of pentosanpolysulfate over placebo after 3 months of treatment, including the evaluation by the patient of global improvement as well as improvement in pain and urgency, the evaluation by the investigator of global improvement, and the data from the pain and urgency scales.

In the analysis of the data derived from the patient followup questionnaire and the investigator evaluation form, ratings that were good or better (at least a 50% decrease in symptoms) were included in the group of patients considered to have experienced significant overall improvement. The assessment of patients in this manner was derived from prior experience in reported studies.[5, 6] It is important to reemphasize that this study was double-blind. Placebo and drug patients were rated identically.

Except for the number of patients with an increase of 20 cc or more in volume per void, 40% of the pentosanpolysulfate and 24% of the placebo patients ($p = 0.02$), there were no other differences between the treatment groups derived from the voiding profiles. This experience was similar to that of the previous study,[5, 6] which probably is a reflection of the fact that the earliest sign of remission of interstitial cystitis is a decrease in pain followed by a decrease in urgency. Changes that occur in voiding profiles do not take place within weeks but within

many months and perhaps 1 year may be required to notice significant improvements in the low volume dysfunctional bladders in these patients. The rehabilitation of the bladder muscle takes much longer than control of the disease complex as measured by a decrease in pain.[5-10] This slow recovery is not surprising, since the disease progresses slowly and insidiously during the years.[11]

It is important to note that patients selected for this study were those with rather severe disease, with longstanding duration and who had experienced minimal (or no) relief from conventional treatment, such as intravesical dimethylsulfoxide, chlorpactin, hydrodilation and others. Of the patients 32% were able to experience significant relief with the drug pentosanpolysulfate compared to 16% on placebo.

The incidence of adverse experiences was similar in patients from both treatment groups in this study (table 4). No adverse experiences were considered to be serious. Treatment was discontinued because of adverse experiences in 3 patients on pentosanpolysulfate and 5 on placebo. There were no clinically significant changes in laboratory results in either group.

To test the validity of the methods used to predict the outcome of interstitial cystitis successfully, the data were analyzed comparing patients who improved (better) to those who reported no improvement (not better). This analysis was as previously reported in a smaller study.[7] Basically, if one compared all patients reporting an improvement (on the global assessment) of at least 50% (regardless of whether they were on drug therapy or placebo) to patients reporting no improvement, then all parameters being monitored can be compared to determine if the patients do, in fact, improve when they say they do and, conversely, do not improve when they say they do not. Patients who report that they are better do, in fact, improve and patients who report no improvement, in fact, do not improve (table 5). For example, patients who claimed to be better had a decrease in the pain scales of 2.3, while those claiming no improvement had only a change of 0.4. These differences were significant ($p < 0.001$). In addition, patients who claimed to be better voided 4.9 times less per day compared to only 0.8 less voids for patients who were not better ($p = 0.0002$, table 6). The average voided volume increased 37 ml. in patients who were better and only 7 ml. in patients who were not better ($p = 0.01$).

In summary, this double-blind, placebo-controlled study demonstrated the efficacy and safety of pentosanpolysulfate for the relief of symptoms of interstitial cystitis, confirming previous data. Global evaluation by patients and investigators showed pentosanpolysulfate to be significantly more effective than placebo and the methodology used in this study provides a model for future investigators. The data from subjective evaluation and analogue scale measurements by the patients for pain and urgency indicated that the differences in favor of drug therapy compared to placebo were statistically significant. The voiding profile data in this study failed to provide statistically significant differences between pentosanpolysulfate and placebo except for the number of patients having an increase of 20 cc or more in average voided volume, which favored pentosanpolysulfate. This finding also confirms the previous experience that the voiding profiles are less sensitive in predicting early disease improvement than are improvements in pain and urgency. Adverse experiences and changes in laboratory values also were similar and unremarkable in both groups. It would appear that, on the basis of this study, pentosanpolysulfate has efficacy ameliorating the symptoms of interstitial cystitis in some patients.

TABLE 5. *Comparison of patients better (on overall assessment) to those not better*

	Better	Not Better	P Value
% Pts. with improvement in pain	100	5	<0.001
Global assessment of pain	(36)*	(110)*	
Av. change in pain scale	−2.3	−0.4	0.0001
% Pts. with improvement in urgency	89	3	<0.001
Global assessment of urgency	(36)*	(112)*	
Av. change in urgency scale	−2.1	−0.5	0.0001

Patients who report themselves better (at least 50% improvement in symptoms on overall global assessment) showed overall good improvement on other scales *compared to patients reporting no improvement (not better).*

* Total number of patients reporting.

TABLE 6. *Comparison of voiding profiles in patients reporting to be better (on overall global assessment) to those claiming not better*

	Better*	Not Better	P Value
Av. increase or decrease in vol. per void compared to baseline			
Mean ± SD	37.4 ± 55.8	7.5 ± 40.7	<0.01
No. pts.	36	96	
Av. increase or decrease in No. voids per day compared to baseline			
Mean ± SD	−4.9 ± 4.3	−0.8 ± 5.3	0.0002
No. pts.	36	96	

* Patients who reported 50% improvement in the overall global assessment. Significant improvement in voided volume and number of voids per day was also noted in these patients when compared to patients claiming no improvement (not better).

Dr. J. Richard Trout developed the statistical plan and performed all of the statistical analyses. Dr. James T. Baldini assisted with development of the protocol, monitoring of the study and preparation of this manuscript.

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