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Treatment and Maintenance of Interstitial Cystitis/Bladder Pain Syndrome in Female Patients with Cetirizine-Famotidine: A Case Series

Reed B. Hogan II[1], Paul H. Moore III[2], Doug Paul[3], Thomas P. Dooley[4*]

[1]GI Associates, Flowood, MS, USA
[2]Division of Urogynecology, Department of Obstetrics and Gynecology, University of Mississippi Medical Center, Jackson, MS, USA
[3]Department of Pharmacy Administration, School of Pharmacy, University of Mississippi, Oxford, MS, USA
[4]Trends in Pharma Development LLC, Pinson, AL, USA
Email: rbhogan@comcast.net, phmoore4@gmail.com, umdrpaul@yahoo.com, *tom@tomdooley.org

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Abstract

Purpose: Interstitial cystitis/Bladder pain syndrome is an inflammatory disorder of the bladder, for which histamine has been implicated in the pathogenesis of the disease. The condition is often refractory to standard-of-care medical treatments, including the antihistamines hydroxyzine or cimetidine, and procedures. Herein we report a physician-sponsored proof-of-principle case series of four adult female patients with chronic painful bladder and frequent urination, who were treated once daily with a low dose H1 + H2 histamine receptor antagonist combination. Materials and Methods: Four adult females with Interstitial cystitis/Bladder pain syndrome were treated once daily with a compounded oral dosage form containing the H1 receptor antagonist-cetirizine 8 mg in combination with the H2 receptor antagonist-famotidine 22 mg. The case series consists of a retrospective review of the symptom severity prior to versus following H1 + H2 treatment. Results and Conclusions: The once daily dual histamine receptor antagonist therapy substantially reduced the pain and urination frequency, and prophylactically maintained all four patients long-term with substantially reduced disease severity. The reduction in symptom severity was achieved at amounts that do not exceed the US FDA approved and exceptionally safe daily doses for the two over-the-counter monotherapies. This case series provides proof-of-principle evidence that a dual antihistamine combination of cetirizine plus famotidine effectively treated and maintained female patients, who were previously refractory to standard-of-care medications and/or procedures.

Keywords

Histamine, Antihistamine, Bladder, Treatment, Prophylaxis

1. Introduction

Interstitial cystitis/Bladder pain syndrome (IC/BPS) is an inflammatory disorder of the bladder [1]. The primary clinical symptom of IC/BPS is chronic pain of the bladder (and/or pelvic region), and the disorder is sometimes termed as "painful bladder syndrome". Associated with the pain are increased frequency of urination when awake and/or while attempting to sleep (*i.e.*, nocturia), and/or urinary urgency. These symptoms and others (e.g., urinary incontinence, mental anxiety) associated with IC/BPS can result in substantial disruptions of normal activities, such as the abilities to work, exercise, sleep, concentrate, and to enjoy sexual intercourse. IC/BPS is a chronic painful bladder condition that is more common in women (*i.e.*, ca. 90 percent of cases). Diagnosis of IC/BPS can be problematic, as there are no specific tests to affirm a diagnosis. Beyond history, physical, and questionnaire data, physicians may use cystoscopy to examine the bladder for inflammation, Hunner lesions, and functional capacity while excluding other etiologies such as foreign bodies, stones, or malignancy.

Initial therapies for IC/BPS have included behavioral changes, physical therapy, and over-the-counter medications, such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and phenazopyridine. Prescription medication options include the tricyclic antidepressant, amitriptyline. Additionally, medications aimed at histamine action or release, such as H1 or H2 receptor antagonists (hydroxyzine or cimetidine, respectively) or pentosan polysulfate are common starting points [1] [2]. Multimodal therapy has been proposed to be more effective than monotherapies in the treatment of IC/BPS [3]. In spite of the multiple available standard-of-care (SOC) medications and procedures, many patients' symptoms remain refractory to treatment for years. Thus, there remains a need for a safe and effective treatment and/or prophylaxis for IC/BPS or the symptoms thereof.

Histamine has been strongly implicated in the pathogenesis of IC/BPS. Methylhistamine and histamine are proposed biomarkers [4] [5] [6], while histamine receptor gene expression has been evaluated in IC/BPS patients [7]. Mast cell counts and physiology have also been investigated as part of this condition's pathophysiology [8] [9] [10] [11]. Monotherapies affecting histamine levels or receptor binding have been used to treat IC/BPS. Hydroxyzine (H1 receptor antagonist) has been used with some limited benefit [12] [13] and is often prescribed as a SOC treatment option. High dose cimetidine (H2 receptor antagonist) for one month was effective at symptomatic relief in a case series report of 9 patients [14]. Pentosan polysulfate is an active pharmaceutical ingredient (API) used in the treatment of IC/BPS, and it affects histamine release [2]. More re-

cently, its use has been limited given its potential for retinal side effects [15].

Histamine plays fundamental roles in modulating inflammation through increased capillary blood flow, vascular permeability, and cytokine release [16] [17]. Mast cells are the hosts for histamine, which can be released into the extracellular environment via mast cell degranulation [18] [19] [20]. Antihistamines are receptor antagonists or inverse agonists that act primarily downstream of mast cell degranulation. Histamine-1 (H1) receptor antagonists (e.g., cetirizine) are administered for allergies, whereas Histamine-2 (H2) receptor antagonists (e.g., famotidine) are administered to control acid in the stomach and heart burn. Prescription branded, generic, and over-the-counter (OTC) drugs of both classes of antihistamines are commercially available essentially worldwide. The OTC H1 and H2 antihistamines (cetirizine and famotidine, respectively) are deemed as exceptionally safe by the US Food and Drug Administration (FDA).

Treatments of diseases with drug combinations that include an H1 receptor antagonist and an H2 receptor antagonist have been successfully used in humans, such as urticaria [21] [22] [23] [24] and diarrhea [25] [26]. In 2020 we reported that a cohort of 110 severe and critical patients hospitalized with SARS-CoV2/Covid-19 were effectively treated with cetirizine plus famotidine, strongly suggesting a substantial reduction in symptom severity and mortality in high acuity Covid-19 patients [27]. It was proposed that the benefit of cetirizine 10 mg and famotidine 20 mg twice daily was due to reducing the pulmonary inflammatory "cytokine storm" downstream of histamine's action, which is common in patients with severe to critical symptoms [27] [28]. Consistent with our findings in humans, H1 + H2 dual antihistamine treatments were also successful using a porcine model of Pseudomonas-induced acute respiratory distress syndrome [29] and a guinea pig model of allergen-induced bronchial obstruction [30]. In aggregate there is a growing body of evidence of the effectiveness of H1 + H2 dual antihistamine therapies in treating diseases of histamine-mediated etiology, such as urticaria, diarrhea, and Covid-19.

In view of this body of evidence in other diseases we chose to test dual histamine receptor blockade as a treatment for IC/BPS, especially treatment-refractory cases, utilizing exceptionally safe APIs. Herein we provide preliminary evidence of the effectiveness of dual histamine receptor blockade in four female patients afflicted with IC/BPS and related symptoms.

2. Materials & Methods

A compounded pharmaceutical formulation was prepared according to US FDA 503A regulations. Number 1 gelatin capsules were prepared by extemporaneous compounding containing cetirizine HCl 8 mg and famotidine 22 mg, plus inert pharmaceutical excipients (e.g., lactose). The selected doses are similar, but not identical to, the US FDA approved daily doses for each API as OTC monotherapies (*i.e.*, cetirizine HCl at 10 mg and famotidine at 20 or 40 mg).

Four adult female patients aged 25 - 57 and afflicted long-term with IC/BPS

(and related urogynecologic conditions) were assessed in the office by a physician. Each patient was deemed as suitable for this compounded medication, based upon self-reported symptoms, medical history, diagnoses, and especially in view of prior SOC medical treatments (or procedures) that provided insufficient symptomatic relief. They were treated orally once daily with compounded cetirizine 8 mg - famotidine 22 mg. The patients were reassessed at subsequent office visits or by phone.

3. Results

Case 1: A 25-year-old female with a medical history of at least 8 years and diagnoses of IC/BPS, chronic irritable bowel syndrome-diarrhea (IBS-D), postural orthostatic tachycardia syndrome (POTS), and possibly Crohn's disease, had previously taken multiple NSAIDs, esomeprazole (proton pump inhibitor), and sucralfate (antacid) without resolution of her urologic and/or gastrointestinal conditions. The patient experienced painful, frequent urination 15 - 20 times per day with incontinence. She described her bladder pain and diarrhea symptoms as 9/10 in severity with significant lifestyle disruption. She was unable to sleep through the night and experienced total disruption of her job. Her work up revealed no significant abnormalities in physical exam or laboratory evaluation.

She was re-assessed by another physician for the uncontrolled IBS-D and was prescribed a compounded pharmaceutical formulation of cetirizine 8 mg plus famotidine 22 mg in an orally ingested gelatin capsule that was administered once daily.

Thereafter the patient experienced substantial reduction in her gastrointestinal symptoms, consistent with the dual antihistamine treatment benefits observed in other IBS-D patients [25] [26]. In addition, her IC/BPS symptoms were much improved, which prior to that date had not been achieved by NSAIDs or other medications. As further evidence of the beneficial effects, the patient requested and received multiple refills of the compounded H1 and H2 receptor antagonist combination medication. Her IC/BPS symptoms remained markedly improved, however they recurred whenever she stopped the compounded combination therapy. Using this treatment, her IC/BPS symptoms no longer interfered with her job or lifestyle, thus providing an improved quality of life.

Approximately three years later, by verbal interview, she described her improvement as "life changing" and reported "at most a 2/10" symptom severity for both IC/BPS and IBS-D. The patient's symptoms recurred if she discontinued treatment with the H1 and H2 receptor antagonist combination medication for 4 - 5 days. She continued to obtain refills of the compounded medication. She stated, "I tell all my (*location*) friends about my miracle medicine." This has been the only effective treatment and prophylaxis for her persistent IC/BPS symptoms. Furthermore, the H1 + H2 compounded medication was well tolerated, with no complications.

Case 2: A 47-year-old female with a diagnosis of at least 5 years duration of

IC/BPS manifesting as pain in the bladder, vagina, occasionally bilateral flanks, vestibulodynia, and cramping. Additionally, the patient experienced severe, painful urinary urgency resulting in frequent urination once per hour and once nightly nocturia. Work up for infection and intrinsic bladder pathology was negative. Prior to presentation, she was previously treated with phenazopyridine, the H1 antihistamine hydroxyzine, and/or acetaminophen.

She was prescribed a compounded pharmaceutical formulation of cetirizine 8 mg plus famotidine 22 mg in an orally ingested gelatin capsule that was administered once daily. In addition, she was started on calcium glycerophosphate (for regulation of dietary acid), while continuing to use hydroxyzine, an H1 antihistamine that is prescribed off-label for IC/BPS.

At follow up 6 weeks thereafter the patient reported that she had experienced substantial reduction in her bladder pain symptoms while taking the cetirizine-famotidine combination. As further evidence of the beneficial effects of the H1 + H2 receptor antagonist combination, the patient reported a reduction in urinary frequency to every 2.5 hours, no nocturia, and only mild urgency. She continued to administer the compounded cetirizine-famotidine drug combination thereafter, as it provided ample symptomatic relief, whereas prior treatments, such as the H1 antihistamine hydroxyzine alone, had been insufficient.

At follow up 6 months later she stated that she is doing very well and feels "normal". At that time, urinary frequency was every 2 hours with no nocturia, and normal urinary urgency. She was advised to continue the cetirizine-famotidine combination and hydroxyzine. Furthermore, the H1 + H2 compounded medication was well tolerated, with no complications.

Case 3: A 57-year-old female manifested symptoms of multi-year duration of bladder pain and overactive bladder, along with other physiologic and mental health disorders. At an office visit one year prior to starting the dual antihistamine combination, the patient expressed that she experienced severe and painful urinary urgency resulting in frequent urination once per 0.5 hour (30 minutes), nocturia 6 times per night, and without incontinence.

Multiple medications, such as Uribel® (a five-drug combination), gabapentin, calcium glycerophosphate, oxybutynin, phenazopyridine, oxycodone, pentosan polysulfate, dicyclomine, and the H1 antihistamine loratadine, and multiple procedures (bladder instillations, cystoscopy with hydrodistention, and intravesical onabotulinumtoxin A injections) were attempted to address her bladder disorder. However, polypharmacy and the multiple procedures failed to ameliorate the severity of this patient's chronic disease state.

Therefore, H1 + H2 histamine receptor blockade was attempted for this recalcitrant condition. She was prescribed a compounded pharmaceutical formulation of cetirizine 8 mg plus famotidine 22 mg in an orally ingested gelatin capsule that was administered once daily, in addition to hydroxyzine.

At follow up 3 months thereafter the patient reported that she had experienced reduction in her bladder pain while taking the cetirizine - famotidine

combination. As further evidence of the beneficial effects of the H1 + H2 receptor antagonist combination, the patient reported a reduction in urinary frequency to every 1.5 hours, nocturia 4 - 5 times nightly, and moderate urgency. At follow up 9 months after starting cetirizine - famotidine she stated that her bladder pain was minimal. Urinary frequency was every 2.5 hours, nocturia 3 times nightly, with mild-to-moderate urinary urgency. She was advised to continue the cetirizine-famotidine combination, hydroxyzine, and gabapentin.

Note that the symptomatic relief achieved by the compounded dual-histamine receptor blockade had not been achieved by prior daily treatments with loratidine, an inhibitor of the H1 receptor or pentosan polysufate that blocks the release of histamine. Thus, monotherapies directed at either histamine action or release had not been effective. Furthermore, the H1 + H2 compounded medication was well tolerated, with no complications.

Case 4: A 42-year-old female who manifested at least 5 years duration of chronic pelvic and bladder pain was assessed by a physician. She reported that the symptoms began after a series of presumptive urinary tract infections, although it was uncertain whether these were culture proven. She reported severe and painful urge to urinate, with frequent urination once per 0.5 hour (30 minutes), nocturia 2 times per night, and without incontinence. In an attempt to alleviate her pain symptoms, she had previously been prescribed gabapentin and hydrocodone/acetaminophen.

Upon presentation, she was prescribed a compounded pharmaceutical formulation of cetirizine 8 mg plus famotidine 22 mg in an orally ingested gelatin capsule that was administered once daily, in addition to hydroxyzine 25 mg once daily.

At follow up 3 months thereafter (by phone) she reported that her symptoms had "improved by 65 percent", and that she was currently only administering the cetirizine-famotidine combination for this urologic condition. Hydroxyzine was only administered as needed. She intended to continue to obtain refills of the compounded cetirizine-famotidine prescription. Furthermore, the H1 + H2 compounded medication was well tolerated, with no complications.

The aggregate results of the four cases are summarized in Table 1.

Table 1. Summary of four cases of IC/BPS in females. Urination frequency at baseline (pre-treated); urination frequency while treated daily with cetirizine 8 mg - famotidine 22 mg; bladder pain while treated daily with cetirizine 8 mg - famotidine 22 mg.

Case	Age	Frequency - Baseline	Frequency - Treated	Pain - Treated
1	25	1.0 hr	less frequent	reduced to 2/10
2	47	1.0 hr	2.5 hr	substantially reduced
3	57	0.5 hr	2.5 hr	substantially reduced
4	42	0.5 hr	less frequent	reduced by 65%

4. Discussion

In this proof-of-principle study, four adult female patients experiencing bladder pain and frequent and/or urgent urination were treated daily with an H1 receptor antagonist and an H2 receptor antagonist. Cetirizine (8 mg) plus famotidine (22 mg) in combination once daily was effective at reducing the level of pain, the frequency of urination, and other urogynecologic symptoms.

As summarized in Table 1, all four females diagnosed with severe IC/BPS for multiple years duration experienced baseline frequent (daytime) urination every 30 - 60 minutes. The frequency was reduced (improved) during cetirizine plus famotidine treatment in the four patients, with Cases 2 and 3 stating a substantial reduction to 2.5 hours. In addition, the four patients reported a substantial reduction in pain, with Case 1 stating the level of pain reduced from 9/10 to only 2/10, and with Case 4 stating the pain was reduced by 65%. However, given this was a physician-led retrospective review of the patients' files, a written pain questionnaire was not administered, but it would have been advantageous. The treatment benefits were demonstrated to endure for months (Cases 2, 3, and 4) to years (Case 1). The symptomatic treatment benefits waned after discontinuing the "maintenance" medication in Case 1, although this variable is unknown for the other three women. The cetirizine plus famotidine dual drug combination was superior in efficacy to prior use of monotherapies directed at the histamine pathways in Cases 2 and 3. In all four females the medication provided near-term effective treatment of acute urination frequency and pain symptoms, followed by maintenance of the improved conditions, thus, demonstrating both a treatment effect and a prophylactic effect. In all four cases the medication was well tolerated, with no complications.

The historic safety in humans around the globe for antihistamines, such as cetirizine and famotidine, provide a distinct advantage to this IC/BPS combination therapy. OTC approvals by the US FDA and other foreign regulatory agencies are merited for only the safest of medications in view of historic pharmaceutical surveillance. Millions of patients in the US alone routinely administer OTC H1 or H2 receptor antagonist medications effectively and safely. For instance, cetirizine is designated as an OTC dosage form at 10 mg and famotidine is an OTC at 10 or 20 mg. The selected doses are under the maximum daily doses for each API as US FDA-approved OTC medications, namely cetirizine at 10 mg maximum daily and famotidine at 40 mg maximum daily.

IC/BPS patients may respond to H1 + H2 dual antihistamine treatment within several days to several weeks. Treatment should be carried out for enough time to substantially resolve or reduce the symptoms (e.g., pain or frequent urination). Patients may administer the combination for the acute treatment and/or prophylaxis (maintenance) of IC/BPS symptoms. Although once daily cetirizine - famotidine combination is likely to be exceptionally safe and well tolerated, the anticipated possible minor side effect of cetirizine in some patients is mild sedation, which is common for H1 antihistamines. Therefore, administration at bed-

time is recommended.

Although not tested in this limited physician-sponsored study, we speculate that the dual drug treatment might beneficially affect the structure and health of bladder tissue by blocking the action(s) of histamine.

5. Conclusions

Based upon the proof-of-principle evidence from these 4 female IC/BPS patients, treatment once daily with the selected H1 + H2 receptor antagonist combination therapy: 1) can reduce the severity of bladder pain; 2) can reduce urination symptoms, such as frequency of urination, nocturia, and urinary urgency; 3) can serve as a prophylactic "maintenance" medication; 4) can reduce symptom severity in patients who have previously administered H1 antihistamine monotherapy with little or no success; 5) can improve quality of life parameters; and 6) can achieve symptomatic relief at doses that do not exceed the US FDA approved daily doses for OTC monotherapies, which are already deemed as exceptionally safe.

Limitations: 1) This is a proof-of-principle case series of only four female patients using retrospective reviews of patient files; 2) Randomized controlled trials are recommended to ascertain the level of efficacy regarding acute treatment vs. long duration prophylaxis (maintenance), female vs. male, with or without a concomitant SOC medication, as well as the level of disease acuity and/or comorbidities that might impact the beneficial effect that is strongly suggested by this case series; 3) It is recommended that future prospective studies include a standard questionnaire, such as the Pain Urgency Frequency or O'Leary-Sant instruments.

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Human Subjects

A physician sponsored study of a prescription medication (compounded or approved) in a limited number of patients may be conducted at the discretion of the physician(s) using his/her professional judgment concerning patient care and treatment options. Institutional Review Board approval is not required for individual case reports and case series with a limited number of patients. The four patients gave their consent to the public disclosure of their research results and the patients' identities are not disclosed.

Author Contributions

RBH: conceptualization, compounding pharmacy, clinical investigation, data curation, and manuscript review; PHM: clinical investigation, data curation, data

analysis, and manuscript revision; DP: conceptualization and manuscript review; TPD: conceptualization, data analysis, principal author, manuscript revision. All authors agreed to the publication of the manuscript.

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Conflicts of Interest

RBH discloses a patent application on dual-histamine receptor blockade in the treatment of IC/BPS, other patents and/or patent applications on dual-histamine receptor blockade in the treatment of diarrhea and Covid-19, and is a shareholder in Hista Rx LLC; PHM has no conflicts of interest to disclose; DP discloses a patent application on dual-histamine receptor blockade in the treatment of IC/PBS, and is a shareholder in Hista Rx LLC; and TPD discloses a patent application on dual-histamine receptor blockade in the treatment of IC/BPS, and is a shareholder in Hista Rx LLC. The patent application on dual-histamine receptor blockade in the treatment of IC/BPS is assigned to Hista Rx LLC.

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Abbreviations

H1 is histamine type-1; H2 is histamine type-2; IC/BPS is Interstitial cystitis/Bladder pain syndrome; OTC is over-the-counter; SOC is standard of care; NSAID is non-steroidal anti-inflammatory drug.