Sympathomimetic amines effectively control pain for interstitial cystitis that had not responded to other therapies

J.H. Check, G. Cohen, R. Cohen, J. Dipietro, B. Steinberg

The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden
Cooper Hospital/University Medical Center, Department of Obstetrics and Gynecology
Division of Reproductive Endocrinology & Infertility, Camden, New Jersey (USA)

Summary

Purpose: To further investigate the efficacy of treatment of interstitial cystitis that had been refractory to standard treatment with sympathomimetic amines. *Methods:* Dextroamphetamine sulfate sustained release capsules up to 30 mg per day were prescribed in women with refractory painful bladder syndrome/interstitial cystitis in six new cases. The patients were carefully evaluated for relief of symptoms. *Results:* All six women found marked relief in their painful bladder syndrome in a rather short length of time. The benefit persisted as long as the therapy was maintained. Temporary cessation resulted in prompt return of symptoms, but resumption of sympathomimetic amines again allowed good relief of bladder pain and related symptoms. *Conclusions:* Because of very few side-effects and no drug dependence in the dosage used, sympathomimetic amines should be considered for first-line therapy.

Key words: Sympathomimetic amines; Interstitial cystitis; Sympathetic hypofunction; Neurotransmitter; Acetylcholine.

Introduction

A common condition relatively unknown to the medical community exists where a defect in the sympathetic nervous system leads to a wide variety of symptoms that are generally refractory to standard medical therapies, but responds quickly and effectively to treatment with sympathomimetic amines [1]. Prior publications have shown that small dosages of dextroamphetamine sulfate have efficiently and effectively controlled urticaria, joint pain, fibromyalgia, chronic fatigue syndrome, inability to lose weight despite dieting, severe headaches, gastrointestinal motility disorders, inflammatory bowel disease, chronic pelvic pain, dysmenorrhea, vulvovaginitis, and vasomotor symptoms [1]. There is also a published case report that demonstrated prompt marked improvement of bladder pain following dextroamphetamine sulfate therapy in two women with long-standing suffering who failed to respond to traditional therapy [2]. The present study evaluated sympathomimetic amine therapy for painful bladder syndrome/interstitial cystitis in a series of six additional cases of chronic painful bladder syndrome refractory to standard therapy.

Materials and Methods

The study was an observational case series without placebo controls. Only women were selected for this study, since this disorder of the sympathetic nervous system occurs predominantly in women. All subjects had to have painful bladder for over a year and had failed to have adequate improvement from standard therapies. For inclusion in the study, the women had to have bladder pain urgency and frequency, despite negative urine cultures for at least 12 months. Furthermore, cystoscopy findings had to be consistent with interstitial cystitis. Dextroamphetamine sulfate extended release capsules were begun at 15 mg daily and increased depending on tolerance and response to a maximum of 30 mg per day in one or two divided doses. To evaluate longevity of treatment benefit, the study only included those women responding to sympathomimetic amines who continued the medication for at least six months. If a woman failed to respond to this treatment, it was suspended; the patient, however, was still included in the study.

Results

Prior to therapy, four of the six women had such severe symptoms that they could not function in daily society. Five of the six women, in addition to dysuria, had nocturia (at least five times per night), frequency, and urgency. Commencing at 15 mg of dextroamphetamine sulfate extended release capsules, all six women showed significant relief in dysuria, urgency, frequency, and nocturia. All patients increased the dosage to either 25 mg or 30 mg per day usually after the first month (with one exception). Within two to six months, their urinary symptoms were either completely gone or so mild as to be very tolerable. Four out of six patients decreased nocturia to once per night and two women had two urinations during the night. All symptoms remained almost completely relieved or cured both at six months and one year evaluations.

Revised manuscript accepted for publication May 14, 2012

Discussion

This was not a controlled study, so one could argue that the sympathomimetic therapy perhaps worked as a placebo. However, all patients did not show any placebo response to pentosan polysulfate sodium, or pelvic floor physical therapy. Thus with the quick and long-lasting benefits with dextroamphetamine sulfate, it seemed highly unlikely that the symptomatic remission was from either placebo effect or spontaneous remission. Further evidence supporting specific benefit from sympathomimetic amine drug therapy was the fact that three women who ran out of medication briefly for a few days (the schedule II drug did not allow refills), the bladder symptoms returned immediately. Resuming dextroamphetamine sulfate once again improved symptoms within 24 hours.

Although none of the women had postural syncope, evidence of a disorder of the sympathetic nervous system was demonstrated by abnormal water load tests in all six patients [1]. The sympathetic nervous system is responsible for maintaining normal intravascular fluid volume in response to the orthostatic position which, because of an increase in hydrostatic pressure, would tend to cause water to extravasate from intravascular to extravascular space were it not for a signal by the sympathetic nervous system causing precapillary sphincters to constrict. An abnormal water load test is determined when following ingestion of 1,500 ml of water over a half-hour period of time, a woman urinates ≥ 75% of the ingested water load over four hours supine, but the next day fails to excrete at least 75% of the water load over four hours while remaining erect.

The autonomic nervous system innervates the mucosal epithelium [3]. It is believed that a diminished sympathetic tone, possibly related to antibodies against ganglionic acetylcholine receptors, leads to diminished function of this mucosal epithelium especially in its role of preventing absorption of toxins from the lumen to the epithelium [4]. The toxins stimulate inflammatory response. Also the sympathetic nervous system innervates lymphoid tissue possibly facilitating inflammatory response [5]. These pain syndromes are not limited to the bladder and do not always include the bladder depending on which sympathetic nerves are involved. Nevertheless, almost all of the various pain syndromes responded quickly and effectively to sympathomimetic amine therapy. The common link is the usual abnormal water load test with ≥ 75% excreted of the water load supine but < 75% standing.

Dextroamphetamine therapy is without dependence or withdrawal symptoms when used in this small dosage. Patients with other types of pain disorders have been treated with this drug for over 30 years without problems [1]. It is generally well-tolerated and if side-effects such as insomnia, palpitations or personality change occur, they are usually transient.

Thus the authors have now demonstrated that in eight consecutive patients (including two from the original case report), severe protracted interstitial cystitis had dramatically responded to this benign therapy. No other patients with painful bladder syndrome had failed to respond to this therapy. Hopefully this case series will generate more widespread interest in evaluating dextroamphetamine sulfate therapy and controlled trials are welcome. Perhaps other novel therapies may be generated, based on the responses seen to sympathomimetic amines for bladder pain. It would be interesting to determine if sympathomimetic amines can also improve bladder pain in male patients.

References

[1] Check J.H., Katsoff D., Kaplan H., Liss J., Boimel P.: "A disorder of sympathomimetic amines leading to increased vascular permeability may be the etiologic factor in various treatment refractory health problems in women". *Med. Hypothesis*, 2008, *70,* 671.

[2] Check J.H., Katsoff B., Citerone T., Bonnes E.: "A novel highly effective treatment of interstitial cystitis causing chronic pelvic pain of bladder origin: case reports". *Clin. Exp. Obstet. Gynecol.,* 2005, *32*, 247.

[3] Straub R.H., Wiest R., Strauch U.G., Harle P., Scholmerich J.: "The role of the sympathetic nervous system in intestinal inflammation". *Gut*, 2006, *55*, 1640.

[4] Check J.H., Cohen R., Katsoff B., Check D.: "Hypofunction of the sympathetic nervous system is an etiologic factor for a wide variety of chronic treatment-refractory pathologic disorders which all respond to therapy with sympathomimetic amines". *Med. Hypoth.,* 2011, *77*, 717.

[5] Magro F., Vieira-Coelho M.A., Fraga S., Serrao M.P., Veloso F.T., Ribeiro T., Soares-da-Silva P.: "Impaired synthesis or cellular storage of norepinephrine, dopamine and 5-hydroxytryptamine in human inflammatory bowel disease". *Dig. Dis. Sci.*, 2002, *47*, 216.

Address reprint requests to:
J.H. CHECK, M.D.
7447 Old York Road
Melrose Park, PA 19027 (USA)
e-mail: laurie@ccivf.com