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Off-Label Drug Uses

Intravesical Heparin: Interstitial Cystitis (Painful Bladder Syndrome)

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts,* a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@ku.edu.

BACKGROUND

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic condition that has been defined as an unpleasant suprapubic sensation associated with the urinary bladder (pain, pressure, discomfort) accompanied by lower urinary tract symptoms of more than 6 weeks duration not due to infection or other causes.[1] Although IC/BPS is more prevalent in women, it may affect men. Etiology is poorly defined and thus hampers both classification and treatment. Current treatments are not uniformly effective.[1-3] Mast cell degranulation within the bladder wall has been proposed as a contributing factor in the inflammatory process, possibly related to histamine release.[2] In addition, patients with IC/PBS may have a dysfunctional or leaky bladder mucous layer, which is susceptible to the diffusion of potassium into the bladder wall, initiating a cascade of depolarization of nerves and muscles, resulting in symptoms (eg, urgency, frequency, pain, and incontinence). Intravesical heparin may restore bladder surface barrier function.

PATIENT POPULATION

Adult patients with signs and symptoms of IC/BPS.

DOSAGE AND DURATION

Various dosage regimens of heparin (20,000 to 50,000 units) alone or with alkalinized lidocaine (1% to 4%) have been used:

- Single intravesical injection: Lidocaine (200 mg)/heparin (50,000 units)/sodium bicarbonate (420 mg) in 15 mL of water, instilled into the bladder via a catheter and allowed to dwell for 30 minutes before drainage.[4]
- Weekly bladder instillations with 4% lidocaine (5 mL)/heparin (20,000 units)/7% sodium bicarbonate (25 mL), instilled into an empty bladder via catheter and allowed to dwell for 30 minutes before drainage.[5]
- Twice-weekly intravesical instillations with heparin (25,000 units) for 3 months.[6]

When lidocaine and heparin are mixed, there is a risk of precipitation without proper alkalinization. Both pH and lidocaine stability should be determined after the components have been mixed prior to administration.[4]

RESULTS

Intravesical heparin in the management of IC/BPS has been studied in controlled and noncontrolled trials enrolling more than 100 treated patients and demonstrating efficacy rates ranging from 56% to 94%. National guidelines recommend intravesical heparin as a second-line treatment option, having potential benefit in a subset of patients with an uncertain benefit/risk ratio.

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Guidelines

American Urological Association (AUA)

The AUA guidelines on the diagnosis and management of IC/BPS are based on expert opinion and evidence-based review of published data and present a tiered approach to treatment. First-line treatment is recommended for all patients and includes education about normal bladder function and self-care practices/behavioral modifications that can improve symptoms. Second-line therapy includes multimodal pain management, physical therapy, and oral or intravesical agents. Medications in this section are considered as treatment options, as most demonstrate limited efficacy in a subset of patients and an uncertain benefit/risk ratio. Oral medications include amitriptyline, cimetidine, hydroxyzine, or pentosan polysulfate sodium (PPS). Intravesical medications include dimethylsulfoxide, heparin, or lidocaine. The guidelines reviewed 3 observational studies evaluating the use of intravesical heparin (10,000 to 25,000 units 2 to 3 times a week) in the management of IC with efficacy rates ranging from 56% to 73%. In the absence of placebo-controlled trials, the benefit /risk ratio was considered uncertain, although adverse events appear to be infrequent and minor. Based on these data and a potential benefit in a subset of patients, this treatment was designated as an option. Third-line treatment includes bladder distention or Hunner lesion treatment. Fourth tier management is sacral/pudendal nerve stimulation. Oral cyclosporine or botulinum toxin injections by an experienced clinician are recommended as fifth-line management. Surgical intervention (eg, substitution cystoplasty or urinary diversion) is suggested as sixth-line therapy.[1]

Controlled Studies

In a double-blinded, placebo-controlled, multicenter, crossover trial, 28 adult patients with IC and moderate symptoms were randomized within 48 hours of study enrollment to receive intravesical active treatment with heparin (50,000 units)/lidocaine (200 mg)/sodium bicarbonate (420 mg) in 15 mL of water or placebo control (sodium bicarbonate 420 mg) in 15 mL of water. The solution was instilled into the bladder via a catheter and allowed to dwell for 30 minutes before drainage. On the day of administration, the patients completed an 11-point analog scale (0-10) for both bladder pain and urgency, requiring a 5/10 score before the first treatment and a 4/10 score before the second treatment within 48 hours of the administration. If criteria were not met, the second treatment was not administered. A washout period between treatments was not provided. The primary outcome measure was the mean percentage change in pain at 12 hours. Secondary outcome measures were a self-reported 6-point global assessment response (GAR) and mean percent change in urgency and pain plus urgency. The projected sample size was initially planned as 40 participants receiving both active and control treatment to detect a difference in response rates at the 95% level. A total of 28 subjects were enrolled because of a national heparin recall, of which 18 completed the trial. The primary endpoint, mean percentage reduction in pain over 12 hours, was 42% and 21% for the active treatment and control groups, respectively ($P = .0363$). Significant differences between the 2 groups were also observed in secondary outcomes, including at least 50% overall improvement response via GAR (50% vs 13%; $P = .0137$), mean percent change in pain and urgency from baseline to 12 hours (38% vs 17%; $P = .0318$), and mean percent change urgency from baseline to 12 hours (35% vs 13%; $P = .0328$). The authors concluded that alkalinized lidocaine and heparin provide up to 12 hours of relief from urgency and pain associated with IC. It should be noted that this study was limited by a small population sample and was terminated prior to achieving enrollment numbers.[4]

Noncontrolled Trials

In an open-label trial, 32 adult patients (mean age, 63.3 years; range, 35-82 years) with IC refractory to conventional therapy received weekly intravesical instillations of heparin (20,000 units)/4% lidocaine (5 mL)/7% sodium bicarbonate (25 mL) for 12 weeks. The dwell time was 30 minutes after instillation. The pH of the solution was 7.5. The primary outcome measure was determined via a patient-reported GAR 7-point scale (range, *markedly worse* [-3] to *markedly improved* [+3]) with efficacy defined as patients reporting *slight* (+1) to *marked* (+3) improvement. The response rate gradually increased over the treatment period, with a response rate of 33.3%, 60%, and 76.7% at weeks 1, 4, and 12, respectively. Post-therapy response rates were 90%, 46.7%, and 16.7% at 1, 2, and 6 months post therapy. [5]

SAFETY

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg, Warnings/Precautions, Adverse Reactions, Drug Interactions).

Adverse events noted in the reviewed data were not serious. In a controlled trial, minor events in

patients receiving alkalinized lidocaine in combination with heparin were similar to placebo in frequency and type, affecting approximately 30% to 50% of patients and including headache, dizziness, lightheadedness, and bladder or urethral pain. No increases in activated partial thromboplastin time (aPTT) or prothrombin time (PT) were observed.[4] Bladder discomfort has occurred with every instillation in 60% of patients treated with intravesical heparin.[5] In an open-label study, gross hematuria was observed only on the day of instillation and was not associated with systemic coagulation disorder.[5]

THERAPY CONSIDERATIONS

Intravesical heparin alone or in combination with alkalinized lidocaine in the management of IC/BPS has been studied in controlled and noncontrolled trials, demonstrating efficacy rates ranging from 56% to 94%. National guidelines recommend intravesical heparin as a second-line treatment option having potential benefit in a subset of patients with an uncertain benefit/risk ratio.

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