Treatment of refractory interstitial cystitis/ painful bladder syndrome with CystoProtek – an oral multi-agent natural supplement

T. C. Theoharides, PhD,[1,2,3] D. Kempuraj, PhD,[1] S. Vakali, MD,[1] G. R. Sant, MD[4]

[1]Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine and Tufts Medical Center, Boston, Massachusetts, USA

[2]Department of Biochemistry, Tufts University School of Medicine and Tufts Medical Center, Boston, Massachusetts, USA

[3]Department of Internal Medicine, Tufts University School of Medicine and Tufts Medical Center, Boston, Massachusetts, USA

[4]Department of Urology, Tufts University School of Medicine and Tufts Medical Center, Boston, Massachusetts, USA

THEOHARIDES TC, KEMPURAJ D, VAKALI S, SANT GR. Treatment of refractory interstitial cystitis/ painful bladder syndrome with CystoProtek – an oral multi-agent natural supplement. The Canadian Journal of Urology. 2008;15(6):4410-4414.

Objectives: *Interstitial cystitis/Painful bladder syndrome (IC/PBS) is a chronic bladder condition of unknown etiology and pathogenesis. However, there is evidence of bladder surface mucosal and glycosaminoglycans (GAG) dysfunction in IC/PBS and GAG replacement therapy has been used to treat the condition. The results of an open label, uncontrolled study of a dietary supplement designed to improve GAG mucopolysaccharides integrity (glucosamine sulfate, sodium hyaluronate and chondroitin sulfate) and reduce bladder wall inflammation (quercetin, rutin) are presented herein.*

Methods: *Two hundred fifty two IC/PBS patients (25 men, 227 women; 18-69 years old), who had failed other treatments, took four CystoProtek capsules /day (mg/ capsule: glucosamine sulfate, 120; chondroitin sulfate, 150; hyaluronate sodium, 10; quercetin, 150; rutin, 20). Symptoms were evaluated using a visual analogue scale (VAS) (severity range from 1-10) before and after treatment (< 6, 6-12 or > 12 months). The women were divided into two severity groups - a more severe A group with a baseline mean VAS score greater than or equal to 5 and a less severe B group with a mean score < 5.*

Results: *Male patients (55.72 ± 9.53 years, n = 25) had a mean VAS score at baseline of 7.6 ± 1.63 which fell 51.8% to 3.94 ± 2.46 ($p < 0.0001$) after 12.46 ± 8.76 months of treatment. The women (n = 227) experienced a 48.8% reduction in the mean VAS score ($p < 0.0001$) after 11.2 ± 8.7 months. The mean VAS score in Group A (49.72 ± 11.39 years, n = 207) fell 52.1% from 7.91 ± 1.55 to 3.79 ± 2.37 ($p < 0.0001$) after 11.06 ± 8.18 months and in Group B (52.40 ± 10.19 years, n = 20) fell 43.5% from 3.15 ± 0.92 to 1.78 ± 1.63 ($p = 0.013$) after 10.10 ± 5.80 months. Patients in Group A and B were further subdivided into Groups A1, B1 (> 12 months), A2, B2 (6-12 months) and A3, B3 (< 6 months treatment); improvement was statistically significant in all the more severe Group A treatment duration subgroups.*

Conclusions: *Dietary supplements targeting the bladder GAGs (chondroitin, glucosamine, hyaluronate) and bladder inflammation (quercetin, rutin) are useful in the treatment of refractory IC/PBS. Prospective randomized trials of such supplements are warranted in both treatment refractory and treatment naïve patients.*

Key Words: GAG (glycosaminoglycans) substitution, IC/PBS (interstitial cystitis/painful bladder syndrome), glucosamine, chondroitin sulfate, hyaluronate sulfate, quercetin, rutin

Accepted for publication October 2008

Acknowledgments

This work was funded by in part by Algonot, LLC (Sarasota, FL). We thank Ms. Jessica Christian for her patience and word processing skills.

Address correspondence to Dr. T. C. Theoharides, Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111, USA

Introduction

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a bladder syndrome of unknown etiology and it is characterized by symptoms of suprapubic, pelvic and genital pain, urinary frequency and nocturia in the absence of a urinary tract infection (UTI).[1] The prevalence of IC/PBS was recently estimated at about 500 cases/100,000 women[2] and IC occurs also in men (about 10%) with recent evidence suggesting that

chronic nonbacterial prostatitis/chronic pelvic pain syndrome (CPPS) men may be a similar to IC/PBS.[3]

Diagnosis of IC is by exclusion based on a history of suprapubic/bladder pain, irritative voiding symptoms, and negative urine culture or by the National Institutes of Health-National Institute of Diabetes, Digestive and Kidney Diseases (NIH-NIDDK) cystoscopic criteria.[1] Defects in the protective glycosaminoglycans (GAG) mucopolysaccharides layer of the bladder,[4] bladder inflammation,[5] increased number and activation of mast cells,[6] neuroimmune dysfunction,[7] and a urinary antiproliferative factor (APF)[8] have all been described in IC/PBS. A large number of oral and intravesical treatments are used although none is curative.[9,10] The only two FDA approved treatments are intravesical dimethyl sulfoxide (DMSO) and an oral GAG replacing agent sodium pentosanpolysulfate (Elmiron).

Intravesical sodium hyaluronate and chondroitin sulfate, singly or in combination,[11-17] oral quercetin,[18] and a quercetin/chondroitin/glucosamine/hyaluronate combination[19] have been reported in open label studies with small numbers of patients. The encouraging results of the open label pilot trial[19] of CystoProtek – an oral multi-agent dietary supplement - led to this larger study in treatment refractory IC/PBS patients.

TABLE 1. **CystoProtek ingredients and sources***

Ingredients	Amount per capsule	Source
Glucosamine sulfate	120 mg	Shell fish chitin
Chondroitin sulfate**	150 mg	Shark cartilage
Hyaluronate sodium	10 mg	Chicken combs
Quercetin dihydrate+	150 mg	Saphora plant
Rutin+	20 mg	Saphora plant
Olive kernel extract	45% w/v	Olive seeds

*All ingredients free of any bovine products or preservatives.
**The most common source of chondroitin in products other than CystoProtek is from imported cow trachea that carries the risk of "mad cow" disease.
+The most common source of quercetin and rutin in products other than CystoProtek is the fava bean plant, ingestion of which could cause hemolytic anemia in those individuals (many of Mediterranean origin) who have glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Materials and methods

CystoProtek is a multi-agent dietary supplement (components listed in Table 1) formulated as soft gel capsules by a GMP certified company (Tischon Corporation, Westbury, NY, for Alaven Pharmaceutical, LLC, Marietta, GA). Treatment refractory IC/PBS patients (18 to 69 years old) took two CystoProtek capsules twice per day with food. Symptoms were assessed by a Global Response Assessment (GRA) Visual Analog Scale (VAS) ranging from 0 (least) to 10 (worst). This VAS has been previously used to assess IC/PBS symptoms.[19,20] The VAS score was recorded at the start of treatment and at 6 or 12 months. Patients in Group A (VAS score equal to or greater than 5) and Group B (VAS score less than 5) were further subdivided according to duration of treatment into Group A1, B1 (> 12 months), A2, B2 (6 to 12 months) and A3, B3 (< 6 months) treatment. Differences were evaluated using the nonparametric Mann-Whitney U test.

Patients with IC/PBS (227 women and 25 men (18-69 years old, Table 2), diagnosed by the NIH-NIDDK criteria of cystoscopy with hydrodistension[1] were treated between 2003-2006. All were refractory to other oral and intravesical treatments and allowed to remain on other non-IC medications for pain (e.g. tramadol) or concurrent medical conditions (e.g. hypertension). Three female patients did not return the VAS evaluation assessment forms and were lost to follow-up. The study was an open label, non blinded, non randomized and non placebo controlled.

Results

The patient characteristics are listed in Table 2. Men (n = 25) had a reduction in the mean VAS overall symptom score of 51.8% - from 7.6 ± 1.63 to 3.94 ± 2.46 ($p < 0.0001$) after 12.46 ± 8.76 months of treatment. The women (n = 227) experienced a 48.8% reduction in the mean VAS with a treatment duration of 11.2 ± 8.7 months ($p < 0.0001$). In order to investigate if this significance could be attributed to a regression to the mean, the women were divided into two severity groups - Group A with a VAS score greater than or equal to 5 and Group B with a score of less than 5, Table 2. In the more severe symptom group A (mean age 49.72 ± 11.39 years, n = 207), the mean VAS score fell 52.1% from 7.91 ± 1.55 to 3.79 ± 2.37 ($p < 0.0001$) after 11.06 ± 8.18 months of treatment. The less symptomatic group B (mean age 52.40 ± 10.19 years, n = 20), experienced a 43.5% reduction in the mean VAS score from 3.15 ± 0.92 to 1.78 ± 1.63 ($p = 0.013$) after 10.10 ± 5.80 months of treatment. There were complete remissions in 5/25 males, 31/207 females in Group A and 8/20 females in Group B.

TABLE 2. **Patient characteristics and effect of CystoProtek on IC/PBS symptoms**

Patients	#	Age (years)	Tx duration (months)	Mean VAS score before	Mean VAS score after	Symptom reduction (%)	p value
Males*	25	55.72 ± 9.53	12.46 ± 8.76	7.60 ± 1.63	3.94 ± 2.46	48.2	p < 0.0001
Group A Females (MS ≥ 5)	207	49.72 ± 11.39	11.06 ± 8.18	7.91 ± 1.55	3.79 ± 2.37	52.1	p < 0.0001
Group A1 (months > 12)	62	53.32 ± 9.99	21.59 ± 6.81	8.13 ± 1.48	3.95 ± 2.57	56.0	p < 0.0001
Group A2 (months ≥ 6-12)	77	48.87 ± 10.96	9.66 ± 2.57	7.83 ± 1.57	3.74 ± 2.36	52.3	p < 0.0001
Group A3 (months < 6)	68	47.43 ± 12.42	3.67 ± 1.07	7.81 ± 1.59	3.70 ± 2.22	52.7	p < 0.0001
Group B Females	20	52.40 ± 10.19	10.10 ± 5.80	3.15 ± 0.92	1.78 ± 1.63	43.5	p = 0.013
Group B1 (months > 12)	5	58.2 ± 14.34	18.8 ± 3.03	3.20 ± 0.84	1.90 ± 2.70	40.6	NS
Group B2 (months ≥ 6-12)	10	50.2 ± 9.22	8.80 ± 2.44	3.15 ± 0.82	2.05 ± 1.12	35.0	p = 0.04
Group B3 (months < 6)	5	51.1 ± 6.32	4.00 ± 0.00	3.10 ± 1.34	1.10 ± 1.34	64.6	p = 0.04

Tx = treatment; P = probability
*All men started with mean VAS score > 5 and were not subdivided further

Patients in Group A and B were further subdivided according to duration of treatment - A1, B1 (> 12 months), A2, B2 (6 to 12 months) and A3, B3 (< 6 months) treatment, Table 2. The mean VAS score in each of the Groups A1, A2 and A3 was reduced significantly ($p < 0.0001$). The small number of patients in group B subgroups did not allow for similar statistical analysis although groups B2 (n = 10) and B1 (n = 5) showed a significant reduction in the mean VAS score ($p = 0.04$).

There were no self reported adverse side effects and no patient had to discontinue treatment. Transient gastrointestinal irritation occurred in 8 patients (7 women and 1 man).

Discussion

In this 252 patient study treatment refractory IC/PBS patients (men and women) achieved a 50% global symptom improvement with CystoProtek - an oral, multicomponent nutraceutical preparation that targets multiple components of bladder surface GAG dysfunction and bladder wall inflammation.

CystoProtek contains a combination of naturally occurring molecules with mechanisms of action that address multiple pathogenetic pathways in IC/PBS. The mucopolysaccharide GAG bladder surface layer is composed primarily of chondroitin sulfate and sodium hyaluronate, with glucosamine sulfate serving as the synthetic building block. Intravesical hyaluronic acid (HA) has been used singly or in combination with intravesical chondroitin sulfate to treat refractory IC/PBS with encouraging symptom response rates of 65%-85%.[11-17] Most of these studies included small number of patients and the largest study (126 patients) was done in a selected group of patients with positive modified potassium sensitivity testing.[17] CystoProtek – an oral multi-agent preparation demonstrated promising overall symptom as well as quality of life improvement in a small pilot study in 37 treatment refractory patients diagnosed by the NIH-NIDDK criteria.[19]

The GAG components in CystoProtek reduce inflammation and inhibit mast cell activation.[21,22] The natural flavonoid quercetin and its glycoside rutin – both have potent anti-inflammatory and mast cell

inhibitory activity.[23] The ingredients in CystoProtek are mixed in olive kernel extract (OKE) to form rudimentary liposomes that improves absorption of chondroitin sulfate.[19] This is critical because the absorption of chondroitin sulfate and quercetin in powder form is < 10%[19] making it difficult to achieve substantial bladder levels when administered in pure powder form. Olive oil is rich in bioflavonoids and has many cytoprotective properties.[24]

The previous open label pilot study of 37 female IC patients showed that CystoProtek (six soft gel capsules per day for 6 months) reduced overall symptoms by 52% from a mean VAS score from 9.0 ± 2.9 to 4.3 ± 2.1 ($p < 0.05$).[19] An open label study in 22 non treatment refractory IC/PBS patients (5 men and 17 women, average age 53.1 years) using an oral preparation containing 500 mg quercetin (twice per day) reported an improvement in global response assessment (GRA) score of approximately 57%.[18] This formulation contained a number of other ingredients in an undisclosed proprietary formula. Intravesical hyaluronic acid was used in non treatment refractory IC patients (20 total) with a response an overall response rate of 65% and reduction in nocturia of 40% and pain of 30%.[15] A recent study of intravesical hyaluronic acid plus chondroitin sulfate in 23 women with treatment refractory IC/PBS reported statistically significant improvements in frequency, urgency, pain and overall quality of life.[16]

IC/PBS presents a unique therapeutic challenge because the disease pathogenesis is unknown and most likely multifactorial. There is no curative therapy for IC.[9] A recent systematic review of the pharmacological treatment of IC/PBS (1470 patients in 21 randomized controlled trials (RCTs)) concluded that only pentosan polysulfate may be "modestly beneficial" for treatment.[10] The mean frequency of global improvement was 19% (range 4%-40%) for control groups and 49% (range 28%-89%) among treatment groups for all the RCTs.

Attempts to "replenish" only individual GAG components may not be optimal treatment especially in treatment refractory patients because of the complex pathophysiology of the disease involving GAG, neuroimmune and inflammatory mast cell components. A truly multimodality approach as represented by CystoProtek clearly has merit as a treatment option in IC/PBS. The global response assessment symptom improvement of 50% in treatment-refractory IC/PBS patients[19] compares favorably with the 49% reported in the recent systematic review.[10] Whether this response rate will be increased in recently diagnosed or treatment naïve patients can only be answered by a prospective, randomized, placebo controlled trial.

There are obvious limitations to the current open label study, not the least of which is the lack of placebo control group. However, obvious logistic and ethical considerations make double blind, placebo controlled, studies difficult especially in IC/PBS patients with high level of pain and the need for prolonged courses of treatment (usually 3-6 months). This explains in part why many published studies in IC/PBS have been open label with small numbers of patients.[9,10] The present study involving 252 patients (227 women, 25 men) is the largest study to date using naturally occurring nutraceuticals and the reported 50% reduction in overall symptom reduction ($p < 0.0001$) significantly exceeds the placebo response effect rate of 19% recently reported in a systematic review.[10]

Conclusions

There is presently no curative therapy for IC. CystoProtek - a dietary supplement for IC/PBS treatment contains multiple mucopolysaccharides that replenish the bladder lining and isoflavinoids that reduce bladder inflammation. Preliminary results from this open label study show that this oral multimodality treatment results in significant symptom improvement in patients refractory to other IC/PBS treatments. Future studies should explore treatment with CystoProtek either singly or in combination with other specific therapies in newly diagnosed, treatment naïve patients.

Disclosure

CystoProtek is trademarked and is covered by US Patents No. 6,635,625; 6,689,748; 6,984,667, as well as European patent EPO No. 1365777 assigned to Theta Biomedical Consulting and Development Co. (Brookline, MA). CystoProtek is marketed by Alaven Pharma (Marietta, GA). Dr. Theoharides own shares in Theta, Inc. and Algonot, LLC. □

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