Title

Beyond a Simple Anesthetic Effect: Lidocaine in the Diagnosis and Treatment of Interstitial Cystitis/bladder Pain Syndrome.

Journal

Urology, 85(5)

ISSN

0090-4295

Authors

Henry, Richard A
Morales, Alvaro
Cahill, Catherine M

Publication Date

2015-05-01

DOI

10.1016/j.urology.2015.01.021

Peer reviewed

Beyond a Simple Anesthetic Effect: Lidocaine in the Diagnosis and Treatment of Interstitial Cystitis/bladder Pain Syndrome

Richard A. Henry, Alvaro Morales, and Catherine M. Cahill

Intravesical local anesthetics, in a wide variety of combinations, are increasingly used to treat patients with interstitial cystitis–bladder pain syndrome (IC/BPS). Lidocaine has demonstrated properties that block the neuroinflammatory cycle associated with IC/BPS at many of the interactive points in this cycle. Intravesical lidocaine has been shown to assist in identifying the bladder as the source of pain in patients with pelvic pain. An appreciation of these anti-inflammatory effects and of the pharmacokinetics of intravesical lidocaine in patients with IC/BPS could lead to a safe and effective diagnosis and treatment for an as yet unidentified subset of patients in the IC/BPS spectrum. UROLOGY 85: 1025–1033, 2015. © 2015 Elsevier Inc.

Although the clinical picture of interstitial cystitis (IC)/bladder pain syndrome (BPS) is widely recognized, its cause(s) remains poorly understood. There are few characteristic or specific clinical or pathologic criteria for the diagnosis of IC/BPS, and specific markers have proven to be inconsistent and unreliable. Thus, despite concerted efforts, IC/BPS has eluded a clear understanding of its etiology and pathogenesis, resulting in failure to develop diagnostic and therapeutic management strategies that significantly and consistently benefit the majority of IC/BPS patients.[1]

The bladder has only a limited response repertoire to injury, making it likely that >1 causal entity is at play in the full spectrum of chronic bladder pain. Classic IC, with mast cell proliferation causing inflammatory lesions (Hunner ulcer) in the bladder wall, is found in <20% of IC/BPS patients.[2] Mast cell–mediated inflammation results in bladder pain with sensitization of peripheral and central sensory nociceptive nerve endings.[3] As in most chronic pain disorders, it is now thought that the pain in IC/BPS is due not only to changes within the bladder but also within the peripheral and central nervous systems involved in the transmission and modulation of nociception.[4-6]

Far more common than classic IC with mucosal ulceration is BPS, with inconsistent clinical and bladder findings, except for a strong association with fibromyalgia and irritable bowel syndrome.[7] This may represent a disease entity having a primary source elsewhere, such as myofascial pain,[8,9] with the colocated spinal cord dorsal horn instigating bladder symptoms via complex and powerful mechanisms, which we now understand as peripheral and central sensitization.[10]

Lidocaine is a common local anesthetic (LA) agent that is also used in a variety of chronic and persistent pain syndromes, including treatment of IC/BPS. This review will present the published clinical experience with intravesical lidocaine, as well as briefly review the anti-inflammatory effects of lidocaine pertinent to IC. Although the authors are aware that intravesical bupivacaine enjoys widespread clinical use, no published experience with this LA was found.

CLINICAL EVIDENCE

We probed the MEDLINE, PubMed, and EMBASE search engines between 1980 and 2014 for citations on IC or BPS and lidocaine or LA in the diagnosis and treatment of IC/BPS. One author (R.A.H.) screened the search results using predefined inclusion or exclusion criteria. Medical subject headings, titles, and abstracts were reviewed. Full articles were assessed for relevance if the abstracts fulfilled the predetermined criteria. Studies involving nerve or spinal blocks or chronic pelvic pain such as vulvar vestibulitis were not included. A quality check of the selected publications was carried out (A.M.) using an adaptation of the Grading of Recommendations Assessment, Development, and Evaluation principles for clinical evidence, where Grading of Recommendations Assessment, Development, and Evaluation scores from high quality

Financial Disclosure: *The authors declare that they have no relevant financial interests.*

From the Department of Anesthesiology and Perioperative Medicine, Queen's University, Kingston, Ontario, Canada; the Department of Urology, Queen's University, Kingston, Ontario, Canada; and the Department of Anesthesiology and Perioperative Care, University of California Irvine, Irvine, CA

Address correspondence to: Alvaro Morales, M.D., Department of Urology, Queen's University, 59 Lakeshore Boulevard, Kingston, ON, Canada K7M 6R4. E-mail: moralesa@queensu.ca

Submitted: December 29, 2014, accepted (with revisions): January 17, 2015

(⊕⊕⊕⊕) to very low (⊕) were given.[11] Controlled randomized studies of high quality would reach up to high quality (⊕⊕⊕⊕), whereas single case reports earned the lowest (⊕) qualification (Table 1).

RESULTS

Evaluation of Literature

Literature search identified 60 qualifying articles but when limited to human subjects, only 15 publications on LAs for treatment of IC/BPS merited inclusion (Table 1) As shown in Table 1, the majority were limited experiences of a single observation, a few cases or open-label uncontrolled studies. Only 1 study was controlled and randomized but had a limited population, meriting a ⊕⊕⊕ rating. Although the preponderance of the evidence augurs well for the diagnostic and therapeutic use of intravesical anesthetics in IC/BPS, the quality of the evidence remains low.

The first case of intravesical lidocaine treating IC was reported in 1989 by Asklin and Cassuto.[12] The patient had severe symptoms (pain and frequency, 2-5 per hour) for 2 years and was found to have the ulcerative form of IC with severe inflammatory changes and a functional bladder capacity of 50-60 mL. Two cystodistension procedures provided a "palliative effect of only 1-2 weeks," with no change in functional bladder capacity. A 0.4% solution of 200-mg lidocaine comprising 10 cc of 2% lidocaine hydrochloride mixed with 40-mL saline was instilled into the bladder daily for 2 weeks, then twice weekly for 4 weeks. The authors reported an excellent response including cessation of pain, decreased frequency to once hourly, an increased bladder volume to 250 mL, only slight edema on cystoscopy, and a marked mast cell count reduction. Three months after this treatment, "general edema and ulcerations had reappeared" along with the original symptoms.

A second case report in 1992 used twice-daily instillations of 300-mg (0.46%) lidocaine in 65 mL of nonalkalinized saline for 10 days, then daily for 20 days to achieve a good response. Further instillations continued twice weekly for another 30 days achieved cystoscopic resolution with ongoing treatment continued twice monthly to maintain the benefits.[13]

Electromotive drug administration (EMDA) describes the use of electric charge to drive the charged lidocaine molecules into the bladder wall. EMDA of intravesical lidocaine was first reported in 1992[14] to perform painless bladder cystodistension in a patient with IC. Eighty milliliters of 1% lidocaine (800 mg) with 1:100,000 epinephrine were instilled into the bladder, and a positive polarity intravesical probe was used for 10 minutes. After a biopsy was completed, the bladder was distended with 50-80 mL increments of distilled water every 3-5 minutes with continuous application of the 15-mA intravesical current to a final bladder volume of 600 mL. Dexamethasone 16 mg was added to the last infusion. The patient's symptoms were greatly improved for 6 weeks after the procedure. Positive outcomes of bladder capacity, voiding frequency, and pain were also reported using EMDA lidocaine followed by cystodistension.[15-17] Although studies using intravesical EMDA have shown improved analgesia when used as an anesthetic for bladder procedures such as hydrodistension, capsaicin instillation, and bladder biopsies, absorption kinetic studies have not been published.[18,19]

Alkalinization of intravesical lidocaine with sodium bicarbonate was first described in 1979 by Higson et al.[20] They administered 40 mL of 1% lidocaine with 40 mL of 8.4% sodium bicarbonate, held in the bladder for 30 minutes, to 20 subjects with urinary frequency, urgency, and incontinence who were diagnosed with detrusor instability at that time. Bladder capacity went from a mean of 146 to 326 mL, with a decrease in mean maximum detrusor pressure from 65.5 to 44.5 cm water. Sodium bicarbonate was added after initial pilot studies, with unbuffered lidocaine providing no effect.

Pharmacokinetic studies investigating nonalkalinized intravesical lidocaine in normal bladders have shown minimal systemic lidocaine absorption. Birch and Miller[21] (1994) instilled 40 mL of 1% lidocaine (400 mg) with 10-mL sterile water catheter flush in 2 groups of subjects, already catheterized for postoperative urinary retention, to be held for 1 and 2 hours, respectively. Plasma levels peaked at 121 ng/mL in 60-90 minutes in the 1-hour group and at 410 and 1580 ng/mL, respectively, in 120 minutes in the 2 subjects in the 2-hour group.

Alkalinization was later investigated by various research groups for use in the management of IC/BPS (Table 1). Alkalinization provided consistent absorption, initially in normal bladders, through a range of doses (4, 5, and 6 mg/kg) providing peak serum levels in the desirable 1-1.5 mcg/mL range, peaking in 30-60 minutes. In the same publication, 5 mg/kg was administered to IC subjects, providing a serum lidocaine peak of 1.3 mcg/mL at 30 minutes with a significant immediate reduction in bladder pain.[22]

A subsequent larger 102-patient, multicenter, placebo-controlled trial performed with a similar daily 1-hour retention dosing strategy of 200 mg of alkalinized lidocaine for 5 days resulted in a serum lidocaine peak of 0.6 mcg/mL at 1.13 hours and furnished significant relief of bladder symptoms beyond the treatment phase.[23] Unfortunately, this study failed to document the immediate response to the initial instillation, which might have allowed early identification of potential responders.

This led other investigators to use a similar intravesical alkalinized lidocaine in combination with known glycosaminoglycan layer enhancers, heparin and hyaluronic acid. In 2005, Parsons[24] initially used 80-mg lidocaine alkalinized with 3 mL of 8.4% sodium bicarbonate and 50,000 units of heparin (15 mL total) in 47 subjects meeting prevailing IC criteria. The second group of 35 subjects received the same solution modified with

Table 1. Summary of qualifying studies using intravesical lidocaine for the treatment of IC/BPS

Treatment-type Author	Grade*	Year	No. of Subjects	Duration	Treatment Used	Comments
Lidocaine plain						
Asklin and Cassuto[12]	⊕	1989	1	4 wks	2% lidocaine (10 mL) in 40 mL saline; 200 mg in 50 mL providing 0.4% solution	Pain free after 2 wks daily treatment; ulceration healed after 4 wks treatment
Giannakopoulos and Champilomatos[13]	⊕	1992	1	8 wks	2% lidocaine (15 mL) in 50 mL saline; 300 mg in 65 mL providing 0.45% solution	Twice daily for 10 days, daily for 20 days, then, twice weekly for 4 wks
EMDA lidocaine (dexamethasone)						
Fontanella et al[14]	⊕	1992	1	1 Rx	1% lidocaine (80 mL) in distilled water; 800 mg with epinephrine 1:100,000	15 mA DC intravesical current 10 min incremental bladder distention to 600 mL
Rosamilia et al[16]	⊕⊕	1997	21	1 Rx	2% lidocaine (150 mL) in distilled water; 3000 mg with epinephrine 1.5 mg + dexamethasone 16 mg	30 mA DC current for 20-30 min incremental bladder distention till patient discomfort; 85% achieved pain reduction >2 at 2 wks with decreased frequency
Riedl et al[17]	⊕	1998	13	1-6/pt	2% lidocaine (100 mL) in distilled water; 2000 mg with 16 mg epinephrine + 16 mg dexamethasone	15 mA DC current for 20 min distention to 200% prior capacity for 1-5 min: 62% judged effective
Alkalinized lidocaine						
Henry et al[22]	⊕	2001	12	1x/d ×2	2%-2.5% lidocaine (5 mg/kg) in 5% dextrose; 3-400 mg + 10 mL 8.4% bicarb	Peak blood levels at/before 30 min 1.3 mcg/mL; urethral irritation
Nickel et al[23]	⊕⊕⊕	2008	102	1x/d ×5	2% lidocaine (10 mL) 200 mg + 8.4% bicarb; held for 1 h	Only placebo study with alkalinized lidocaine; 78% positive response
Lidocaine/heparin ± alkalinization						
Parsons[24]	⊕⊕	2005	47	1 Rx	1% lidocaine (8 mL) 40,000 U heparin; 3 mL 8.4% bicarb	75% and 94% positive response rate
	⊕⊕		35	2 wks	Second group received 8 mL of 2% lidocaine (160 mg)	
Welk and Teichman[26]	⊕⊕	2008	23	3x/wk; 3 wks	8 mL 2% lidocaine, 4 mL 8.4% bicarb, and 2 mL (10,000 U/mL) heparin in 14 mL	15/23 had >50% improvement
Butrick et al[8]	⊕⊕	2009	408	1x/wk; 3 wks	20 mL 2% lidocaine, 20,000 U heparin; 40 mg triamcinolone (?volume)	
Parsons et al[25]	⊕⊕	2011	28	1 Rx	1.3% lidocaine (200 mg), 420 mg bicarb 50,000 U heparin in 15 mL	Treatment held in bladder for 30 min; bicarb used as control; poor responders received second Rx 1 day later; average serum level 0.51 μg/mL
Matsuo et al[27]	⊕	2011	1	2x/wk; 1 y	200 mg lidocaine, 7% bicarb, and 20,000 U heparin in 50 mL	Increased bladder capacity from 90 to 300 mL; IC symptom index improved from 20 to 80.
Alkalinized lidocaine + hyaluronic acid						
Lv et al[28]	⊕⊕	2012	48 (3 groups)	1x/wk; 8 wks, monthly ×4	10 mL 2% lidocaine + 5 mL 8.4% bicarb + 40 mg HA (16), HA alone (16), and lidocaine/bicarb (16)	Treatment held for 1 h, weekly for 8 wks and then monthly for 4 mo. No difference in HA groups; poor response in alkalinized. lidocaine group
Continuous intravesical lidocaine						
Nickel et al[29]	⊕	2012	16	2 wks	200 or 650 mg LiRIS lidocaine slowly released into bladder over 2 wks	64% positive response rate
Intravesical lidocaine in diagnosis of IC						
Taneja[30]	⊕⊕	2010	22	1 Rx	2% lidocaine (20 mL) 400 mg	Strong correlation between cessation of pain and cystoscopic bladder findings of IC

bicarb, bicarbonate; BPS, bladder pain syndrome; DC, direct current; EMDA, electromotive drug administration; HA, hyaluronic acid; IC, interstitial cystitis; LiRIS, lidocaine-releasing intravesical system; pt, patient; Rx, treatment.
* Level of evidence.

the addition of an extra 80 mg of lidocaine for a total 160-mg dose. The duration of retention was not reported. Seventy-five percent of group 1 and 94% of group 2 subjects reported >50% improvement of symptoms.

A second study by Parsons et al[25] (2012) with 18 completed subjects compared 200-mg lidocaine with 50,000 U heparin and 420-mg sodium bicarbonate in 15 mL total volume, with the control group receiving sodium bicarbonate only. The solution was held for 30 minutes, with blood samples drawn at 60 minutes. Treatment was repeated once more the following day in subjects who still had pain and urgency scores above 3 of 10. Serum lidocaine levels ranged from 0.24 to 2.0 mcg/mL, with an average of 0.51 μg/mL, and pain and urgency scores decreased by 35%.

The study by Welk and Teichman,[26] in 2008, investigated the effect on dyspareunia with a similar solution (8 mL of 2% lidocaine + 4 mL of 8.4% bicarbonate and 2 mL of heparin) held for 1 hour and then voided, 3 times weekly for 3 weeks in patients with IC/BPS. Eighty-five percent of subjects with focal bladder tenderness only on vaginal examination had resolution of dyspareunia compared with 29% of subjects who had more diffuse pelvic muscle tenderness.

Matsuo et al[27] published a single case report (in Japanese 2011) with the longest studied use of intravesical lidocaine (200 mg) with bicarbonate and 20,000 U heparin administered twice weekly for 1 year. The patient's bladder capacity increased from 90 to 300 mL and IC symptom index from 20 to 80.

Lv et al[28] (2012) studied the efficacy of alkalinized lidocaine (200 mg) vs hyaluronic acid (40 mg) with a combined third group, administered weekly for 8 weeks and then monthly for 4 months. Both lidocaine groups did well initially during the weekly phase of treatment. Although there was no difference between the hyaluronic groups at the end of the monthly treatments, the lidocaine-only group did poorly at the lower frequency monthly treatment, with 14 of 15 failing to complete the study after the first 8 weeks.

More recently, researchers have developed a continuous lidocaine-releasing intravesical system (LiRIS) loaded with solid lidocaine hydrochloride minitablets (200 or 650 mg).[29] A silicone container absorbs urine to dissolve the lidocaine contents, whereas the osmotic pressure created forces the solution out of the container through a small orifice in a controlled release over 14 days. A study evaluating the effects of LiRIS reported a 64% positive response rate. Interestingly, the 200-mg LiRIS was more effective than the higher 650-mg dose. These results are encouraging, especially because the total dose delivered (140 or 500 mg) over 14 days provided only 10-35 mg per day.

Surprisingly, only 1 study investigating the usefulness of intravesical lidocaine in diagnosing IC has been published.[30] Nonalkalinized 2% lidocaine (20 mL) provided significant reduction in pain in 68% of subjects (15 of 22) with as yet undiagnosed BPS, with almost total cessation of pain in 50% of patients. Thirteen of the 15 responders had cystoscopic findings suggestive of IC (Hunner ulcer in 5 of 13 patients and glomerulations or petechial patches in 8 of 13 patients), whereas all the nonresponders had unremarkable bladders with other causes for their pain subsequently identified.

Butrick et al[8] published a retrospective chart review in 2009 looking at the response rate in patients who presented to their urogynecologic referral center over a 3-year period (2004-2006) with pelvic pain and/or bladder dysfunction. One of the standard treatments during this period entailed intravesical nonalkalinized lidocaine (200 mg) combined with 20,000 units of heparin and 40-mg triamcinolone administered weekly. Most patients received at least 3 treatments. Seventy-one percent of all patients felt the intravesical treatments were beneficial, with a 73.7% response in their IC/BPS group and 50% in patients diagnosed with vulvodynia and/or dyspareunia. The most common final diagnosis in the nonresponding patients was myofascial pain (51%).

COMMENT

The Mechanism of Pain in IC/BPS: The Neuroinflammatory Process

The concept of a subpopulation of silent nociceptor neurons that only responded to a stimulus capable of causing tissue damage was first postulated over a century ago.[5]

Neurogenic inflammation (Fig. 1) occurs when acute peripheral inflammation activates and sensitizes nociceptors,[4-6] setting up a response known as a dorsal root reflex.[30] Dorsal root reflexes are abnormal, likely occurring only after there has been persistent strong stimulation. Bidirectional transport of potent neuropeptides, produced in the nociceptor cell body located in the dorsal root ganglion, to the bladder (peripheral sensitization) and the dorsal horn of the spinal cord (central sensitization) provokes receptors (lowering the activation threshold) responsible for pain transmission as well as enhancing peripheral inflammation.[31,32] Released neuropeptides such as substance P, calcitonin gene-related peptide, nerve growth factor, and vasoactive intestinal peptide are well characterized and have been shown to alter bladder mucosal permeability, smooth muscle contractility, and local blood flow and to influence cellular mediators of the immune system.

Thus, peripheral sensory neuronal structural and physiochemical changes found in the inflamed bladder are mirrored by neuronal changes (plasticity) in the dorsal root ganglia and sensory receiving areas of the bladder in the spinal cord. Bladder afferent cell bodies in thoracolumbar and sacral dorsal root ganglia undergo hypertrophy in response to intravesical irritants resulting in spontaneous activity in normally "silent" C-fiber nociceptors. Activated C-fibers are one of the histologic

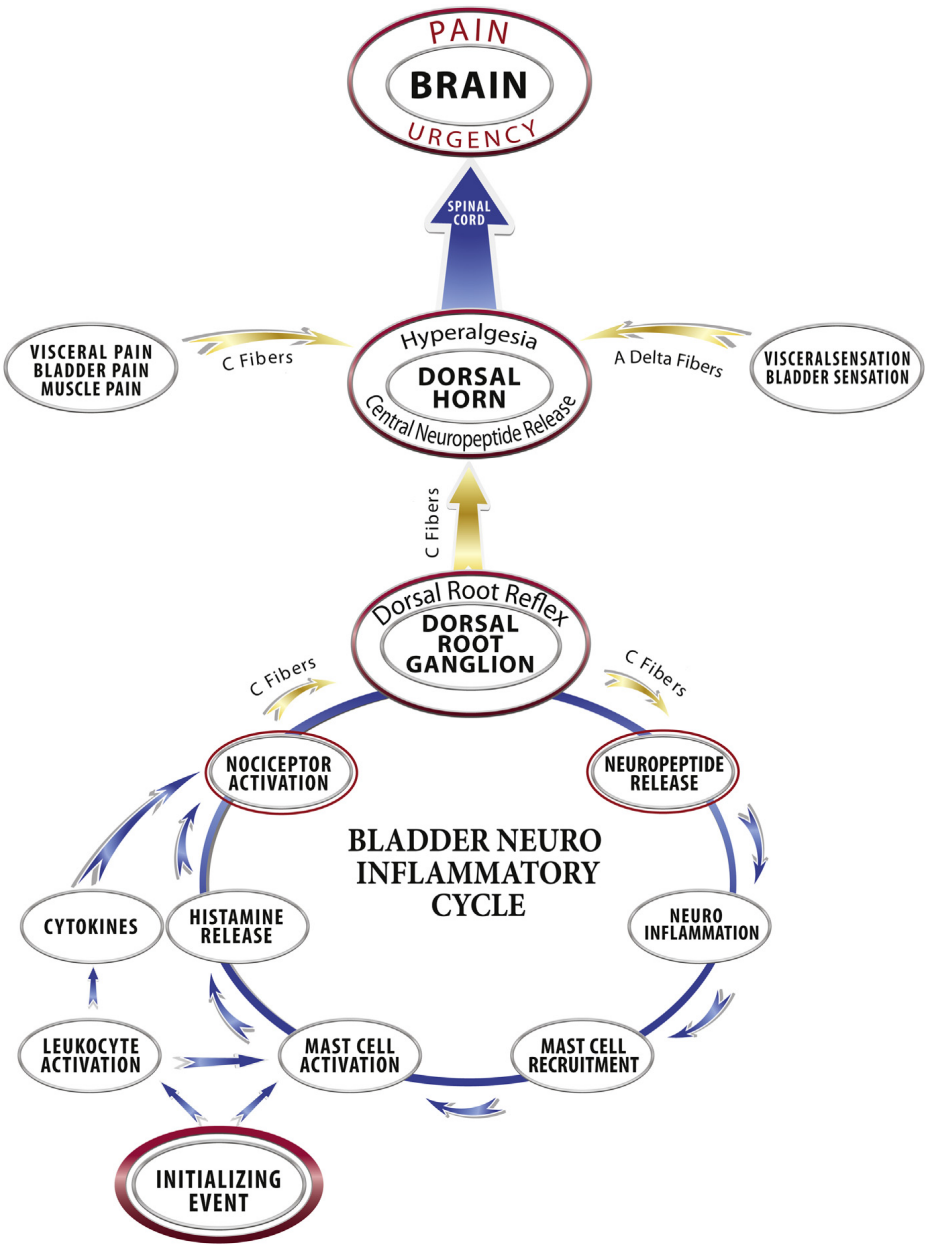

Figure 1. The neuroinflammatory cycle in interstitial cystitis. An initializing event (or combination of factors) triggers sufficient release of leukocyte and mast cell mediators to activate C-fiber nociceptors, triggering the dorsal root reflex to release neuropeptides from both the central (dorsal horn) and peripheral (bladder) nerve terminals. The nociceptor dorsal root reflex causes central hyperalgesia in the dorsal horn, with all sensations at this level amplified to unpleasant degrees. Concurrently, peripheral neurogenic inflammation in the bladder, with mast cell recruitment, activation, and degranulation, perpetuates the inflammatory cycle. (Color version available online.)

features of IC and are implicated directly in the maintenance of the inflammation in IC.[33]

Mast Cells: The Concept of a Looped Self-perpetuation of IC

Perpetuation of the inflammatory reaction seen in IC is established in a highly potent mediator microenvironment. Reciprocal activation of mast cells by neuropeptides and sensory nerves by mast cell mediators (particularly histamine) maintains this ongoing inflammatory process. Mast cells, by virtue of their location, responsiveness to neuropeptides, and diverse potent mediator production, play a central role in the chronic inflammation of IC.[2,3]

These nerve-associated activated mast cells show evidence of piecemeal degranulation and have been suggested as a characteristic ultrastructural feature of IC.[3] The surrounding urothelium shows fluid engorgement, widened intercellular spaces with disruption of the permeability barrier, and cell injury with accelerated turnover. Neural changes consisting of swollen axons and supportive elements and degeneration and depletion of

myelinated axons resemble those changes found in inflammatory bowel disease and experimentally in cortical rat brain slices incubated with peritoneal mast cells.[34,35] Vascular changes with bloated endothelial cells, focal degeneration, and fragmentation are also a consistent feature and confirm vascular injury.[36,37]

Local Anesthetics as Anti-inflammatory Agents

Concurrently, as the neurogenic inflammatory model of IC was being developed, so has our appreciation of the anti-inflammatory properties of LAs and their potential clinical applications.[38,39] Beyond their well-known sodium channel interaction causing nerve conduction suppression, LAs also affect potassium and calcium channels and membrane function, suppressing intercellular mechanisms vital to inflammation such as migration, exocytosis, and phagocytosis.[40]

LAs have a well-demonstrated inhibitory effect on chemotactic-induced leukocyte margination, adherence, movement into tissue, and activation, as well as phagocytosis, metabolism, and function.[40] LAs dose-dependently and reversibly inhibit leukocyte adhesion to the capillary wall, possibly by interfering with the actions of adhesion receptors (integrins and leukocyte adhesion molecule-1) in the leukocyte membrane. Cytokines produced by the innate bladder immune system and the activated C-fibers profoundly influence chemotaxis and oxidative metabolic activity. The release of the cytokines interleukin-1, interleukin-8, and interleukin-1B is dose-dependently inhibited by lidocaine and bupivacaine. Lidocaine inhibits normal random leukocyte motility both by their effects on the cytoskeleton, by attenuating the release of chemoattracting agents from leukocytes and stimulating secretion of the anti-inflammatory molecule interleukin-1 antagonist.[38,39]

Lidocaine has been shown to have therapeutic anti-inflammatory effects on eosinophil activity when used in the treatment of asthma.[41] LAs have also been shown to play a significant role in the treatment and prevention of neuropeptide-induced peripheral and central sensitization.[42]

Lidocaine has been found to inhibit histamine release from challenged mast cells.[43] This action was found to be critically concentration dependent and exhibits a biphasic response: slight potentiation of histamine release occurring at 1 mM (0.027%) and complete inhibition of histamine release at 20 mM (0.5%). Subsequent investigation of this phenomenon showed that lidocaine induced a strong inhibition of activated mast cell histamine release, with increasing effect at higher pH.[44] LAs have also been shown to competitively inhibit histamine-1 receptors and the release of histamine in skin by platelet-activating factor.[43]

Another possibly relevant but less-known property of these drugs is a broad-spectrum bactericidal effect that is also concentration dependent. Lidocaine has also been shown to inhibit the growth of *Candida albicans* and interfere with viral replication.[38,39] The antimicrobial properties of LAs may explain the low rates of infection associated with LA use, despite the powerful and broad range of anti-inflammatory properties they exhibit. These properties may prove beneficial when using LAs in the urinary tract.

Breaking the Self-perpetuating Inflammatory Loop in IC

This conceptual approach to IC and awareness of lidocaine activity makes a robust case for the investigation of LAs to suppress and even halt the (possibly) self-perpetuating neurogenic inflammation in IC. It should not be surprising then that intravesical lidocaine has been successful in both identifying the bladder as the source of pain and controlling IC pain. Studies have shown lidocaine to reversibly inhibit all the formative looped events associated with neurogenic inflammation.

Although LAs administered systemically have been found effective in pain conditions such as burns, bowel obstruction, and peritonitis, the majority of their therapeutic effects are concentration dependent and may require tissue levels in keeping with their neuronal blocking (local) concentrations.[45] These LA tissue levels are toxic and potentially lethal when found in the brain or the heart (causing seizures and dysrhythmia, respectively). As such, LAs are usually administered locally to the desired site of action, where the anesthetic effect is desired. In IC, the target is the bladder wall. Targeting the upregulated but distant dorsal root ganglia and spinal cord dorsal horn relies on axonal transport to these target sites. Safe dosing mandates keeping systemic levels of the drug below the systemic toxic threshold (5 mcg/mL plasma) and requires some pharmacokinetic knowledge and understanding pertaining to both lidocaine and the bladder.

Permeability of Bladder Epithelium

Bladder urothelium has low permeability to charged ions and small molecules such as sodium, urea, and water. This impermeability is attributed to tight junctions between the apical membrane cells and is most effective at preventing absorption of ionized molecules, as found in the urine.[46] Mishina et al[47] showed that absorption of a weak base molecule was profoundly affected by pH of the bladder content and was optimal at pH >6. Because the route of entry is considered to be directly transmembranal, rather than between cells, lipid solubility (partition coefficient) and molecular size were also shown to be important determinants for the absorption of substances through the bladder epithelium. Not surprisingly, intravesical unbuffered lidocaine has been shown to have negligible absorption.[21]

The effect of inflammation on the integrity of the bladder urine to blood barrier is widely considered to break this protective effect. Absorption of salicylate was found to be 8 times higher in cats with IC than in those with normal bladders.[48] We did not find any studies

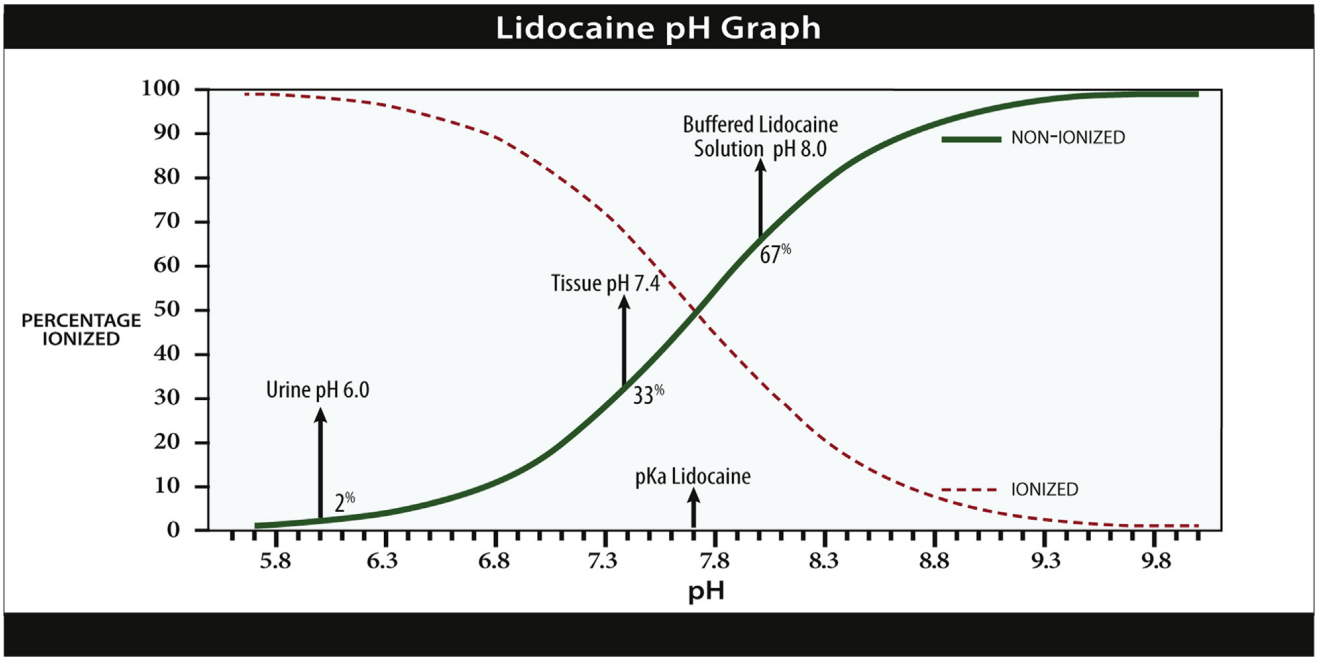

Figure 2. The effect of pH on lidocaine ionization in solution. At pH of 7.7 (pKa), 50% of the lidocaine is in the base form. At pH of around 7.4, this drops to 33% and down to 1%-2% at a common urine pH of 6 and the pH range in which the lidocaine is manufactured to maintain ionized lidocaine in solution. Buffering the lidocaine solution will markedly elevate the base percentage to around 60%. (Color version available online.)

comparing the absorption of unbuffered lidocaine in healthy vs IC bladders.

Pharmacokinetics of Intravesical Lidocaine

LA absorption and diffusion through tissue is largely affected by the following equation:

$$\text{Absorption } \alpha \frac{\text{lipid solubility} \times \text{concentration}}{\text{molecular weight} \times \text{ionized fraction (pKa/pH)}}$$

Because the commonly used amide LAs are all of a similar structure, molecular weight can largely be ignored as a variable factor between different LAs. Lipid solubility affects potency and is corrected for in the concentration of each formulation. Lidocaine is provided in concentrations from 0.5% to 10% (topical airway spray), with most preparations being in the 1% or 2% range for injection and 4% for topical use. This is contrasted with bupivacaine, which, being more lipid soluble, is provided in the 0.25%-0.5% range.

The remaining absorption variable is the ionized fraction of the drug. LAs are amphiphatic molecules, having both a water-soluble cationic and a lipid-soluble free base form. The state of the drug in an aqueous solution is pH dependent and predicated by the pKa of the drug, which is really an expression of hydrogen ion affinity in an aqueous solution. LAs are weak bases. Lidocaine, the weakest, has a pKa of 7.7. Being a logarithmic scale, the relative concentrations of each state are profoundly affected by even small changes in pH (Fig. 2).

LAs are generally formulated as acidic aqueous solutions of their ionized form by lowering the pH of the solution to well below the pKa of the drug, usually to pH around 5.0, causing 99% of the molecules to be ionized. This acidification is the reason that LAs sting when first injected. On injection, tissue buffering raises the pH of the injected solution, transforming the LA into its base form, allowing diffusion into the targeted nerves.

The bladder is ideally suited for topical anesthesia with its ability to provide residency of the drug for as long as voiding can be postponed. Healthy bladder mucosa is however well designed to prevent absorption of ionized molecules, essentially preventing reabsorption of urine. Tight junctions between the bladder epithelial cells prevent ionized molecules slipping through the cracks between cells, leaving only the lipid-based cell membrane as a route of entry. With urine pH usually in the pH 5-6 range, the acidic urine keeps lidocaine in the ionized state, essentially ion-trapping the drug. Raising the pH of the bladder contents will increase the absorption of lidocaine.

LA toxicity is determined by the systemic level of the drug, which in turn is primarily dependent on the rate of absorption from the site of deposition.[49] Mild toxicity is felt as a ringing in the ears and perioral numbness when lidocaine levels exceed 5 mcg/mL. The dose for lidocaine that reliably produces serum levels in the safe range of 1-3 mcg/mL are 1-1.5 mg/kg intravenously and 4-5 mg/kg when infiltrated into tissue. The maximum safe intravesical dose is likely in the 5 mg/kg (lean body weight) range, depending on the urine pH, bladder perfusion, and, to a lesser extent, the concentration of the solution used. Time to peak systemic levels is 15-30 minutes.[22]

The bladder wall in patients with IC is inflamed and thought to lose the charged ion and water-impermeable barrier provided by the tight junctions, thereby making the bladder permeable to urine solutes (eg, potassium) and ionized drugs such as lidocaine. This change in permeability could be used in identifying patients with classic or ulcerative IC, who would be expected to have a significant reduction in bladder pain with nonalkalinized intravesical lidocaine although inflammation was present.

CONCLUSION

Although lidocaine appears to be a promising candidate drug to interrupt the self-perpetuating neuroinflammatory cycle found in IC, only weak evidence exists for supporting its clinical use. Lidocaine is a familiar and readily available LA with a reassuring safety margin when used intravesically. However, there remain many unanswered questions pertaining to the ideal formulation, dosing regimen, and patient population.[50]

Current widespread use of intravesical lidocaine (and bupivacaine) by clinicians for the treatment of IC in the absence of an approved product is not an unusual scenario. This review aims to condense our knowledge surrounding LA treatment for bladder IC/BPS. A full appreciation of the broad-spectrum neuroinflammatory suppressive effects of LAs and their potential efficacy in the treatment of IC will help in guiding and encouraging physicians and researchers in the future investigation of this class of drugs.

There remains a need for an optimized intravesical lidocaine preparation with proven reliability in the early identification of lidocaine-responsive bladder pain patients, as well as an identified optimum preparation, frequency, and duration of treatment required to induce a sustained remission, if that is indeed possible. In the interim, a suitable, inexpensive, and safe approach may be daily instillations of 10-20 mL of 2% lidocaine (2-400 mg), with or without alkalinization, for at least a week to identify a clinical response that justifies ongoing treatment. Once an optimum treatment regimen is found, large-scale, well-designed, clinical trials are needed to provide much needed answers.

References

1. Moutzouris D, Falagas ME. Interstitial cystitis: an unsolved enigma. *Clin J Am Soc Nephrol*. 2009;4:1844-1857.
2. Hofmeister MA, He F, Ratliff TL, et al. Mast cells and nerve fibers in interstitial cystitis (IC): an algorithm for histologic diagnosis via quantitative image analysis and morphometry (QIAM). *Urology*. 1997;49(5A suppl):41-47.
3. Elbadawi A. Interstitial cystitis: a critique of current concepts with a new proposal for pathologic diagnosis and pathogenesis. *Urology*. 1997;49(5A suppl):14-40.
4. Christmas TJ, Rode J, Chapple CR, et al. Nerve fibre proliferation in interstitial cystitis. *Virchows Arch A Pathol Anat Histopathol*. 1990;416:447-551.
5. Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. *Cell*. 2009;139:267-284.
6. Levine JD, Fields HL, Basbaum AI. Peptides and the primary afferent nociceptor. *J Neurosci*. 1993;13:2273-2286.
7. Nickel JC, Tripp DA, Pontari M, et al. Interstitial cystitis/painful bladder syndrome and associated medical conditions with an emphasis on irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome. *J Urol*. 2010;184:1358-1363.
8. Butrick C, Sanford D, Hou Q, et al. Chronic pelvic pain syndromes: clinical, urodynamic, and urothelial observations. *Int Urogynecol J Pelvic Floor Dysfunct*. 2009;20:1047-1053.
9. Rudick CN, Chen MC, Mongiu AK, et al. Organ cross talk modulates pelvic pain. *Am J Physiol Regul Integr Comp Physiol*. 2007;293:R1191-R1198.
10. Lai HH, Qiu CS, Crock LW, et al. Activation of spinal extracellular signal-regulated kinases (ERK) 1/2 is associated with the development of visceral hyperalgesia of the bladder. *Pain*. 2011;152:2117-2124.
11. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-926.
12. Asklin B, Cassuto J. Intravesical lidocaine in severe interstitial cystitis. Case report. *Scand J Urol Nephrol*. 1989;23:311-312.
13. Giannakopoulos X, Champilomatos P. Chronic interstitial cystitis. Successful treatment with intravesical lidocaine. *Arch Ital Urol Nefrol Androl*. 1992;64:337-339.
14. Fontanella UA, Rossi CA, Stephen RL. Iontophoretic local anaesthesia for bladder dilatation in the treatment of interstitial cystitis. *Br J Urol*. 1992;69:662-663.
15. Gurpinar T, Wong HY, Griffith DP. Electromotive administration of intravesical lidocaine in patients with interstitial cystitis. *J Endourol*. 1996;10:443-447.
16. Rosamilia A, Dwyer PL, Gibson J. Electromotive drug administration of lidocaine and dexamethasone followed by cystodistension in women with interstitial cystitis. *Int Urogynecol J*. 1997;8:142-145.
17. Riedl CR, Knoll M, Plas E, et al. Electromotive drug administration and hydrodistention for the treatment of interstitial cystitis. *J Endourol*. 1998;12:269-272.
18. Jewett MA, Valiquette L, Sampson HA, et al. Electromotive drug administration of lidocaine as an alternative anesthesia for transurethral surgery. *J Urol*. 1999;161:482-485.
19. Dasgupta P, Fowler CJ, Stephen RL. Electromotive drug administration of lidocaine to anesthetize the bladder before intravesical capsaicin. *J Urol*. 1998;159:1857-1861.
20. Higson RH, Smith JC, Hills W. Intravesical lignocaine and detrusor instability. *Br J Urol*. 1979;51:500-503.
21. Birch BR, Miller RA. Absorption characteristics of lignocaine following intravesical instillation. *Scand J Urol Nephrol*. 1994;28:359-364.
22. Henry R, Patterson L, Avery N, et al. Absorption of alkalized intravesical lidocaine in normal and inflamed bladders: a simple method for improving bladder anesthesia. *J Urol*. 2001;165(6 Pt 1):1900-1903.
23. Nickel JC, Moldwin R, Lee S, et al. Intravesical alkalinized lidocaine (PSD597) offers sustained relief from symptoms of interstitial cystitis and painful bladder syndrome. *BJU Int*. 2009;103:910-918.
24. Parsons CL. Successful downregulation of bladder sensory nerves with combination of heparin and alkalinized lidocaine in patients with interstitial cystitis. *Urology*. 2005;65:45-48.
25. Parsons CL, Zupkas P, Proctor J, et al. Alkalinized lidocaine and heparin provide immediate relief of pain and urgency in patients with interstitial cystitis. *J Sex Med*. 2012;9:207-212.
26. Welk BK, Teichman JM. Dyspareunia response in patients with interstitial cystitis treated with intravesical lidocaine, bicarbonate, and heparin. *Urology*. 2008;71:67-70.
27. Matsuo T, Shida Y, Hayashida Y, Sakai H. Intravesical therapy of heparin and lidocaine for interstitial cystitis: a case report. *Acta Urologica Japonica*. 2011;57:513-516.
28. Lv YS, Zhou HL, Mao HP, et al. Intravesical hyaluronic acid and alkalinized lidocaine for the treatment of severe painful

bladder syndrome/interstitial cystitis. *Int Urogynecol J*. 2012;23:1715-1720.
29. Nickel JC, Jain P, Shore N, et al. Continuous intravesical lidocaine treatment for interstitial cystitis/bladder pain syndrome: safety and efficacy of a new drug delivery device. *Sci Transl Med*. 2012;4:143ra100.
30. Taneja R. Intravesical lignocaine in the diagnosis of bladder pain syndrome. *Int Urogynecol J*. 2010;21:321-324.
31. Basbaum AI. Spinal mechanisms of acute and persistent pain. *Reg Anesth Pain Med*. 1999;24:59-67.
32. Rees H, Sluka KA, Westlund KN. Do dorsal root reflexes augment peripheral inflammation? *Neuroreport*. 1994;5:821-824.
33. Julius D, Basbaum AI. Molecular mechanisms of nociception. *Nature*. 2001;413:203-210.
34. De Groat WC, Yoshimura N. Afferent nerve regulation of bladder function in health and disease. *Handb Exp Pharmacol*. 2009;194:91-138.
35. Theoharides TC, Dimitriadou V, Letourneau R, et al. Synergistic action of estradiol and myelin basic protein on mast cell secretion and brain myelin changes resembling early stages of demyelination. *Neuroscience*. 1993;57:861-871.
36. Letourneau R, Pang X, Sant GR, Theoharides TC. Intragranular activation of bladder mast cells and their association with nerve processes in interstitial cystitis. *Br J Urol*. 1996;77:41-54.
37. Lundeberg T, Liedberg H, Nordling L, et al. Interstitial cystitis: correlation with nerve fibres, mast cells and histamine. *Br J Urol*. 1993;71:427-429.
38. Hollmann MW, Durieux ME. Local anesthetics and the inflammatory response: A new therapeutic indication? *Anesthesiology*. 2000;93:858-875.
39. Cassuto J, Sinclair R, Bonderovic M. Anti-inflammatory properties of local anesthetics and their present and potential clinical implications. *Acta Anaesthesiologica Scand*. 2006;50:265-282.
40. MacGregor RR, Thorner RE, Wright DM. Lidocaine inhibits granulocyte adherence and prevents granulocyte delivery to inflammatory sites. *Blood*. 1980;56:203-209.
41. Hunt LW, Swedlund HA, Gleich GJ. Effect of nebulized lidocaine on severe glucocorticoid-dependent asthma. *Mayo Clin Proc*. 1996;71:361-368.
42. Kissin I, Lee SS, Bradley EL Jr. Effect of prolonged nerve block on inflammatory hyperalgesia in rats: prevention of late hyperalgesia. *Anesthesiology*. 1998;88:224-232.
43. Kazimierczak W, Peret M, Maslinski C. The action of local anaesthetics on histamine release. *Biochem Pharmacol*. 1976;25:1747-1750.
44. Suzuki T, Ohishi K, Kida J, Uchida M. Influence of pH on the inhibitory effects of local anesthetics on histamine release induced from rat mast cells by concanavalin A and compound 48/80. *Eur J Pharmacol*. 1984;98:347-355.
45. Swanton BJ, Shorten GD. Anti-inflammatory effects of local anesthetic agents. *Int Anesthesiol Clin*. 2003;41:1-19.
46. Negrete HO, Lavelle JP, Berg J, et al. Permeability properties of the intact mammalian bladder epithelium. *Am J Physiol Ren Physiol*. 1996;271:F886-F894.
47. Mishina T, Watanabe H, Kobayashi T, et al. Absorption of anticancer drugs through bladder epithelium. *Urology*. 1986;27:148-157.
48. Gao X, Buffington CA, Au JL. Effect of interstitial cystitis on drug absorption from urinary bladder. *J Pharmacol Exp Ther*. 1994;271:818-823.
49. Scott DB, Jebson PJ, Braid DP, et al. Factors affecting plasma levels of lignocaine and prilocaine. *Br J Anaesth*. 1972;44:1040-1049.
50. Parsons CL. Should local anesthetic bladder cocktails include sodium bicarbonate? Yes. *J Urol*. 2014;191:895-896.