The Role of Pentosan Polysulfate in Treatment Approaches for Interstitial Cystitis

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Studies of the mechanisms and causes of interstitial cystitis (IC) and of the properties of pentosan polysulfate have provided a scientific rationale for using pentosan polysulfate to treat IC. In randomized, double-blind studies, patient and investigator evaluations of pentosan polysulfate in the treatment of IC resulted in favorable assessments of the drug. In addition, IC patients in two out of four randomized, prospective trials improved significantly in most variables with treatment by oral pentosan polysulfate; in the two other studies, the IC patients improved in some domains with pentosan therapy, although not significantly. Importantly, two longer-term, patient-evaluation studies showed that a longer duration of treatment with pentosan polysulfate resulted in greater improvements in patients' response rates and outcomes. The results indicate that treatment should be continued for 6 months or longer in order to show significant improvement. Of particular interest are studies suggesting that a potassium test may possibly predict the response of IC patients to treatment with pentosan polysulfate. [Rev Urol. *2002;4(suppl 1):S21–S27*]

Key words: Interstitial cystitis • Pentosan polysulfate • Bladder epithelium • Potassium chloride test

Pentosan polysulfate was initially intended in the 1950s to be an oral anticoagulant to replace parenteral heparin, but the anticoagulant activity of pentosan was found to be too weak to be clinically useful for this purpose. In the 1980s, however, basic science advances in the study of interstitial cystitis (IC) raised the possibility that pentosan polysulfate might be a useful therapy for IC. This article is a review of the scientific rationale for using pentosan polysulfate to treat IC and of the clinical data that supports pentosan polysulfate's primary role in the pharmacologic management of IC.

Scientific Rationale for the Use of Pentosan Polysulfate as Therapy for Interstitial Cystitis

The bladder epithelium has a lumenal coating of core proteoglycans, covalently attached glycosaminoglycans (GAG), and loosely adherent mucin.[1] The bladder mucin layer is responsible for preventing mucosal binding of calcium or protein.[2] This protective mucin effect was duplicated by the exogenous administration of pentosan polysulate in studies of animals in whom mucin was diminished.[3,4] Similarly, because the bladder mucin coating diminishes bacterial adhesion to bladder epithelium, the exogenous administration of the GAG-depleted bladder restored antibacterial properties.[5]

Bladder-surface GAG is an important means to defend epithelial integrity and prevent urine permeability across the epithelium.[6] Parsons and colleagues[7] measured bladder epithelial integrity indirectly in healthy subjects. Urea was instilled into the bladder for 45 minutes, and the recovery of urea was measured. The healthy women volunteers had a 5% loss of urea. After control epithelial-surface GAG was temporarily damaged with exogenous protamine sulfate, these same volunteers had a repeat 45-minute instillation of urea, and the urea loss increased to 22% ($P < .02$).[7] Interestingly, these healthy volunteers reported urgency and discomfort after protamine treatment, and these symptoms were reduced after subsequent administration of intravesical heparin.

Most IC patients have evidence of abnormal bladder epithelial permeability.[8,9] Parsons and associates[10] reported a follow-up study to the urea instillations they had previously performed in healthy subjects. They instilled urea into the bladders of healthy subjects and IC patients and again measured the amount of urea lost after 45 minutes. They found that the healthy individuals had lost 4% compared with a loss of 25% for IC patients ($P < .05$). Because these two studies used an indirect measure of bladder permeability (specifically, the difference between urea instilled into the bladder and urea collected 45 minutes later with bladder catheterization), some researchers felt that the study did not directly prove that permeability was at issue. To address this concern, Chelsky and colleagues[11] tested a more direct measure of epithelial permeability using radioactive diethylenetriaminepentaacetic acid (DTPA). The mean DTPA absorption across the epithelium after 30 minutes in 10 IC patients was 2.32% versus 1.27% for 9 controls ($P = .07$). The authors claimed that there was no statistical difference in permeability between groups, and many clinicians have quoted this paper to diminish the role of bladder permeability in IC. However, I would interpret their data differently. Based on the small numbers of patients tested (n = 19), their study power was only 30%, implying that their ability to prove a legitimate difference, if present, was only 30%. Moreover, the 83% increased mean permeability in their IC cohort almost reached statistical significance, so it is likely that had they studied two more patients, the study would have confirmed epithelial permeability in IC. Stated simply, their published data shows a 93% probability that there is a more than 80% increased mean permeability in IC patients compared controls.

Most IC patients have evidence of abnormal bladder epithelial permeability.

The potassium (KCl) test, popularized by Parsons, provides evidence that exogenous administration of intravesical potassium crosses the bladder epithelium and stimulates submucosal sensory nerves in IC patients.[12] Unfortunately, the exact nature of epithelial dysfunction in IC has not been identified. When electron micrography is used, no morphological differences in bladder epithelium are seen between IC patients and controls.[13] However, qualitative deficiencies in particular mucin components have been identified in IC patients, such as GP51.[14,15]

Properties of Pentosan Polysulfate

Pentosan polysulfate binds to bladder epithelium in colloidal suspension in animal models.[16] Moreover, pentosan polysulfate binds to uroepithelium with sufficient strength to resist bladder washing.[17] Further, pentosan polysulfate is effective at restoring epithelial permeability-barrier function in mucin-deficient bladders. In a rabbit study, bladders were pretreated with buffered saline, followed by the instillation of 14C-urea. In one cohort, bladders were then treated with protamine sulfate in order to damage surface mucin. In another cohort, bladders were treated with buffered saline and protamine sulfate and then treated with pentosan polysulfate. There was a significant increase in 14C-urea in the blood of rabbits treated with protamine only compared to that of controls ($P = .01$), but there was no statistical difference between controls and pentosan-polysulfate treated animals ($P = .92$).[18] These results imply (but do not prove) that pentosan polysulfate may restore epithelial barrier integrity in bladders

Table 1
Assessment of Response After 3 Months of Treatment with Pentosan Polysulfate (% Patients Improved)

Parameter*	Pentosan	Placebo	*P*-Value
Overall investigator evaluation	26	11	.03
Patient assessment			
Overall improved	28	13	.04
Pain questionnaire	27	14	.08
Pain scale	46	29	.07
Pressure to urinate	22	11	.08
Urgency scale	39	46	ns

*Investigators assessed patient outcomes by patient examination and voiding profiles. Investigators could rate patients as "worse," "no change," "fair," "good," "very good," or "excellent." Efficacy outcomes were based on a follow-up questionnaire completed by the patient after 3 months. Patients were asked if they felt improved overall compared to the beginning of the study, and if they had improved, they were asked to rate the improvement as "slight" (25%), "moderate" (50%), "great" 75%, or "complete cure" 100%. These same parameters were used to assess their perceived urgency and pain.

Table adapted from Mulholland SG, Hanno P, Parsons CL, et al. Pentosan polysulfate sodium for therapy of interstitial cystitis: a double-blind placebo-controlled clinical study. *Urology.* 1990;35:552–558, with permission from Elsevier Science.

where abnormal epithelial permeability is problematic. An alternate mechanism by which pentosan polysulfate treats IC has been proposed: experimental evidence shows that the drug stabilizes mast cells, which are implicated in about two thirds of IC cases.[19] In summary, the various studies described above provide a scientific basis for using pentosan polysulfate in the treatment of IC.

Double-Blind Studies of Pentosan Polysulfate Efficacy

In a study by Mulholland and colleagues,[20] 110 patients were randomized to oral pentosan polysulfate 100 mg 3 times daily versus placebo in a double-blinded format. Patient follow-up was for a minimum of 3 months. All patients were diagnosed using National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) criteria. To enter the study, patients had to discontinue all other therapies and then go on the study drug alone (pentosan polysulfate or placebo). The outcomes were assessed by patient questionnaires and by investigator evaluations. At baseline, there were no statistical differences between the drug-treated versus placebo-treated patients with respect to mean age (43 vs 45 years), percent women (91% vs 87%), mean years of IC symptoms (7 vs 6), prevalence of Hunner's ulcers (8% vs 4%), mean anesthetic capacity (569 cc vs 585 cc), or percent of patients with severe disease (59% vs 59%), respectively. The efficacy outcomes of the study after 3 months favored patients treated with pentosan polysulfate compared to placebo (Table 1). [20]

In a similar study by Parsons and associates,[21] 148 patients were randomized to oral pentosan polysulfate 100 mg 3 times daily versus placebo. Again, patients were diagnosed according to NIDDK criteria and followed for 3 months. The study was conducted in a randomized, prospective, double-blind format. Patient global ratings were used, and success was defined as a minimum of 50% improvement in the global ratings. Safety outcomes were also assessed. At baseline, there were no statistical differences between drug-treated versus placebo-treated patients with respect to mean age (43 vs 46 years), percent women (100% vs 93%), mean years of symptoms (6.6 vs 6.6), prevalence of Hunner's ulcers (4% vs 4%), prevalence of glomerulations (99% vs 99%), and mean anesthetic capacity (656 cc vs 601 cc), respectively. Similar to the study by Mulholland et al, patients rated their improvement overall, for pain, and for pressure to urinate, and for improved sexual intercourse by questionnaire where they could rate their change as "worse," "no better," or "improved," and if improved, then to rate the improvement as slight (25%), moderate (50%), great (75%), or symptoms gone (100%). However, in this study, success was considered improvement > 50%. Patients also completed pain and urgency scales at baseline and at the study end. The scales were a 6-point analog scale and success was considered an improvement at least 1 point or greater. The efficacy outcomes rated by an investigator evaluation showed that 36% of pentosan-treated versus 15% of placebo-treated patients improved >50% (P = .002). Patient-rated assessments again favored patients treated with pentosan polysulfate compared to those receiving placebo (Table 2). There were no significant side effects and no differences between cohorts for side effects.

Two earlier randomized, double-blind studies comparing pentosan polysulfate and placebo were reported. One multicenter study conducted by Holm-Bentzen and associates[22] entered patients under two separate protocols. In protocol A, IC patients were studied if they fulfilled anesthetic hydrodistension criteria, which included biopsy evidence of detrusor masto-

cytosis (>28 mast cells per mm^2). In protocol B, no definite evidence of anesthetic hydrodistension criteria were required and all patients had <28 mast cells per mm^2. In protocol B, however, symptoms had to have a minimum baseline severity (nocturia > 3 and high symptom scores). Importantly, because some patients benefit from anesthetic hydrodistension, patients were not started on the study drug until the symptoms recurred. Patients were randomized either to pentosan polysulfate 200 mg orally twice daily or placebo for 4 months. After 4 months, a cystoscopy under anesthesia, including hydrodistension and a bladder biopsy, was repeated. There were 43 patients in protocol A, and 39 completed the study; 72 patients were in protocol B, and 66 completed the study. There was a greater improvement in total symptom scores in pentosan-treated patients in protocol B than there was in controls ($P < .05$). Moreover, the pretrial to posttrial cystoscopic appearance of the bladder improved to a greater extent in both protocols for pentosan-treated patients than it did in controls ($P < .01$). The mean anesthetic capacity increased pretrial to posttrial in pentosan-treated patients from 260 cc to 475 cc in protocol A versus 300 cc to 300 cc ($P < .05$). Also in protocol A, mast cell counts decreased significantly for both pentosan-treated and placebo-treated patients ($P < .01$), but there was no statistical difference between groups. In protocol B, no significant change in cystoscopic appearance or mast cell counts was evident. Individual symptom assessments were not statistically different in either protocol A or B when pentosan-treated and placebo-treated patients were compared.

Table 2
Patient-Rated Response After 3 Months of Treatment with Pentosan Polysulfate (PPS) (% Improvement)

Patient-Rated Improvement*	PPS	Placebo	*P*-Value
Overall	32	16	.01
Pain questionnaire	38	18	.01
Pain scale	66	51	.005
Pressure to urinate	30	18	.04
Urgency scale	61	43	.01
Improved sexual intercourse	31	18	.06

*See note to Table 1 regarding measures of improvement.

PPS, pentosan polysulfate.

Adapted, with permission from Parsons CL, Benson G, Childs SJ, et al. A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosanpolysulfate. *J Urol.* 1993;150:845–848.

An earlier trial reported by Bade and colleagues[23] studied 20 patients who satisfied NIDDK criteria. Patients were randomized either to intravesical pentosan polysulfate (300 mg in 50 cc of normal saline) twice weekly or placebo. Although the first instillations were done in a hospital, patients were taught to self-catheterize, and they administered the study drug at home for 3 months. At baseline, the mean anesthetic capacity was 305 cc versus 243 cc, with no statistical difference in symptoms. There was 1 dropout in the pentosan group. After 3 months, 4 of 9 pentosan-treated patients reported overall subjective improvement compared with 2 of 10 placebo-treated patients ($P > .05$). In addition, the only significant specific improvement was that the awake cystometry capacity had improved from 226 cc to 265 cc ($P < .05$) in pentosan-treated patients, but was unchanged in the placebo cohort (202 cc to 208 cc). After the trial, 11 patients continued to receive pentosan instillations in an open-label trial, and after 18 months, 8 patients chose to continue pentosan instillations. The clinical significance of this study is limited because of the unique intravesical administration and twice-weekly dosing of the study drug.

These results support the observation that a patient often requires therapy longer than 6 months merely to see improvement.

Thus, of these four randomized, prospective studies, those reported by Mulholland and Parsons showed statistical improvements or trends in most variables favoring oral pentosan polysulfate over placebo. However, in the studies reported by Holm-Bentzen and Bade, with smaller numbers of patients, there were no statistical improvements for most variables, but with some trends favoring pentosan polysulfate treated patients.

The Impact of Treatment Duration

Two studies showed that a patient's response rate improves the longer the patient is on pentosan polysulfate therapy. In an open-label study by Hanno,[24] of 2089 IC patients enrolled, 90% were women, 94% were white,

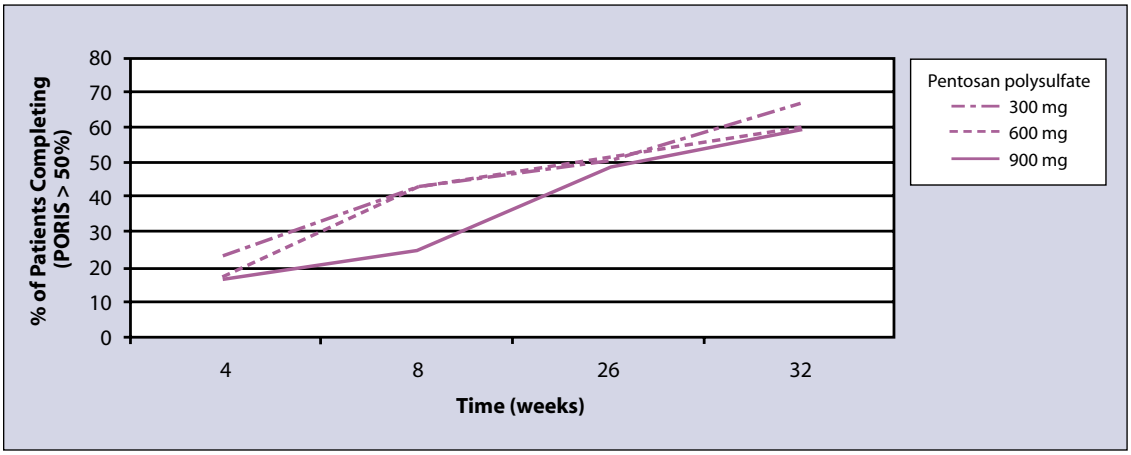

Figure 1. *Dose-ranging study of pentosan polysulfate sodium for interstitial cystitis. Success is defined as >50% reduction in a patient's overall rating of improvement of symptoms (PORIS).*

61% had had symptoms a minimum of 3 years, and two thirds were 21–50 years of age at enrollment. The global improvement ratings for overall outcome, pain, and urgency scores showed steady improvement through 2 years of pentosan polysulfate treatment. Of patients who showed improvement, most had done so by 2 years, so that there was a plateau phase (no new patient responders) between 2 to 3 years of therapy, so that the overall response rate reached nearly 65%. Separate pain and urgency scores and frequency and nocturia scores showed greatest responses within the first year of treatment and noted relatively steady scores thereafter.

In a recent multicenter trial by Nickel and associates,[25] 380 patients were randomized prospectively and in a double-blind format to receive 300 mg, 600 mg, or 900 mg of pentosan daily in three divided doses. The study authors also reported phenomena that favored long-term therapy. Success was defined as >50% reduction in a patient's overall rating of improvement of symptoms (PORIS). At baseline, patients were well randomized, with no statistical differences in percentages of women, race, mean duration, mean voids per day, and mean voided volume. Through 32 weeks of follow-up, patients in all three dosage groups fared equally well, with approximately 60% of the patients achieving a successful reduction in PORIS outcomes.

The inference from the study is that the duration of pentosan polysulfate treatment seems more important and beneficial to the patient outcome than the dosage does.

Importantly, the percentage of patients showing success on the PORIS scale improved steadily throughout the 32-week trial (Figure 1). Unlike the Hanno study, which was conducted for 3 years, this dose-ranging trial showed no plateau phase. The inference is that had the study been conducted for a longer duration, perhaps more patients would have shown >50% reduction in symptoms.

The safety data from the dose-ranging study showed that adverse effects were not statistically different among groups for headache, asthenia, or alopecia. However, abdominal pain and diarrhea increased as the dose increased. The inference from the study is that the duration of pentosan polysulfate treatment seems more important and beneficial to the patient outcome than the dosage does. Overall, 61% (230) of the patients completed the study, with only 5% of the patients dropping out because of lack of efficacy. This observation is important, because Jepsen and colleagues[26] showed a dropout rate of >80%. In the Jepsen study, patients had failed other therapies and were placed on pentosan polysulfate on a compassionate-use basis. As many as 81% of the patient dropouts occurred in the first 6 months of therapy, and nearly half of all dropouts occurred because of lack of effect. These results support the observation that a patient often requires therapy longer than 6 months merely to see improvement.

Can Patient Outcomes to Pentosan Polysulfate Therapy Be Predicted?

Several studies have attempted to address the issue of predicting the outcomes of pentosan treatment. In a retrospective study we conducted,[27] we hypothesized that the potassium test should predict response to pentosan-based therapy, because a positive potassium test implies an epithelium

Table 3
Potassium Leak Test and Patient Outcomes Resulting from Pentosan Polysulfate Therapy

	Potassium Test–Positive	Potassium Test–Negative	*P*-Value
Mean follow-up (months)	18	13	.40
% patients with > 25% pain score decrease	78	40	.01
% patients with > 50% pain score decrease	57	27	.06
% patients with > 25% frequency decrease	83	47	.02
% patients with > 50% frequency decrease	52	40	.40
% patients with > 25% nocturia decrease	83	53	.05
% patients with > 50% nocturia decrease	43	33	.60
% patients with > 25% improvement in all symptoms	78	33	.02
% patients with > 50% improvement in all symptoms	39	27	.30

Data from Teichman and Nielsen-Omeis.[27]

dysfunction, and the presumed mechanism of action of pentosan polysulfate is to treat this dysfunction. In our study, patients were stratified by a baseline potassium test (23 positive versus 15 negative). All patients were treated with a heparinoid (oral pentosan polysulfate or intravesical heparin) and an antidepressant (oral amitriptyline or paroxetine hydrochloride). The minimum follow-up was 6 months. The baseline characteristics were well matched between patients with a positive and negative potassium test. The mean age was 52 versus 56 years, mean duration of symptoms was 9 versus 10 years, mean pain (rated on a 5-point analog scale) was 3 versus 3, mean daytime frequency was 60 versus 45 minutes, mean episodes of nocturia were 4 versus 4, and mean anesthetic capacity was 683 versus 708 cc, respectively. Initially, a 25% reduction in symptoms favored patients who had tested positive, but this trend did not reach statistical significance for a 50% reduction in symptoms (Table 3).

In a recent abstract, Grégoire and colleagues[28] presented retrospective data on 189 patients with IC. Out of 127 patients who had a potassium test, 105 patients (83%) tested positive. In this series, 57 patients were treated with pentosan polysulfate for a mean duration of 16 weeks. Among the patients who had tested positive on the potassium testing, 73% responded to pentosan polysulfate. Only 3 patients who received pentosan polysulfate had tested negative, so a statistical analysis could not be done. But interestingly, among the pentosan polysulfate–treated patients who did not undergo potassium testing, only 45% improved. Although tempting to extrapolate the meaning of this latter comparison, any inferences would be speculative as there is no means to determine which of these untested patients would have tested potassium positive or negative.

Conclusions

Pentosan polysulfate is an efficacious therapy for patients with IC, and the response to treatment appears greatest when patients are treated for 6 months or longer. The potassium test may predict the response to pentosan polysulfate therapy. ■

Main Points

- Various studies of the causes of interstitial cystitis (IC) and the properties of pentosan polysulfate provide a scientific basis for using pentosan polysulfate to treat IC.
- Randomized, double-blind studies of pentosan polysulfate in the treatment of IC resulted in favorable assessments of the drug by patient and investigator evaluations.
- IC patients in two out of four randomized, prospective trials improved significantly in most variables through oral pentosan polysulfate treatment; IC patients in the two other studies improved in some domains, although not significantly, with pentosan therapy.
- Two longer-term, patient-evaluation studies showed that a longer duration of treatment with pentosan polysulfate resulted in greater improvements in patients' response rates and outcomes. The results indicate that treatment should be of 6-months or longer duration.

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