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Pentosan Polysulphate Sodium

comforting life during IC

PRODUCT MONOGRAPH

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Interstitial Cystitis: An Overview

Introduction

Interstitial cystitis (IC) is a chronic pain condition. It is defined as a syndrome of urinary frequency, urgency, pelvic pain relieved with voiding, nocturia and dyspareunia. The International Continence Society (ICS) states that IC is synonymous with the term 'painful bladder syndrome' (PBS). PBS is characterised by 'suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and nighttime frequency, in the absence of proven urinary infection or other obvious pathology'.[1] A person with IC characteristically does not fit into any other disorder, including urinary tract infections (UTIs), carcinoma, or radiation- or drug-induced cystitis.[2]

Epidemiology of IC

There have been variable reports on the prevalence of IC. According to a population-based study, the prevalence of IC in women was found to be 18.1 per 100,000. The combined prevalence in both sexes was 10.6 cases per 100,000. The annual incidence of new female cases was 1.2 per 100,000. Out of the total cases, 10% were severe cases and 10% were in men.[3] In 'The Nurses' Health Study', the prevalence of IC was 67 per 100,000 in women and 52 per 100,000 in men.[4]

Median age for the onset of IC is 40 years, with usual age of onset ranging between 30 and 70 years. Disease prevalence seems to be on rise among young and middle-aged women. Around 90% of the cases occur in women, with men comprising the remaining 10%; children can be affected rarely. It is unusual to find late deterioration in symptoms. A history of UTI is twice more likely in patients with IC as compared to controls.

IC onset is subacute rather than insidious, with classically full-blown disease occurring in a relatively short time. Another study has shown that IC reaches its final state quickly, and there is less chance of further deterioration in symptom severity.[3]

Spontaneous remission is seen in up to 50% of patients, with a duration ranging from 1 to 80 months (mean 8 months). As compared to patients undergoing chronic dialysis for renal failure, quality of life of IC patients is lower.

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Aetiology and Pathogenesis

Although various studies have come up with several hypotheses about the causation of IC, there exists an uncertainty about the aetiopathogenesis. Some of the possible causative factors of IC are given below.

Defect in glycosaminoglycan layer

A commonly accepted theory is that symptoms of IC may arise due to a defect in the glycosaminoglycan (GAG) layer covering the bladder urothelium. GAGs are physiological molecules that are highly hydrophilic and protective, as they form a stable layer of water between the urothelium and bladder lumen. This layer of GAGs acts as a barrier between toxins (bacteria, microcrystals, ions, proteins and other substances in the urine) and bladder urothelium, and protects it from injury by these toxins. Any damage in this layer leads to IC.[5] Increased amounts of some unspecified toxic substance (ie, potassium) permeate the bladder wall due to a suspected deficiency in the surface GAG-mucin layer. This leads to inflammation and pain.

Some researchers are of the view that this GAG alteration reflects the inflammatory process rather than being the cause of it.[5] Figure 1 depicts a model for IC, which proposes that inflammation begins with irritation of the GAG layer initiating further disruption. This model is useful in identifying potential treatment targets for IC/PBS.[1]

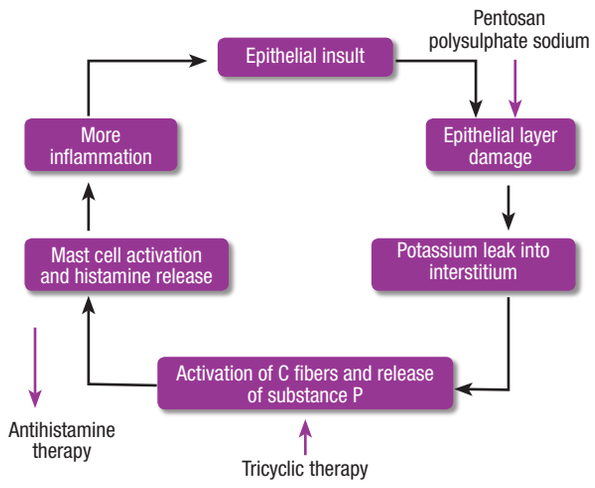

Figure 1. Pathogenetic model for IC/PBS, along with various therapies targeted at different points in the pathogenic process.

Treatment with GAG 'replacements', such as sodium pentosan polysulphate (an exogenous, oral GAG) and heparin or hyaluronic acid administered intravesically was quite successful in symptom relief.[5]

Urinary tract infection

The clinicopathologic presentation of IC and UTI shares common clinical characteristics. The difference lies in the fact that it is possible to culture uropathogenic bacteria from UTI patients, and antibiotics show a greater response in UTI patients as compared to patients with IC. History of UTI is common in patients with IC, and both these conditions have similar morbidity. It is possible to trace the aetiology of IC to low-count bacteriuria, fastidious organisms (usually unrelated with clinical symptoms) or even cryptic nonculturable microorganisms.[5]

Immunologic response theory

According to the immunologic theory, IC is an autoimmune disorder, related to either a nonspecific or a bladder-specific antibody or to a mast cell activity. However, immunologic studies in recent past have seen that there is lack of specificity with regards to IC. The most probable reason for generation of antibody could be damage to bladder tissues rather than a primary cause of the inflammation. Even the theory of IC being a primary mast cell disorder has been disreputed.[5]

Neurogenic cause

The histopathologic observation of bladder showing the neural proliferation and chronic perineuritis in the bladder wall has given rise to the concept of neurogenic aetiology for IC. This neural proliferation can lead to cardinal IC symptoms of pain and urinary frequency and urgency.[5]

Clinical Presentation and Diagnosis

Patients having IC/PBS present with a symptom complex that includes urinary frequency, urinary urgency, nocturia, and bladder or pelvic pain that may be temporarily relieved by voiding. The

progression of these symptoms could be in the order of mild and intermittent to severe and constant. Voiding symptoms are usual, but not always present in IC. In those who present without voiding symptoms, diagnosis can be misdirected, as pain may not be perceived as being generated from the bladder. Thus, IC/PBS can be misdiagnosed as other disorders such as endometriosis, vulvodynia, vaginitis or prostatitis.[1]

Table 1 provides diagnostic approaches to IC. The National Institutes of Health–National Institute of Diabetes & Digestive & Kidney Diseases (NIH-NIDDK) in mid-1980s circulated the clinical and cystoscopic diagnostic criteria for research studies on IC (Table 2). Although originally promoted as research criteria, these inadvertently became the de facto criteria for clinical diagnosis. The symptoms in IC patients frequently overlap and may be seen as urologic, gastrointestinal, gynaecologic and originating from pelvic floor, including the prostate. IC is most likely to be present in patients with frequency-urgency syndrome, PBS and chronic pelvic pain syndrome.[6]

Table 1. Clinical Diagnosis of IC

Clinical	Morbidity
Pain; bladder irritability	Treatment predictors
Exclusion infection/cancer	
O'Leary-Sant symptom scores	**Urodynamics**
	Sensory instability
Clinical and cytoscopic (NIH-NIDDK)	Motor instability
Ulcer, nonulcer interstitial cystitis	
General, spinal anaesthesia	**Potassium sensitivity test**
60% rate underdiagnosis	25% underdiagnosis
Useful in prognosis	False positive/negative
	Potentially painful
Bladder biopsy	Low sensitivity/specificity
Variable utility	
Histologic subtyping	**Urinary markers**
Country/region specific	GP-51; APF
	Potentially useful

NIH-NIDDK, National Institutes of Health-National Institute of Diabetes & Digestive & Kidney Diseases; GP-51, glycoprotein-51; APF, antiproliferative factor.

Table 2. The National Institutes of Health–National Institute of Diabetes & Digestive & Kidney Diseases (NIH-NIDDK) Research Criteria for IC[5]

Inclusion criteria
Cystoscopy findings of glomerulation or classic Hunner's ulcer
Symptoms of bladder pain or urinary urgency
Exclusion criteria
Younger than 18 years
Urinary frequency while awake less than eight times a day
Nocturia less than twice a night
Maximal bladder capacity >350 mL while awake
Absence of intense urge to void with bladder filled to 100 mL of gas or 250 mL of water at medium filling rate during cystometry
Involuntary bladder contractions on cystometrogram at medium filling rate
Symptoms persisting for <9 months
Symptoms relieved by antimicrobial agents (antibiotics and urinary antiseptics), anticholinergic drugs or antispasmodics
Urinary tract or prostatic infection in the past 3 months
Active general herpes or vaginitis
Urethral diverticulum
Uterine, cervical, vaginal or urethral cancer within the past 5 years
History of cyclophosphamide or chemical cystitis, tuberculosis or radiation cystitis
History of bladder tumours (benign or malignant)

Management

Nonpharmacologic therapy

The key to successful treatment of IC/PBS is conservative or behavioural therapy. The main principles of nonpharmacologic management are patient education about symptoms, behaviour modification for urinary urgency and frequency, physical therapy for trigger point release, stress reduction and dietary manipulation. Dietary modifications can be used as a first-line therapy for the management of IC. Around 50% to 60% IC patients are able to recognise acidic fluids or foods that exacerbate symptoms or cause a flare-up.[2] Common acidic foods include alcohol-containing beverages, carbonated drinks, caffeine, spicy foods, tomatoes and vinegar. Management of mental and emotional stress is important

to control the disease, although it remains unclear if stress is a precipitant or consequence of IC/PBS.[1,2]

Multimodal pharmacologic approach

The pharmacologic therapy for IC/PBS aims to restore bladder surface integrity, modulate neuronal dysfunction and reduce any coexisting inflammation. A multimodal pharmacologic approach is required to achieve these goals by targeting the specific points in the postulated cycle of the disease (Figure 1).[1]

PPS: The only approved drug

The only oral drug currently approved by the US Food and Drug Administration (FDA) for the treatment of IC is pentosan polysulphate sodium (PPS). It provides the bladder with a compound that is structurally similar to bladder surface GAG layer. Although its mechanism of action largely remains unclear, it promotes restoration of the defective layer, thereby preventing further urothelial insult. The approved dose of PPS is 100 mg three times per day. Although its action seems to be of utmost help to patients, some of them respond slowly to treatment, as it may take several months before any relief is noted. Treatment with PPS should continue for at least 6 months.[1,7]

Suppression of mast cell degranulation with antihistamines

Oral antihistamine hydroxyzine may play a significant role in the management of IC. It is recommended to suppress mast cell degranulation, a constant feature of the pathologic inflammatory response. Hydroxyzine is a unique antihistamine as it brings about this specific suppression. Studies have suggested that hydroxyzine is efficacious for patients with biopsy-documented bladder mastocytosis or mast cell activation and for patients with a history of allergies.[5] Dosing starts at 25 mg, given at bedtime, and may increase to 50 to 100 mg/d during the allergy season.[1,7]

Antidepressants

The beneficial effects of tricyclic antidepressants in IC include central and peripheral anticholinergic actions, blocking reuptake of serotonin and norepinephrine, and antihistaminic properties.[5] Amitriptyline is an oral tricyclic antidepressant that has found use in IC/PBS for regulation of bladder pain and urgency by modulating neuronal dysfunction. It has antihistaminic properties also. As per clinical studies, amitriptyline in the dose of 25 to 75 mg/d taken at bedtime provides mild-to-moderate central pain modulation in majority of patients with IC/PBS. It has been found to be safe and effective in patients with IC/PBS for up to 4 months.[1,7]

Oral drugs for IC/PBS are generally effective, although a few have shown mixed results. The lack of consistent results from studies could be due to ambiguity in the diagnosis of IC/PBS. It could also be due to the previously restrictive diagnostic criteria, which used to isolate patients with very severe, possibly refractory, disease that may not respond to conservative therapy. Some patients may show response to one- or two-drug therapy, but a considerable fraction of patients may require all treatment modalities simultaneously.[1,7]

Pentosan Polysulphate Sodium

Product Information

PPS is a semisynthetic sulphated polysaccharide. It is a heparin-like macromolecular carbohydrate derivative and resembles GAGs, chemically and structurally.[8] Its chemical structure is described in Figure 2.

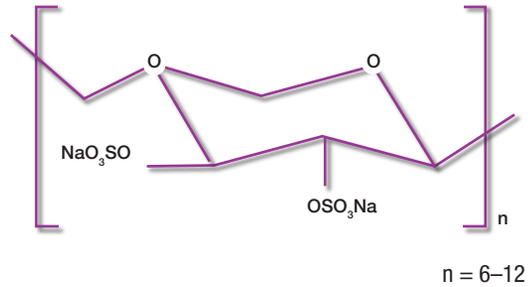

Figure 2. Chemical formula of pentosan polysulphate.

Indication

PPS is indicated in IC for relief of bladder pain or discomfort.

Mechanism of Action

The specific mechanism of action of pentosan polysulphate is unknown. However, many theories have shown its efficacy in providing symptom relief in IC. One of the widely accepted theories suggests that PPS has the ability to replace damaged parts of the GAG layer lining the bladder. The GAG layer is the mucous coating on the transitional epithelium of the bladder, which protects the bladder lining. This GAG layer potentially controls the cell permeability by preventing most solutes from coming into contact with the cell membranes. Therefore, any kind of harm to this GAG barrier has the potential to make the bladder epithelium more permeable to urinary substances, potentially leading to the development of IC.[8]

In patients with damaged GAG layer, exogenously administered polysaccharides such as polysulphate fix the gaps and decrease the IC symptoms (Figure 3). Intravesical pretreatment with pentosan polysulphate has the ability to reduce the damage done by the cytotoxic substance acrolein in transitional cells in the bladder of female rats. This implies an improvement of GAG layer properties by pentosan polysulphate. Bladder epithelial permeability in humans has been seen to be reduced with pentosan polysulphate treatment. This has been detected by employing the potassium sensitivity test. At the end of the study, IC patients having clinical improvement with PPS treatment had a higher reduction in potassium sensitivity

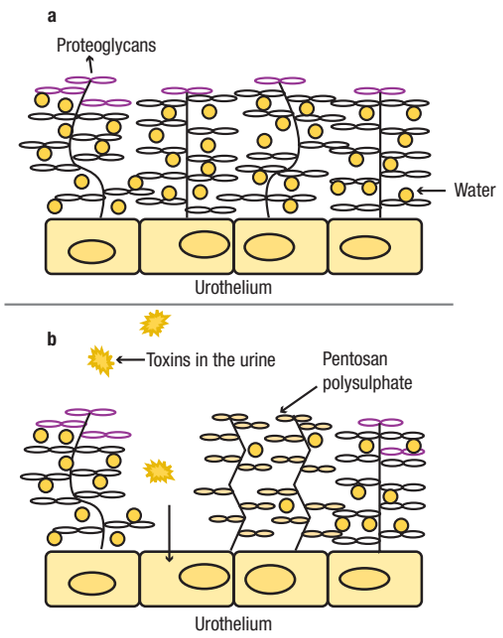

Figure 3. A suggested mechanism of action of pentosan polysulphate. In case of intact GAG layer on the bladder endothelium, (a) the anionic charge of the proteoglycans traps water between the spaces in the GAG layer, thereby creating a barrier to toxins and bacteria and regulating permeability. When this GAG layer is damaged, (b) there is penetration of toxins in the epithelial layer. Pentosan polysulphate helps in the repair of GAG layer and restores the permeability function of the barrier.

in their bladder (compared with baseline) than those who did not improve clinically.[8,9]

Many studies have proposed and supported a cytoprotective effect of PPS that causes a reduction in inflammation of the bladder mucosa in IC patients. The nuclear factor-κB is a nuclear transcription factor mediating the inflammatory response in chronic inflammatory diseases such as rheumatoid arthritis. Pentosan polysulphate has been seen to inhibit the nuclear factor-κB, as seen in an in vitro study of human uroepithelial cells. The histopathologic examination of bladder in IC patients shows that it has activated mast cells. Pentosan polysulphate appears to inhibit (in a dose-dependent manner) the stimulation of connective tissue mast cells and mucosal mast cells. Therapy with PPS results in significant decrease in histamine secretion (compared with untreated mast cells). This effect of PPS is a supplementary action of the drug, resulting in clinical symptom improvement in IC patients.[8]

Clinical Pharmacology

Pharmacokinetics

Pharmacokinetic profile of PPS has been studied in healthy volunteers. No data are available for persons aged <16 years.[8]

Absorption

Healthy female volunteers were studied in a clinical pharmacology trial on pentosan polysulphate. The volunteers received a single oral dose of 300 or 450 mg of PPS containing radiolabelled drug as a solution under fasting conditions. In this study, the maximal levels of plasma radioactivity were seen approximately at a median of 2 hours (range 0.6–120 hours) after dosing. Evaluation of urinary excretion of radioactivity led to the observation that a mean of approximately 6% of a radiolabelled oral dose of PPS is absorbed into the systemic circulation.[10]

Food effects

Pentosan polysulphate has been administered with water 1 hour before or 2 hours after the meals in clinical trials. It is unknown if food has any effect on absorption of PPS.[10]

Distribution

In preclinical studies with parenterally administered radiolabelled PPS, it has been seen that pentosan is distributed to the uroepithelium of the genitourinary tract. As compared to the genitourinary tract, less amounts of the drug have been found in the liver, spleen, lung, skin, periosteum and bone marrow. Penetration in erythrocytes in animals is also low.[10]

Metabolism

Although pentosan is less absorbed, the fraction of oral dose absorbed is metabolised by partial desulphation in the liver and spleen, and by partial depolymerisation in the kidney to a large number of metabolites. Continued dosing can saturate both desulphation and depolymerisation.[10]

Excretion

When an oral solution of a 300- or 450-mg dose of PPS containing radiolabelled drug is administered to groups of healthy subjects, there is a decline in plasma radioactivity with mean half-lives of 27 and 20 hours, respectively. Among orally administered dose of PPS,

a large proportion (mean 84% in the 300-mg group and 58% in the 450-mg group) is excreted unchanged in the faeces. Urinary excretion is a mean of 6% of an oral dose, mostly as desulphated and depolymerised metabolites. Very small amount of intact drug (mean 0.14% of orally administered dose) is recovered in urine.[10]

Pharmacodynamics

PPS has been observed to attach to the bladder wall mucosal membrane in clinical study models. The cell permeability of the bladder mucosa may be controlled with pentosan that acts as a buffer, thereby preventing irritating solutes in the urine from reaching the cells.[10]

Clinical trials

Pentosan sulphate was evaluated for pain relief in patients with chronic IC in two clinical trials. All patients met the NIH definition of IC based upon the results of cystoscopy, cytology and biopsy. In a blinded, randomised, placebo-controlled study, 151 patients (145 women, 5 men and 1 unknown) were evaluated with a mean age of 44 years (range 18–81 years). Placebo as well as pentosan polysulphate 100 mg three times a day was prescribed to approximately equal number of patients for 3 months. Patients' own assessment was the basis of clinical improvement in bladder pain. It was noticed that 38% of patients on pentosan polysulphate and 18% of patients on placebo showed >50% improvement in bladder pain.[10]

In another clinical trial, a retrospective analysis of 2499 patients who received pentosan 300 mg a day without blinding was conducted. Of the 2499 patients, 2220 were women, 254 were men and 25 were of unknown sex. The patients had a mean age of 47 years, and 23% were over 60 years of age. Overall, 1192 (48%) received pentosan polysulphate for 3 months, 892 (36%) for 6 months and 598 (24%) for 1 year. Unblinded evaluations of patients were conducted every 3 months to observe the patients' rating of overall change in pain in comparison to baseline and to calculate the difference in 'pain/discomfort' scores. At baseline, pain/discomfort scores for the original 2499 patients were severe or unbearable in 60%, moderate in 33%, and mild or none in 7% of patients. Table 3 shows the extent of the patients' pain improvement.[10]

Table 3. Pain Scores in Reference to Baseline in Open-label Physician's Usage Study[a] (N = 2499)[10]

Efficacy parameter	3 months[b]	6 months[b]
Patient rating of overall change in pain (recollection of difference between current pain and baseline pain)[c]	N = 1161 Median = 3 Mean = 3.44 CI: (3.37, 3.51)	N = 724 Median = 4 Mean = 3.91 CI: (3.83, 3.99)
Change in pain/discomfort score (calculated difference in scores at the time point and baseline)[d]	N = 1440 Median = 1 Mean = 0.51 CI: (0.45, 0.57)	N = 904 Median = 1 Mean = 0.66 CI: (0.61, 0.71

[a]Trial not designed to detect onset of pain relief.
[b]CI = 95% confidence interval.
[c]Six-point scale: 1 = worse; 2 = no better; 3 = slightly improved; 4 = moderately improved; 5 = greatly improved; 6 = symptom gone.
[d]Three-point scale: 1 = none or mild; 2 = moderate; 3 = severe or unbearable.

At 3 months, 29% of the patients in the study had pain scores that improved by one or two categories. By 6 months, an additional 116/2499 (5%) of patients had improved pain scores among the 892 patients who continued taking pentosan. After 6 months, <1.5% of patients in the study reported the first onset of pain relief (see Table 4).[10]

Table 4. Number (%) of Patients with New Relief of Pain/discomfort in the Open-label Physician's Usage Study[a] (N = 2499)[10]

	At 3 months[b] (n = 1192)	At 6 months[c] (n = 892)
Considering only the patients who continued treatment	722/1192 (61%)	116/892 (13%)
Considering all the patients originally enrolled in the study	722/2499 (29%)	116/2499 (5%)

[a]First-time improvement in pain/discomfort score by one or two categories.
[b]Number (%) of patients with improvement of pain/discomfort score at 3 months when compared to baseline.
[c]Number (%) of patients without pain/discomfort improvement at 3 months who had improvement at 6 months.

Dosage

As per the recommendations, the dose of pentosan polysulphate is 300 mg/d taken as one 100-mg capsule orally three times daily. The capsules should be taken with water at least 1 hour before or 2 hours after the meals.[10]

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A reassessment after 3 months is required for patients receiving pentosan polysulphate. In case no improvement is observed and limiting adverse events are not present, pentosan polysulphate may be continued for another 3 months. In patients whose pain is not improved by 6 months of treatment, the clinical value and risks of continued treatment are unknown.[10]

Adverse Effects

Pentosan polysulphate has been evaluated in clinical trials in a total of 2627 patients with a mean age of 47 years (range 18–88 years, with 581 [22%] over 60 years of age). Out of 2627 patients, 128 patients were in a 3-month trial and the remaining 2499 patients were in a long-term, unblinded trial (Table 5). The mortality rate was 6/2627 (0.2%) in patients receiving the drug over a period of 3 to 75 months. It appeared that the mortality was related to other concurrent illnesses or procedures, except in one patient for whom the cause was not known. Serious adverse events occurred in 33/2627 (1.3%) patients.

An unblinded clinical trial was carried out on 2499 IC patients treated with pentosan polysulphate. Of the 2499 patients, 1192 (48%) received pentosan polysulphate for 3 months, 892 (36%) for 6 months, 598 (24%) for 1 year, 355 (14%) for 2 years and 145 (6%) for 4 years.

The following adverse events were reported in these 2499 IC patients treated with pentosan polysulphate: frequency (1%–4%), alopecia (4%), diarrhoea (4%), nausea (4%), headache (3%), rash (3%), dyspepsia (2%), abdominal pain (2%), liver function abnormalities (1%) and dizziness (1%).

Frequency (<1%)

GIT: Vomiting, mouth ulcer, colitis, oesophagitis, gastritis, flatulence, constipation, anorexia and gum haemorrhage

Haematologic: Anaemia, ecchymosis, increased prothrombin time (PT), increased partial thromboplastin time (PPT), leucopenia and thrombocytopenia

Hypersensitive reactions: Allergic reaction and photosensitivity

Table 5. Adverse Effects in Placebo-controlled Clinical Trials of Pentosan Polysulphate 100 mg Three Times a Day for 3 Months[10]

Body system/adverse experience		Elmiron® (n = 128)	Placebo (n = 130)
CNS overall	Number of patients[a]	3	5
	Insomnia	1	0
	Headache	1	3
	Severe emotional lability/ depression	2	1
	Nystagmus/dizziness	1	1
	Hyperkinesia	1	1
GI	Overall number of patients[a]	7	7
	Nausea	3	3
	Diarrhoea	3	6
	Dyspepsia	1	0
	Jaundice	0	1
	Vomiting	0	2
Skin/Allergic	Overall number of patients[a]	2	4
	Rash	0	2
	Pruritus	0	2
	Lacrimation	1	1
	Rhinitis	1	1
	Increased sweating	1	0
Other	Overall number of patients[a]	1	3
	Amenorrhoea	0	1
	Arthralgia	0	1
	Vaginitis	1	1
Total events		17	27
Total number of patients reporting adverse events		13	19

[a]Within a body system, the individual events do not sum to equal overall number of patients because a patient may have more than one event.

Respiratory system: Pharyngitis, rhinitis, epistaxis and dyspnoea

Skin and appendages: Pruritus and urticaria

Special senses: Conjunctivitis, tinnitus, optic neuritis, amblyopia and retinal haemorrhage

Warning and Precautions

General

Pentosan polysulphate has a weak anticoagulant (1/15 of the activity of heparin) activity. Incidence of rectal haemorrhage has been reported at a daily dose of 300 mg. Bleeding complications of ecchymosis, epistaxis and gum haemorrhage have also been reported. It is necessary to evaluate the patients who are about to undergo invasive procedures or those having signs/symptoms of

underlying coagulopathy or other increased risk of bleeding (due to other therapies such as coumarin anticoagulants, heparin, t-PA, streptokinase, high-dose aspirin or nonsteroidal anti-inflammatory drugs) for haemorrhage. Patients with diseases such as aneurysms, thrombocytopenia, haemophilia, gastrointestinal ulcerations, polyps or diverticula require a detailed evaluation before initiating pentosan polysulphate therapy. Pentosan polysulphate should be prescribed with caution to patients with a history of heparin-induced thrombocytopenia.

Pentosan polysulphate may cause alopecia. Alopecia started within the first 4 weeks of treatment in clinical trials with pentosan. Alopecia areata limited to a single scalp area was the most common variety reported in 97% of the cases.[10]

Hepatic insufficiency

No studies of pentosan polysulphate have been conducted in patients with hepatic insufficiency. Impaired hepatic functions can impact the pharmacokinetics of pentosan polysulphate, as there is evidence of hepatic contribution to the elimination of pentosan polysulphate. Pentosan polysulphate in this patient population should be prescribed cautiously.[10]

Mild elevations (<2.5 times normal), reported 3 to 12 months after the initiation of pentosan polysulphate therapy, of elevated transaminase, alkaline phosphatase, Y-glutamyl transpeptidase and lactic dehydrogenase occur in around 1% of patients. These elevations were not associated with jaundice or other clinical signs or symptoms of liver impairment. These biochemical changes have been noticed to be of transient nature, associated with mild increases in PTT and PT (<1% for both) or thrombocytopenia (0.2%).

Patient information

Pentosan polysulphate should be taken as prescribed. Bleeding time may be increased, as pentosan polysulphate has a weak anticoagulant effect.[10]

Laboratory test findings

No effect of PPS has been found on PT or PTT up to 1200 mg/d in 24 healthy male subjects treated for 8 days. Inhibition of factor Xa generation in plasma and thrombin-induced platelet aggregation in human platelet-rich plasma ex vivo has been observed with pentosan polysulphate.[10]

Carcinogenicity, mutagenesis and impairment of fertility

In animal studies, no clear evidence of drug-related tumorigenesis or carcinogenic risk has been observed. PPS was not clastogenic or mutagenic when tested in the mouse micronucleus test or the Ames test (*Salmonella typhimurium*). No investigation of the effect of PPS on spermatogenesis has been conducted.[10]

Pregnancy category B

Animal studies have not shown any evidence of impaired fertility or harm to the foetus from pentosan polysulphate. There are no adequate and well-controlled studies in pregnant women. Pentosan polysulphate should be used in pregnancy only if required, as animal studies are not always predictive of human response.[10]

Nursing mothers

There is no evidence on pentosan's excretion in human milk. Pentosan polysulphate should be prescribed with caution to a nursing woman, as many drugs are excreted in human milk.[10]

Paediatric use

As there are no studies of pentosan use in persons aged <16 years, its safety and effectiveness in paediatric patients are yet to be established.[10]

Contraindications

A known hypersensitivity to the drug, structurally related compounds or excipients is a clear contraindication for its use in patients.

Therapeutic Efficacy in IC

In comparison with placebo

Mulholland and colleagues conducted a double-blinded study in 110 patients who were randomised to oral pentosan polysulphate 100 mg three times daily vs placebo.

- Patients were followed up for a minimum of 3 months.
- The diagnosis was based on NIDDK criteria.

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- Discontinuation of all other therapies was required to enter the study.
- Patient questionnaires and investigator evaluations were used to assess the outcomes.

No statistical differences at baseline were observed between the drug- and placebo-treated patients with respect to mean age (43 vs 45 years), percentage of women (91% vs 87%), mean years of IC symptoms (7 vs 6 years), prevalence of Hunner's ulcers (8% vs 4%), mean anaesthetic capacity (569 vs 585 cc) or percentage of patients with severe disease (59% vs 59%). At 3 months, the results favoured patients treated with pentosan polysulphate compared to placebo (Table 6).[11]

Another randomised, prospective and double-blind study by Parsons and associates evaluated 148 patients who were given oral pentosan polysulphate 100 mg three times daily vs placebo. Similar to the study by Mulholland and colleagues, patients were diagnosed according to NIDDK criteria and followed up for 3 months. Patient global ratings were used, with a minimum of 50% improvement in the global ratings being defined as success. Assessment of safety outcomes was also done.

No statistical differences were observed at baseline between drug- and placebo-treated patients with respect to mean age (43 vs 46 years), percentage of women (100% vs 93%), mean years of symptoms (6.6 vs 6.6 years), prevalence of Hunner's ulcers (4% vs 4%), prevalence of glomerulations (99% vs 99%) and mean anaesthetic capacity (656 vs 601 cc). Patient ratings for overall improvement, pain, pressure to urinate and improved sexual intercourse were 'worse', 'no better' or 'improved'. They were also required to rate the improvement as:

- Slight (25%)
- Moderate (50%)
- Great (75%)
- Complete cure (100%)

Improvement >50% was considered as success. Patients were also asked to complete pain and urgency scales at baseline and at the end of the study. A six-point analogue scale was used, with an improvement at least one point or greater being considered as success. The study observations were:

Table 6. Response Assessment Post 3 Months[2] Treatment with Pentosan Polysulphate (Percentage of Patients Improved)[11]

Parameter[a]	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

[a]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.

- Thirty-six percent of pentosan-treated vs 15% of placebo-treated patients improved >50% ($P = .002$).
- Patients treated with pentosan polysulphate compared to those receiving placebo were favoured by patient-rated assessments (Table 7).
- No significant side effects as well as differences between cohorts for side effects were noticed.[11]

Pentosan vs other drugs

Studies have observed that the efficacy of pentosan polysulphate is significantly less than cyclosporin and is not very different from hydroxyzine, or a combination of pentosan polysulphate and hydroxyzine, or placebo in reducing IC symptoms.8 A study conducted over a period of 6 months compared the efficacy of cyclosporin with pentosan polysulphate in patients with IC. The study observations were:

- There was significantly smaller reduction in the 24-hour urination frequency in pentosan polysulphate recipients than in cyclosporin recipients.
- Anticipated primary end point of a 50% reduction in frequency in 24 hours was not achieved by any patient in pentosan

Table 7. Response (Patient-rated) Post 3 Months[2] Treatment with Pentosan Polysulphate (PPS) (Percentage of Patients Improved)[11]

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

polysulphate group as compared to 34% patients in cyclosporin recipients ($P<.001$).

- A significantly smaller reduction in the VAS score was seen in pentosan group as compared to cyclosporin. There was an improvement in the visual analogue scale (VAS) score for pain in both pentosan polysulphate and cyclosporin groups (–1.6 to –4.7 cm).
- Cyclosporin may be useful for patients who have not benefited from other IC therapies; however, patients on cyclosporin need to be regularly monitored for blood pressure and serum creatinine levels.[8]
- At least three previous unsuccessful treatments for IC were observed in more than half of the study population.
- None of the patients had tried pentosan polysulphate previously.
- Mean age of the patients in the study was 58 years, relatively higher than the patients reported in other studies.[8]

A 6-month pilot study evaluated hydroxyzine, pentosan polysulphate, a combination of the two drugs or placebo to treat patients with IC. Patients, median age of 45 years, had a moderate degree of IC for a minimum of 24 weeks prior to entering the trial.[8] Patients on pretreatment with hydroxyzine and/or pentosan polysulphate were allowed to participate. The observations from the study were:

- Proportion of GRA responders was numerically greater in the group receiving pentosan polysulphate alone than in the group receiving placebo or hydroxyzine alone.
- There were more responders in the pentosan polysulphate treatment arms (34%) as compared to the treatment arms without pentosan polysulphate (18%) ($P = .064$).
- In comparison, there was no significant difference in the proportion of GRA responders in the combined hydroxyzine arms (31%) vs the no hydroxyzine arms (20%).

The study had a possible bias due to patient withdrawals, limited study design and limited statistical power due to low rates of recruitment. Therefore, these results need to be interpreted with caution.[8]

Long-term treatment with pentosan polysulphate

Clinical studies have revealed that the longer the patient on pentosan polysulphate therapy, the better the response rate.[11] An open-label study[11] conducted in 2089 IC patients observed that:

- Two years of continuous treatment with pentosan results in steady improvements in the global improvement ratings for overall outcome, pain and urgency scores.
- Maximum improvement was seen at the end of study period.
- There was a plateau phase (no new patient responders) between 2 and 3 years of therapy. Therefore, the overall response rate reached nearly 65%.
- Analysis of pain and urgency scores and frequency and nocturia scores showed that maximum responses were seen within the first year of treatment, with scores remaining steady thereafter.

Another trial prospectively randomised 380 patients in a double-blind format to receive 300, 600 or 900 mg of pentosan daily in three divided doses.[11] This study also favoured long-term therapy with pentosan polysulphate. Success was defined as >50% reduction in a patient's overall rating of improvement of symptoms (PORIS). The study observed:

- There were no statistical differences in percentages of women, race, mean duration, mean voids per day and mean voided volume at the baseline.

- Patients in all three dosage groups showed improvement through 32 weeks of follow-up.
- Approximately 60% of the patients achieved a successful reduction in PORIS outcomes.
- A steady improvement was seen in the percentage of patients showing success on the PORIS scale throughout the 32-week trial (Figure 4).

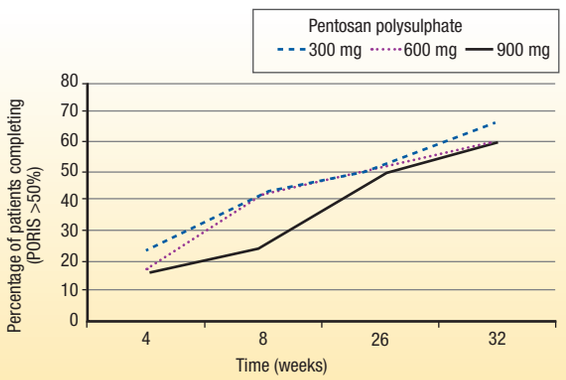

Figure 4. Dose-ranging study of PPS for IC. Definition of success was more than 50% reduction in a PORIS.[11]

- There was no plateau phase, in contrast to the study quoted previously.
- Adverse effects were not statistically different among the groups for headache, asthenia or alopecia. However, abdominal pain and diarrhoea increased with an increase in the dose.

Therefore, it can be concluded that more patients would have shown >50% reduction in symptoms had the study been conducted for a longer duration. Also, the duration of pentosan polysulphate treatment may be more important and beneficial to the patient than the dosage. Overall, 61% (230) of the patients completed the study, with only 5% of the patients withdrawing because of lack of efficacy. This observation is important, as a dropout rate of >80% has been noticed by some studies.[11]

Pentosan in combination with other drugs

The GAG-rich bladder surface mucus is the primary regulator of epithelial permeability. The utility of both PPS and heparin in the treatment of IC is due to the fact that a structurally similar exogenous sulphated polysaccharide could effectively treat IC by compensating for the dysfunction of the natural bladder mucus.[12] It is believed that heparin and PPS work by replacing or aiding in the recovery of the individual's dysfunctional bladder mucus. This aid or repair of the bladder mucus reduces epithelial permeability and protects them from symptom provocation by noxious molecules. The safety and efficacy of the combined administration of oral PPS and subcutaneous low-dose heparin were evaluated in a clinical study (Figure 5).[12]

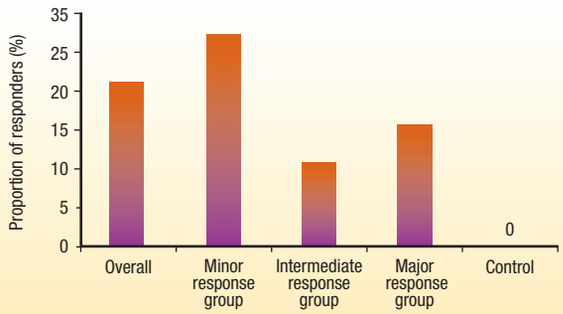

Figure 5. Efficacy of combined therapy with pentosan polysulphate plus heparin in adults with IC.[12]

Out of 58 participants in the trial, two received off-label doses of pentosan polysulphate throughout the study and 56 received pentosan polysulphate 300 mg/d. Heparin was administered subcutaneously at a dosage of 5000 units three times daily for 2 days, followed by 5000 units twice daily for 12 days, to 41 patients (mean age 45.6 years). Patients were stratified into a minor response group (n = 22), an intermediate response group (n = 8) and a major response group (n = 11) according to their response to 6 months of pentosan polysulphate treatment.

The study results were:

- As compared to baseline, there was a significant reduction in pain in the pentosan plus heparin group.
- The maximum decrease in pain score at 3 and 6 months was seen in the minor response group (11.4 and 9.1 mm) as compared to intermediate (both 3 mm) and major response groups (1.7 and 1.5 mm), respectively.

- The concomitant use of pentosan polysulphate and heparin was more effective than the use of pentosan polysulphate as a monotherapy.

A combination of pentosan polysulphate with hydroxyzine has shown advantage over either drug alone.[8]

Summary

IC is a bladder syndrome of unknown aetiology. The pathophysiology of IC is complex, with the most likely cause being multifactorial, and includes genetic and environmental factors. It has been observed that the patients with IC have a defective GAG barrier function, leading to depolarisation of sensory nerves by solutes from the bladder, with subsequent symptom provocation. On the basis of this observation, patients are frequently treated with oral pentosan polysulphate. Pentosan polysulphate is a semisynthetically produced heparin-like macromolecule carbohydrate derivative that chemically and structurally resembles GAG molecules. Currently, pentosan polysulphate is the only approved drug for IC. Clinical studies have shown that pentosan polysulphate is an efficacious therapy for patients with IC. Maximum treatment response can be achieved when patients are treated for 6 months or longer.

Key Points

- Studies evaluating the pathophysiology of IC and properties of pentosan polysulphate offer a scientific basis for using pentosan polysulphate to treat IC.
- Favourable assessments of the drug by patient and investigator evaluations have been seen in randomised, double-blind studies of pentosan polysulphate in the treatment of IC.
- Significant improvement in most variables in IC patients randomised to oral pentosan polysulphate has been observed.
- Studies have also shown that a longer duration of treatment with pentosan polysulphate results in greater improvements in patients' response rates and outcomes. Therefore, the treatment should be of 6 months' or longer duration.

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Notes

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