

A novel highly effective treatment of interstitial cystitis causing chronic pelvic pain of bladder origin: case reports

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Summary

Purpose: To determine if a very effective therapy for idiopathic orthostatic cyclic edema – dextroamphetamine sulfate – would alleviate symptoms of chronic pelvic pain of bladder origin/interstitial cystitis.

Methods: Two women with interstitial cystitis that had been refractory to various therapies were treated with dextroamphetamine sulfate (20 mg/day) without any other treatment. The diagnosis of idiopathic edema was made by abnormal water load test and interstitial cystitis diagnosed by elevated scores on the pelvic pain and urgency and frequency symptom scale.

Results: Both patients quickly improved their bladder symptoms and all pain and urgency was gone within a week. The interstitial cystitis remained in remission as long as the women stayed on their medication. One woman proved Koch's postulates by stopping the medication because of forgetting it and symptoms resumed quickly only to disappear again upon resuming therapy.

Conclusions: Dextroamphetamine sulfate can be a very effective therapy for recalcitrant cases of interstitial cystitis. Prospective placebo controlled studies are needed to determine what percentage of patients with this debilitating condition have concomitant idiopathic edema as determined by abnormal water load test and how well a larger series will respond to this novel therapy.

Key words: Interstitial cystitis; Sympathomimetic amines.

Introduction

Chronic pelvic pain affects approximately 15% of the adult female population [1]. The American College of Obstetricians and Gynecologists defined chronic pelvic pain as "non-cyclic pain of six or more months duration that localizes to the anatomic pelvis, abnormal wall at or below the umbilicus, lumbosacral area or the buttocks and is of sufficient severity to cause functional disability or lead to medical care [2].

Endometriosis and interstitial cystitis are the two most common causes of chronic pelvic pain syndrome [3, 4]. Frequently they occur together [3, 4]. Interstitial cystitis may affect one in 4.5 women [5].

There have been many theoretical mechanisms proposed to explain the etiology of interstitial cystitis including autoimmunity [6, 7]. Mastocytosis with increased levels of the neuroleptic substance P secreted from sensory nerve endings which then transmits pain and stimulates inflammation has also been hypothesized [8]. Thus an abnormal release of histamines from these cells may cause the initial damage to the bladder glycosaminoglycan (GAG) layer. Another hypothesis involves hypersensitization of small sensory nerve fibers that can trigger neurogenic inflammation through the release of neuropeptides including SP, neurokinin A, and calcitonin gene-related protein [9].

The theory favored by most clinicians is that the cause of interstitial cystitis involves changes in epithelial permeability. The theory holds that damage or alterations to the GAG

layer (mucus) allows transepithelial absorption of urea and potassium, which leads to tissue damage and pain [10].

A wide variety of pathologic conditions have been associated with interstitial cystitis. These include migraine headaches, chronic fatigue syndrome, and skin disorders. There is another condition that was described over 50 years ago which also is associated with the same wide variety of conditions. Furthermore, similar to interstitial cystitis nocturia is a common symptom. This condition is known as idiopathic orthostatic cyclic edema [11]. These symptoms, including chronic refractory urticaria, frequently respond to treatment with sympathomimetic amines especially dextroamphetamine sulfate [12, 13]. We considered that interstitial cystitis may be another pathologic condition associated with idiopathic orthostatic edema. Thus we attempted to treat two women with a presumed diagnosis of interstitial cystitis that was refractory to other treatments with dextroamphetamine sulfate.

Case Report

Case 1

A 36-year-old woman presented for evaluation and hopefully treatment of moderate pelvic pain. The pain first started out premenstrually at age 28. A laparoscopy found Stage I endometriosis which was removed by laser vaporization, but the pain was not relieved and progressed to daily pain. It was worse after intercourse and lasted 24 hours. However, she described the worst pain as an intense pressure in the bladder made worse by walking with the pain feeling like a vice, starting at the urethra and radiating to the bladder. She complained of nocturia two to three times per night.

She had an intense feeling of urgency after urination but no burning. She sought the opinion of a urologist. Based on her symptoms, consistently negative urine cultures and the findings on cystoscopy, she was diagnosed with interstitial cystitis.

She was treated empirically with various antibiotics but none improved her symptoms. In fact ciprofloxacin made her worse. Also oxybutynin chloride and finasteride made her worse. Imipromine hydrochloride did not help. Neither did diet therapy (avoidance of chocolate, caffeine, tomatoes, oranges). She was never treated with pentosan polysulfate sodium.

She next came to our reproductive endocrinology program hoping to find a hormonal cause of her problems. Her free thyroxine level and thyroid stimulating hormone level was normal. The urinalysis was negative for protein. Her chemistry showed a normal liver and renal function.

Her water load test showed a four-hour urinary excretion of 1620 ml following a 1500 ml water load supine but only 1000 ml standing. She was evaluated by answering the eight questions on the pelvic pain and urgency/frequency (PUF) patient symptom scale. She scored an 18 out of a possible 35 score. According to a previous study this would give her a 76% likelihood of having a positive potassium sensitivity test [5].

Based on the abnormal water load test we considered therapy with dextroamphetamine sulfate. She was started on 20 mg/day extended release capsules. All of her pelvic pain and bladder symptoms disappeared within two days. She remained in remission for the next one and a half years while she continued the therapy. She discontinued treatment because of wanting to become pregnant again and the symptoms did not return for the six months it took her to become pregnant, and the first six months of her pregnancy where she is at this time.

It is well known that idiopathic edema leads to unexplained weight gain. During the year and a half of treatment she lost 15 pounds.

Case 2

The 24-year-old woman first noted pain in her pelvis intermittently for six months and then on a daily basis but it was excruciating for the three days before her menses. Intercourse made the pain worse. She complained of urinary urgency after urination and when it occurred it always bothered her and was described as severe. She had nocturia two times per night.

Multiple urine cultures proved negative. Nevertheless she was treated with various courses of antibiotic therapy which did not help. In fact ciprofloxacin seemed to make it worse.

She was a co-worker of case 1. Rather than seek the opinion of a urologist she came to our clinic based on the success of case 1. Further history evaluation found that she had severe migraines which started at the same time as the pelvic pain. She also stated that her mother had similar symptoms.

She performed the water load test and excreted 1460 ml of urine supine and 780 ml standing. Her PUF score was 26 which has a 91% correlation with a positive potassium sensitivity test.

She was treated with dextroamphetamine sulfate – 10 mg capsules upon awakening and 10 mg at noon. Her pelvic pain and bladder symptoms improved the next day and were completely gone within one week. Also her headaches disappeared. Furthermore she lost 11 pounds in the first three months and 27 pounds within the year. She has remained symptom free for the entire year except for a five-day period that occurred two months after initiation of therapy when she forgot to take her pills with her on a vacation. The symptoms disappeared the day after restarting therapy.

Discussion

A water load test is used to diagnose idiopathic edema once other causes of inability to clear a free water load have been excluded, e.g., hypothyroidism, congestive heart failure, cirrhosis, or nephrosis [11, 14]. The original test considered failure to excrete more than 55% of an ingested water load of 1500 cc in 30 minutes over a four-hour period to be abnormal [11]. By modifying the definition to 75%, a much larger percentage of women appear to have this diagnosis [15]. The 75% cut-off was able to identify a group of women unable to lose weight despite proper dieting and exercise who responded to dextroamphetamine sulfate therapy [15].

The fact that these two women who had abnormal water load tests with interstitial cystitis responded so quickly and so completely to sympathomimetic therapy that had been resistant to other treatments strongly suggests that idiopathic orthostatic cyclic edema may be a cause of interstitial cystitis. The fact that symptoms resumed quickly once treatment was temporarily stopped in the second patient but with marked improvement upon restarting the amphetamine, strongly suggests that the improvement was not merely related to spontaneous remission. However case 1 demonstrates that once the bladder has been quieted from symptoms for two years a remission without drugs can continue. It remains to be seen for how long.

The theory for the mechanism of how amphetamine works for idiopathic orthostatic edema is as follows. Studies involving albumin labeled with I^{123} found that women with idiopathic orthostatic edema compared to normal women fail to maintain the albumin load after a few circulations after standing [14]. Albumin is small enough that it would leak through the capillary membrane were it not for closure of the precapillary sphincter in response to the increase in hydrostatic pressure that occurs with standing. A defect in the response from the sympathetic nerve endings allows water to leak from intravascular to extravascular spaces in the orthostatic position. Evidence to support this theory was provided by a study showing that radioactively labeled albumin leaks from the intravascular space in the standing position in women with idiopathic edema but not in normal women [14]. Evidence that sympathomimetic amines work by correcting this defect was provided by the demonstration that a short pretreatment of dextroamphetamine sulfate immediately prior to injecting the albumin to standing women with edema improves toward normal the escape of radioactively labeled albumin [14].

The common defect in vascular or epithelial permeability (according to the leading theory of etiology for interstitial cystitis) could lead to pain with interstitial cystitis. We have treated women and seen marked improvement in headache pain and joint pain following amphetamine therapy. We have even demonstrated marked improvement following dextroamphetamine treatment in esophageal pain in a woman refractory to all other therapies [16]. Theoretically, this improvement seen in these

two women may have been secondary to the effects of amphetamine on improving the alterations in epithelial permeability of the bladder allowing exposure to caustic substances. However since this theory has also helped women with intractable hives, it could stabilize degranulation of most cells with release of histamines. The sympathomimetic amines may also negate the abnormalities related to the neurophysiological hypothesis if that mechanism is operative.

Hopefully the dramatic response seen in these two case reports will lead to prospective placebo controlled studies. Using the water load test one needs to determine what percentage of women with interstitial cystitis have idiopathic orthostatic edema. Other questions that need to be answered are what percentage of interstitial cystitis patients with abnormal water load tests will also improve their symptomatology following amphetamine therapy? Also will any patients with normal free water clearance in the erect position improve following amphetamine therapy?

A relationship between vulvar vestibulitis syndrome (VVS) and chronic pelvic pain of bladder origin has been established [17]. Future studies may also determine efficacy of amphetamine therapy for VVS.

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