Etiology of Interstitial Cystitis and the Role of Pentosanpolysulfate in IC Therapy

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26.1 Introduction

For over 40 years I have studied the bladder epithelium and interstitial cystitis (IC). I have seen over 9000 patients and conducted extensive basic laboratory and clinical research on IC that has substantially changed my concepts of the disease. My understanding now is that there is one primary disease process that generates bladder symptoms of urgency, frequency, pain and incontinence (in any combination) in women of all ages and men less than 55 (before the age of bladder outlet obstruction). This pathologic process is a dysfunctional, "leaky" bladder epithelium that allows urinary potassium to diffuse into the bladder interstitium and directly depolarize, nerves, muscles, cause bladder symptoms and injure tissue. The rare but not separate severe form of this process is the patient historically diagnosed with IC [1].

Six major discoveries lead to my new concepts of IC.

1. Bladder surface mucus, sometimes called the GAG layer, protects the transitional epithelium from bacterial, protein and calcium adherence providing a universal protective anti-adherence barrier [2, 3].
2. The GAG layer controls the permeability of the epithelium to small molecules in rodents and in normal human volunteers [4, 5].
3. IC patients have a leaky epithelium compared to normal human subjects to both urea and potassium [6, 7].
4. The GAG layer injured chemically in both rodents and humans results in a leaky epithelium and this injury is reversed by both heparin and pentosanpolysulfate (PPS, Elmiron) [2, 4, 5, 7–10]. This discovery led to the use of PPS to treat IC and became the first and to date only FDA approved oral medical therapy for IC [5, 8–13].
5. The discovery of the role potassium plays in the generation of bladder symptoms. If the GAG layer is defective, "leaky", urine potassium will diffuse into the bladder wall,

Comment: In the original Chapter that I wrote for this book on Pentosanpolysulfate (PPS) therapy I began with a comment that not much was known about IC etiology and go on to describe the rationale for the use of PPS in IC and its success rates. Compared to 28 years ago my concepts about interstitial cystitis have changed dramatically on the basis of new and solid scientific evidence. Substantial progress was made in the understanding of the etiology of IC, the mechanism of action for PPS in the disease as well as the potential new uses of PPS in bladder symptoms in general. There were so many changes and so much new information that I needed to rewrite the chapter (and this is a good thing) so that I could adequately explain all of these changes. The significant progress over the past three decades is self evident when the chapters are compared. I found redoing this chapter to be quiet fascinating.
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depolarize muscles, nerves and cause symptoms and tissue injury. A potassium sensitivity test (PST)was developed to identify the presence of a leaky epithelium, normal subjects are not sensitive to intravesical potassium but those with a leaky bladder epithelium are [14]. Symptomatic patient populations were tested and found to have lower urinary dysfunctional epithelium (LUDE) including IC, radiation cystitis, urethral syndrome, overactive bladder, prostatitis, gynecologic chronic pelvic pain patients, vulvodynia and endometriosis and all were equally potassium sensitive [1, 7, 14–22]. Table 26.1 contains the summation of the data from over 40 studies in the world literature. These data are creating an entirely new paradigm for both urology and gynecology patients concerning bladder symptoms and chronic pelvic pain. Bottom line is all of these patients have LUDE and see specialists urologists or gynecologists based on the symptoms bothering them the most and receive a myriad of traditional diagnoses (or misdiagnoses if you will) but in reality all have only one basic disease process. Bottom line the PST is the best and most widely substantiated diagnostic test for IC/epithelial dysfunction (LUDE) with a 81% sensitivity and 99% specificity.

6. The recent identification of toxic urinary cationic metabolites that bind to and injure the GAG layer and initiate the epithelial dysfunction cascade. Most of them are nucleic acid metabolites and are very toxic to cultured urothelial cells. These urine cations are 2.5 times higher in the urine of IC patients compared to control subjects and are neutralized by Tamm Horsfall Protein (THP) PPS and heparin [21, 23]. We believe these cations are the root cause of IC.

Table 26.1 KCl test results in symptomatic patient groups

Group	N	% Positive	P value[a]
IC [1, 7, 14–17, 24]	3786	81%	<0.0001
Normal subjects [7, 14–17]	228	1.3%	
OAB [25]	116	71%	<0.0001
Prostatitis [18, 20, 22]	72	81%	<0.0001
Gyn chronic pelvic pain [16, 17, 19]	378	82%	<0.0001
Vulvodynia [19]	122	84%	<0.0001
Urethral syndrome [15]	116	55%	<0.0001
Radiation cystitis [14]	5	100%	<0.01

These data are summarized from over 40 papers in the world literature and the direct references are cited for some [1, 7, 14–22] and the rest are cited in a review article that is also referenced [19]

[a]All Groups compared to the control group

26.2 Pentosanpolysulfate

As mentioned, chemical injury of the normal bladder surface mucus will cause an injury to the barrier effect of the epithelium [2–5, 7–10]. It was also discovered that this injury in both rodents and humans can be reversed with an intravesical treatment of the bladder surface with either heparin of pentosanpolysulfate (PPS) [2, 4, 5, 7–10, 26]. As a direct result of these observations it was hypothesized that heparinoids might beneficially impact on diseases where the mucosa was dysfunctional such as interstitial cystitis. PPS has an oral form that is about 2.5% bio-available. It was then tried in several opened labeled and a double blind study [13] to determine if it had efficacy in IC and the drug was successful at relieving symptoms after several months of therapy [27, 28]. Bear in mind that in the early 1980s when these initial studies were done IC for the most part was only recognized in its severe form where symptoms were chronic and unrelenting. It was 20 plus years later that IC was indeed discovered to have a beginning where symptoms are mild and intermittent [29]. And In this early phase is far more common than the rare severe but classical form of IC. So the initial experience with IC was on the severe patients and the positive results that were obtained were quite promising. These studies led to key pivotal clinical trials. The company conducting the trials met with the United States Food and Drug Administration (FDA) and developed a protocol that was acceptable to the FDA. Basically the two trials were randomized, prospective, multicentered placebo controlled trials. The entry criteria were strictly defined and utilized the NIDDK

criteria which were developed shortly before these clinical trials began. These two studies used the the Global Assessment Response of symptoms (known as the GAR) as the primary outcome measure which was first reported by Parsons [13]. The GAR was statistically validated as an outcome measure for IC clinical trials in the larger of these two studies [12] and is now widely used for this purpose. Patients entered were defined as having severe disease for at least 1 year with moderate or worse symptoms of pain and urgency, had a cystoscopy under anesthesia, completed a 3 day voided log (at the beginning and end of the trial) and were begun on PPS 100 mg TID for 3 months. At the end of the study the global assessment of symptoms questionnaire was filled out by each patient. It is a six point scale with patients reporting (1) worse (2) 0% improved (3) 25% improved (4) 50% improved (5) 75% improved (6) 100% improved. Better was predefined in the protocols as 50% or greater improvement and those not reaching this level were deemed no better. The percent of patients reporting better is summarized in Table 26.2 for each study. These studies were the basis for approval of PPS to treat IC by the Food and Drug Administration in the United States in 1996.

26.3 Dose of Pentosanpolysulfate for Therapy

PPS should be the basis for any single or multimodal therapy for IC since it treats the root cause of IC the epithelial dysfunction [30]. Severe patients usually require the multiple therapy approach to address both the epithelial problem and their symptoms. The approved dosage of PPS is 300 mg per day. A subsequent study showed that longer durations of therapy up to 8 months resulted in a higher success rate of improvements in patients up to 70% [31]. Currently, I routinely start female patients on 200 mg of PPS BID and if not better in 4 months increase the dose to 300 mg BID. For severe patients if not better at 6–8 months I will increase it to 300 mg TID. Males I routinely start on 300 mg BID. I never stop the PPS until the patients lose all or most of the symptoms but frequently add other therapies to control their symptoms. In general PPS (or other heparinoids) are the only drugs the reverse the course of the disease and reduce the epithelial leak of potassium allowing the bladder to heal [30]. It should always be the primary foundation of therapy. It is important to have patience and continue therapy and encourage people (especially patients with many years of severe symptoms) to stay on treatment indefinitely even years before success may be obtained. Explaining to the patient that PPS can reverse the course of the disease is helpful so that they realize that staying on the medication is critical along with other treatment modalities that may be added to their therapeutic regimen. PPS has been on the Unites States market for over 20 years. This long experience with the drug has shown that it is very benign and well tolerated and has been used in well over 100,000 people with an excellent safety profile in both the low and high doses of medication reported herein.

I have reported successful use of PPS in 42 children and the dose by weight that I have employed is presented in Table 26.3 [32]. In General children responded quicker and better to therapy which is probably not surprising since

Table 26.2 Summary of two pivotal PPS trials

	N	Placebo GAR*	Drug GAR*	P value[a, b]
Mulholland 1990 [11]				
Overall improved	110	13%%	28%	0.04
Pain improved		14%	27%	0.08
Pressure to urinate improved		11%	22%	0.08
Parsons 1993 [12]				
Overall improved	148	15%	36%	0.002
Pain improved		18%	38%	0.005
Pressure to urinate improved		18%	30%	0.04

[a]GAR is the global assessment response In both studies drug did significantly better that placebo. These studies were the basis for FDA approval in the USA in 1996 of PPS for treating IC

[b]Compares active drug to placebo

Table 26.3 Dose of PPS for use in children by weight

Weight (lbs)	Dose
25–45	50 mg BID[a]
45–70	100 mg BID
70	200 mg BID

[a]If child cannot take a pill empty capsule into 1 ounce of water and have the child drink it. PPS is acid stable and not affected by the stomach

they have had disease for a shorter time and tend to heal faster than do adults.

26.4 Mechanism of Pentosanpolysulfate Action

Since intravesical PPS will restore an experimentally injured GAG layer in either normal rodents or adult humans the hypothesis for its mechanism of action in IC patients was that in restores the GAG layer by coating the bladder surface [7, 10, 30]. But more recently our discoveries of cations in urine that injure the GAG layer has led to a new and/or additional hypothesis [21, 23].

I believe that "sometimes the obvious is the reality" and in the case of IC that urine is the cause of the disease, not the nerves, spinal cord, pelvic floor or other systemic remote issues. If there were no urine in the bladder then no disease would exist. IC has a beginning usually early in the life of most patients (by ages 18–25) [29] with mild and intermittent symptoms and in the unfortunate individuals progresses over decades to a more chronic and debilitating condition. It is the older patients with years of more severe disease that develop associated problems secondary to the chronic disease process such as e.g. pelvic floor dysfunction. So what starts the disease process? What causes the GAG layer to become dysfunctional?

The urinary bladder has a hostile environment to deal with namely urine and the toxic byproducts of metabolism it contains. Fortunately the marvelous impermeable GAG layer confines them to the bladder lumen for the most part rendering them harmless. But this is not always the case. IC patients have a dysfunctional GAG layer and as a consequence the highly concentrated urinary potassium levels are allowed to diffuse into the bladder wall and depolarize muscles, nerves and ultimately destroy tissue [1]. A key question is what causes the GAG layer to become abnormal? Our hypothesis has been that urinary cationic metabolites containing amino groups will bind to and impair the function of this layer similar to what protamine does in normal rodents and humans where it causes a leaky epithelium [4–7]. Based on this hypothesis, all urinary cationic molecules were isolated from urine of normal human subjects using ion-exchange cartridges in attempt to determine if it contained these postulated toxins. The positively charged compounds were isolated and identified by using a combination of high performance liquid chromatography (HPLC) and mass spectroscopy (MS) [21]. Once these molecules were identified they were purchase commercially and used in cell cultures of bladder epithelial cells to determine if they would injure and kill the cells. For a positive control protamine (very cytotoxic to the cultured cells) was used and compared on a weight basis to the isolated urinary cations for cytotoxicity. Four of these cations were found to be very toxic and surprisingly turned out to be metabolites of DNA and they are significantly elevated in the urine of IC patients [21]. The entire cation content was extracted from the urine of both normal subjects and IC patients. The toxic cations were over two fold increased in the urine of the IC patients [21, 23].When the fractions of cations from both groups were compared in our cytotoxicity assay, all of the patient fractions were more toxic than all of the normal subjects and hence by definition a good diagnostic test [21]. Another study on the cation content in urine was conducted that compared patients with active symptoms to patients significantly improved on PPS therapy and both groups had the same elevated levels compared to control subjects [23]. These data are important because it seems that these cations are not a result of the IC disease process since they do not go down at all when patients are significantly improved. The discovery of these toxic cationic metabolites is a major and very important piece of the IC puzzle. We believe that these toxic

DNA metabolites injure the bladder GAG layer by binding to it and begin the whole IC cascade. The cytotoxicity of the whole cation fractions, as well as, the individual toxic compounds from patients and control subjects was exposed to both Tamm Horsfall Protein and PPS and each compound completely neutralized the toxic effect of these cations. The ability of PPS to sequester these toxic cations is probably the mechanism for the activity of PPS in urine and explains why it is successful in treating IC patients. Some of my patients with severe IC symptoms have over four times the cation levels of normal people and explains why we have found these patients do better if prescribed much higher doses of PPS.

The role that toxic urinary cations may play in the initiation of bladder symptoms and IC opens the door for the development of new drugs that target these metabolites for sequestration. Determining the cation levels in patients, particularly severe ones, will help guide therapy by increasing the presence in urine a level of medication necessary to effectively neutralize these toxins. Since PPS is very capable of performing this task what is needed is a form of PPS that has better gastrointestinal absorption to deliver higher levels of this drug to the urine that will likely result in a much higher rate of improvement in patients. It is interesting that PPS was the first and currently only approved oral drug for IC in the United States and the new understanding of its mechanism of action shows that the original hypothesis to use it in IC was essentially correct. And that a new drug does not necessarily need to be developed to do the same thing what needs to be accomplished is delivering more PPS to the urinary tract.

The Combination of epithelial dysfunction or LUDE disease and potassium problems occur in many patients with bladder symptoms (e.g. OAB, prostatitis) and gynecologic chronic pelvic pain. PPS therapy may be very useful in these patient populations no matter what their classical diagnosis is. Interestingly, PPS was introduced in IC patients at a time when the disease was considered rare but it may be the therapeutic of choice for tens of millions of patients with bladder and pelvic pain symptoms based primarily on new understandings of the etiology of bladder symptoms and its mechanisms of action in the urinary tract.

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