

## CITATIONS FOR INTERSTITIAL CYSTITIS

IntUrolNephrol. 2010 Sep;42(3):629-35. Epub 2009 Sep 26.

Urine cytokines suggest an inflammatory response in the overactive bladder: a pilot study.

Tyagi P, Barclay D, Zamora R, Yoshimura N, Peters K, Vodovotz Y, Chancellor M.

Source

Department of Urology, William Beaumont Hospital, Royal Oak, MI 48073, USA.

Abstract

PURPOSE:

To study the hypothesis of detecting bladder inflammation associated with overactive bladder (OAB) through altered urine levels of cytokines, chemokines, and growth factors.

METHODS:

Midstream urine specimens were collected from a prospective study done on eight asymptomatic control subjects and 17 idiopathic OAB patients. The urine was analyzed by a multiplex panel screen for 12 chemokines, cytokines, growth factors, and soluble receptors using Luminex™ xMAP® technology. Protein concentration values were normalized to the levels of creatinine.

RESULTS:

This analysis revealed a significant elevation of seven key proteins in the urine of OAB patients relative to controls (\*P < 0.05). A greater than tenfold elevation was measured in OAB, relative to controls, in the levels of monocyte chemoattractant protein-1 (MCP-1), soluble fraction of the CD40 ligand (sCD40L) in urine was obtained from OAB patients relative to controls. At least five fold elevations were detected in the levels of macrophage inflammatory protein (MIP-1β), IL-12p70/p40, IL-5, epidermal growth factor (EGF), and growth-related oncogene GRO-α compared to controls. Significant threefold elevation was also noticed in the urine levels of sIL-2Rα, and IL-10 in the OAB group. The levels of the remaining proteins tested were not statistically significantly different from control values.

CONCLUSIONS:

The presence of elevated levels in urine of inflammatory biomarkers involved in inflammation and tissue repair suggests a role for inflammation in OAB, and may help in diagnosis and treatment of this disease.

Rev Urol. 2010 Fall;12(4):e181-9.

State of the art in intravesical therapy for lower urinary tract symptoms.

Kaufman J, Tyagi V, Anthony M, Chancellor MB, Tyagi P.

## Abstract

Intravesical therapy is the routine first-line treatment for effectively delaying or preventing the recurrence of bladder cancer. This route of drug administration has also shown tremendous promise in the treatment of interstitial cystitis/painful bladder syndrome (IC/PBS) and potentially overactive bladder to justify investments for further improvements. This review takes a bird's eye view into the current status of intravesical therapy, with emphasis on liposomal nanoparticles, in diseases associated with lower urinary tract symptoms (LUTS). Ongoing efforts to advance the field of intravesical drug delivery include development of sustained-release drug implants and efforts to improve delivery of biotechnological products including large protein acting as neurotoxins and small interfering RNAs.

## Bladder Instillation of Liposomes for Bladder Coating and Drug Delivery Platform

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Article first published online: 1 SEP 2009

DOI: 10.1111/j.1757-5672.2009.00040.x

The clinical use of exogenous polysaccharides for the treatment of interstitial cystitis (IC) has lent credence to the concept of a dysfunctional urothelium as the cause of lower urinary tract symptoms (LUTS). Studies have shown that lipids in the apical membrane of the urothelium form an integral component of the permeability barrier in the bladder. This premise is supported by the therapeutic effect of empty liposomes in the irritated bladder. Instillation of liposomes comprised of natural phospholipids can augment bladder barrier function and support repair following injury from protamine sulfate and irritation with high potassium concentration. The mechanism of action proposed for the therapeutic effect of empty liposomes is that liposomes form a coat on the injured urothelium and block irritation of submucosal afferent nerves. Reduced afferent excitation after liposome instillation is reflected in prolonged intercontractile interval in cystometry. Liposomes offer a powerful new treatment option for IC using an intravesical route and as a platform for intravesical drug delivery.

Am J Physiol Cell Physiol. 2007 Jan;292(1):C106-14. Epub 2006 Jul 12.

EGF and HB-EGF modulate inward potassium current in human bladder urothelial cells from normal and interstitial cystitis patients.

Sun Y, Chen M, Lowentritt BH, Van Zijl PS, Koch KR, Keay S, Simard JM, Chai TC.

## Source

Division of Urology, University of Maryland, 22 S. Greene Street, S8D18, Baltimore, MD 21201, USA.

## Abstract

Interstitial cystitis (IC) is an idiopathic condition characterized by bladder hyperalgesia. Studies have shown cytokine and purinergic signaling abnormalities in cultured bladder urothelial cells (BUC) from IC patients. We performed single-cell electrophysiological studies in both normal and IC BUC. A strongly inward rectifying potassium current with conductance of the Kir2.1 channel was identified in normal BUC. This current was significantly reduced in IC BUC. Kir2.1 protein and mRNA were detected in both IC and normal BUC. Epidermal growth factor (EGF) caused a dose-dependent decrease in the inward potassium current in normal BUC. EGF is secreted in higher amounts by IC BUC and is known to decrease Kir2.1 conductance by phosphorylation of Kir2.1. Genistein, a nonspecific phosphorylation inhibitor, increased the inward potassium current in IC BUC and blocked the effect of EGF on normal BUC. Treatment of IC BUC with heparin-binding epidermal growth factor-like growth factor (HB-EGF), previously shown to be secreted in lower amounts by IC BUC, significantly increased inward potassium current. These data show that the inward potassium current in BUC can be modulated by EGF and HB-EGF. Changes in BUC membrane potassium conductance caused by altered levels of EGF and HB-EGF may therefore play a role in the pathophysiology of IC.

PMID:

16837648

[PubMed - indexed for MEDLINE]

BiochimBiophysActa. 2011 Sep;1810(9):875-8. Epub 2011 May 26.

Brief treatment with heparin-binding EGF-like growth factor, but not with EGF, is sufficient to accelerate epithelial wound healing.

Tolino MA, Block ER, Klarlund JK.

Source

Ophthalmology and Visual Sciences Research Center, the Eye and Ear Institute, University of Pittsburgh, Pittsburgh, PA 15213, USA.

Abstract

BACKGROUND:

Heparin-binding EGF-like growth factor (HB-EGF) contains, in contrast to EGF, a domain that binds to negatively charged glycans on cell surfaces and in extracellular matrix. We speculated that a short exposure to HB-EGF induces prolonged biological effects such as healing of wounds after immobilization in tissues.

METHODS:

Epithelial cell sheets in tissue and corneas in organ culture were treated briefly with HB-EGF or EGF and binding of the growth factors, time course of activation of the EGF receptor, and healing of wounds were compared.

#### RESULTS:

Treating human corneal epithelial cells for 2 min with HB-EGF resulted in 8h of detectable activation of the EGF receptor, but activation was much shorter after EGF treatment. A brief treatment with HB-EGF, but not with EGF, induced significant acceleration of healing in wounds in epithelial sheets in tissue and organ culture. Bound HB-EGF was detectable up to 16 h after brief treatments. Neutralizing antibodies added after HB-EGF treatment blocked acceleration of healing, demonstrating the role of bound HB-EGF in accelerating healing.

#### CONCLUSIONS:

A brief exposure to HB-EGF, but not to EGF, is sufficient to induce prolonged activation of the EGF receptor and to enhance healing.

#### GENERAL SIGNIFICANCE:

Bound HB-EGF can serve as a pool that induces prolonged activation of the EGF receptor. EGF has been used experimentally to treat poorly healing wounds, but the frequent applications that are necessary have hampered its use clinically. The findings imply that HB-EGF may be a useful long-acting alternative to EGF.

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Can J Urol. 2007 Aug;14(4):3599-607.

The role of the bladder surface in interstitial cystitis/painful bladder syndrome.

Teichman JM, Moldwin R.

#### Source

Division of Urology, St. Paul's Hospital, Department of Urologic Sciences, University of British Columbia, Vancouver, British Columbia, Canada.

#### Abstract

#### INTRODUCTION:

Interstitial cystitis (IC) is a potentially severe and debilitating condition of the bladder. Numerous factors have been implicated in its pathogenesis.

#### MATERIALS AND METHODS:

A literature review was conducted on the following topics: urothelium, mucosal lining, interstitial cystitis, bladder, and glycosaminoglycans.

#### RESULTS:

A commonly proposed cause for IC is a defect or alteration in the bladder surface leading to increased permeability to noxious urinary solutes and ultimately to tissue inflammation and neurogenic upregulation. Support for this concept is drawn from studies of the structure, function, and composition

of the bladder surface. The cause(s) of this alteration is not known, although recent research has implicated changes in the levels of growth factors and/or compounds that protect against irritants and potentially "toxic" factors. The etiology of IC is likely multifactorial.

#### CONCLUSIONS:

Alterations of the bladder surface are observed in IC, and may play an important role in the etiology of this condition.

PMID:

17784979

[PubMed - indexed for MEDLINE]

Med Hypotheses. 1998 Jul;51(1):79-83.

A hypothesis for the etiology of interstitial cystitis based upon inhibition of bladder epithelial repair.

Keay S, Warren JW.

Source

Department of Medicine, University of Maryland School of Medicine, Baltimore, USA.

Abstract

Interstitial cystitis (IC) is a chronic bladder disease characterized by distinct bladder mucosal abnormalities, for which the etiology is unknown. Although the epidemiology of this disorder is similar to that of bacterial cystitis, prospective studies using sensitive culture techniques and polymerase chain reaction assay for a variety of microorganisms have failed to identify a specific infectious etiology for IC. We have identified a low-molecular-weight peptide in the urine of IC patients that inhibits the proliferation of normal bladder epithelial cells in vitro. We therefore propose a model of IC, in which this peptide inhibits bladder epithelial regeneration following damage (such as that caused by bacterial cystitis). The chronically damaged epithelium is prone to colonization with various microorganisms, and the resulting exposure to these microorganisms, other urinary antigens, and/or damaged epithelial cells prompts the low-level inflammatory response commonly seen in this disorder.

PMID:

9881843

[PubMed - indexed for MEDLINE]

J Urol. 2000 Dec;164(6):2112-8.

Bladder epithelial cells from patients with interstitial cystitis produce an inhibitor of heparin-binding epidermal growth factor-like growth factor production.

Keay S, Kleinberg M, Zhang CO, Hise MK, Warren JW.

## Source

Division of Infectious Diseases, Department of Medicine, University of Maryland School of Medicine and Research Service, Department of Veterans Affairs Medical Center, Baltimore, Maryland, USA.

## Abstract

### PURPOSE:

The etiology of interstitial cystitis is unknown. We previously identified an interstitial cystitis urine factor, antiproliferative factor, that inhibits proliferation of bladder epithelial cells in vitro and complex changes in epithelial growth factor levels, including profound decreases in heparin-binding epidermal growth factor-like growth factor (HB-EGF). Bladder and renal pelvic catheterization of patients with interstitial cystitis indicated that the antiproliferative factor is made and/or activated in the distal ureter or bladder. Therefore, we determined whether bladder epithelial cells from interstitial cystitis cases produced the antiproliferative factor and whether purified antiproliferative factor could alter production of growth factors known to be abnormal in interstitial cystitis.

### MATERIALS AND METHODS:

Antiproliferative factor activity was determined by 3H-thymidine incorporation into primary bladder epithelial cells. The antiproliferative factor was purified by size fractionation followed by sequential chromatography involving ion exchange, hydrophobic interaction and high performance liquid chromatography. HB-EGF, epidermal growth factor, insulin-like growth factor and insulin-like growth factor binding protein 3 levels were determined by enzyme-linked immunosorbent assay.

### RESULTS:

Bladder epithelial cells from patients with interstitial cystitis produced a single antiproliferative factor with the same purification profile as that purified from interstitial cystitis urine. Purified antiproliferative factor specifically inhibited HB-EGF production by bladder epithelial cells in vitro, and the effect of interstitial cystitis urine or purified antiproliferative factor on bladder cell proliferation was inhibited by recombinant human HB-EGF in a dose dependent manner. Similar to urine HB-EGF, serum HB-EGF was also significantly lower in interstitial cystitis cases than in controls.

### CONCLUSIONS:

Bladder epithelial abnormalities in interstitial cystitis may be caused by a negative autocrine growth factor that inhibits cell proliferation by down-regulating HB-EGF production. Furthermore, decreased levels of urine and serum HB-EGF indicate that interstitial cystitis may be a urinary tract manifestation of a systemic disorder.

J Urol. 2000 May;163(5):1440-4.

Bladder stretch alters urinary heparin-binding epidermal growth factor and antiproliferative factor in patients with interstitial cystitis.

Chai TC, Zhang CO, Shoenfelt JL, Johnson HW Jr, Warren JW, Keay S.

#### Source

Division of Urology, Department of Surgery, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA.

#### Abstract

##### PURPOSE:

The etiology of interstitial cystitis is unknown. Urine from patients with interstitial cystitis has been shown to inhibit urothelial proliferation through a putative antiproliferative factor and to contain decreased levels of heparin-binding epidermal growth factor-like growth factor (HB-EGF) compared to controls. Stretch of detrusor smooth muscle cells is known to stimulate HB-EGF production. Because bladder hydrodistention sometimes alleviates the symptoms of interstitial cystitis, we determined whether the stretch stimulus of hydrodistention alters antiproliferative factor activity and/or HB-EGF in interstitial cystitis urine specimens.

##### MATERIALS AND METHODS:

Urine was collected immediately before, and 2 to 4 hours and 2 weeks after hydrodistention from 15 patients with symptoms and cystoscopic findings compatible with interstitial cystitis and 13 controls. Hydrodistention was performed with the subject under general or regional anesthesia and bladders were distended to 80 cm. water 3 times. Urinary HB-EGF was measured by enzyme-linked immunosorbent assay and urinary antiproliferative factor activity was determined by measuring 3H-thymidine uptake by normal human bladder urothelial cells.

##### RESULTS:

Hydrodistention significantly increased urinary HB-EGF in patients with interstitial cystitis toward normal control values (before distention  $p = 0.003$ , 2 weeks after distention  $p = 0.67$ ). Urine antiproliferative factor activity decreased significantly after hydrodistention in patients with interstitial cystitis. However, antiproliferative factor activity in interstitial cystitis and control specimens was still statistically different 2 weeks after distention (before distention  $p = 0.000004$ , 2 weeks after distention  $p = 0.04$ ).

##### CONCLUSIONS:

Bladder stretch increased HB-EGF and conversely reduced antiproliferative factor activity in urine from patients with interstitial cystitis but not controls up to 2 weeks after distention. These results provide additional evidence for the possible role of antiproliferative factor and decreased HB-EGF in the pathophysiology of interstitial cystitis. To our knowledge this is also the first human study to show that in vivo bladder stretch can alter urinary factors that regulate cell growth.

##### PMID:

10751853

[PubMed - indexed for MEDLINE]  
IntUrolNephrol. 2010 Sep;42(3):629-35. Epub 2009 Sep 26.

Urine cytokines suggest an inflammatory response in the overactive bladder: a pilot study.

Tyagi P, Barclay D, Zamora R, Yoshimura N, Peters K, Vodovotz Y, Chancellor M.

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RESULTS:

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CONCLUSIONS:

The presence of elevated levels in urine of inflammatory biomarkers involved in inflammation and tissue repair suggests a role for inflammation in OAB, and may help in diagnosis and treatment of this disease.

Kaohsiung J Med Sci. 2011 Oct;27(10):437-40. doi: 10.1016/j.kjms.2011.06.002. Epub 2011 Jul 23.

Safety and dose flexibility clinical evaluation of intravesical liposome in patients with interstitial cystitis or painful bladder syndrome.

Lee WC, Chuang YC, Lee WC, Chiang PH.

#### Source

Department of Urology, Chang Gung Memorial Hospital, Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan.

#### Abstract

To present single institution open-label experience with intravesical liposomes (LPs), a mucosal protective agent, in patients with interstitial cystitis/painful bladder syndrome (IC/PBS) and to assess the safety and efficacy on IC/PBS symptoms. A total of 17 symptomatic IC/PBS patients were treated with intravesical LPs (80mg/40mL distilled water) once a week for 4 weeks (n=12) or twice a week treatment for 4 weeks (n=5). The primary outcome was the change in the O'Leary-Sant Symptom/Problem score and O'Leary-Sant total Score from baseline to Week 4 and Week 8. Other outcome measurements included the changes in pain scale, urgency scale, voiding log, and patient global assessment. Both weekly and biweekly LP instillation regimens were well tolerated. The incidence of urinary incontinence, retention, or unanticipated adverse changes was not noted at any dose either during the treatment or at the 4-week follow-up. The O'Leary-Sant Symptom/Problem score, O'Leary-Sant total Score, and pain score were significantly improved from baseline at both dose regimens with added benefit with the biweekly regimen. Intravesical LPs treatment is safe and its efficacy has sustained duration. Furthermore large-scale, placebo-controlled studies are warranted to assess the efficacy for this promising new treatment for IC/PBS.

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J Control Release. 2010 Dec 1;148(2):147-59. Epub 2010 Sep 8.

Intravesical drug delivery: Challenges, current status, opportunities and novel strategies.

GuhaSarkar S, Banerjee R.

#### Source

Department of Biosciences & Bioengineering, Indian Institute of Technology, Bombay, Powai, Mumbai 400076, India.

#### Abstract

The urinary bladder has certain unique anatomical features which enable it to form an effective barrier to toxic substances diffusing from the urine into the blood. The barrier function is due to the epithelial surface of the urinary bladder, the urothelium, which has characteristic umbrella cells, joined by tight junctions and covered by impenetrable plaques, as well as an anti-adherent mucin layer. Diseases of the urinary bladder, such as bladder carcinomas and interstitial cystitis, cause acute damage to the bladder wall and cannot be effectively treated by systemic administration of drugs. Such conditions may benefit from intravesical drug delivery (IDD), which involves direct instillation of drug into the bladder via a catheter, to attain high local concentrations of the drug with minimal systemic effects. IDD however has its limitations, since the permeability of the urothelial layer is very low and instilled drug solutions become diluted with urine and get washed out of the bladder during voiding, necessitating repeated

infusions of the drug. Permeation enhancers serve to overcome these problems to some extent by using electromotive force to enhance diffusion of the drug into the bladder wall or chemical molecules, such as chitosan, dimethylsulphoxide, to temporarily disrupt the tight packing of the urothelium.

Nanotechnology can be integrated with IDD to devise drug-encapsulated nanoparticles that can greatly improve chemical interactions with the urothelium and enhance penetration of drugs into the bladder wall. Nanocarriers such as liposomes, gelatin nanoparticles, polymeric nanoparticles and magnetic particles, have been found to enhance local drug concentrations in the bladder as well as target diseased cells. Intravesical drug carriers can be further improved by using mucoadhesive biomaterials which are strongly adhered to the urothelial cell lining, thus preventing the carrier from being washed away during urine voiding. This increases the residence time of the drug at the target site and enables sustained delivery of the drug over a prolonged time span. Polymeric hydrogels, such as the temperature sensitive PEG-PLGA-PEG polymer, have been used to develop in situ gelling systems to deliver drugs into the bladder cavity. Recent advances and future prospects of biodegradable nanocarriers and in situ gels as drug delivery agents for intravesical drug delivery are reviewed in this paper.

J Urol. 2009 Oct;182(4):1393-400. Epub 2009 Aug 15.

Intravesical liposome versus oral pentosanpolysulfate for interstitial cystitis/painful bladder syndrome.

Chuang YC, Lee WC, Lee WC, Chiang PH.

Source

Department of Urology, Chang Gung Memorial Hospital Kaohsiung, Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan, Republic of China. [chuang82@ms26.hinet.net](mailto:chuang82@ms26.hinet.net)

Abstract

PURPOSE:

We evaluated the safety and efficacy of intravesical liposomes, a mucosal protective agent, compared to oral pentosanpolysulfate sodium for interstitial cystitis/painful bladder syndrome.

MATERIALS AND METHODS:

We performed a prospective longitudinal study of the effect of 2 independent treatments (intravesical liposomes and oral pentosanpolysulfate sodium) in patients with interstitial cystitis/painful bladder syndrome. Ten possible responses (or measures) to treatment were monitored at 3 time points, including baseline, and weeks 4 and 8. A total of 24 patients with interstitial cystitis/painful bladder syndrome were evaluated in a 1:1 ratio to intravesical liposomes (80 mg/40 cc distilled water) once weekly or to oral pentosanpolysulfate sodium (100 mg) 3 times daily for 4 weeks each.

RESULTS:

No patient had urinary incontinence, retention or infection due to liposome instillation. There were no unanticipated adverse events and no significant worsening of symptoms during followup. Statistically

significant decreases in urinary frequency and nocturia were observed in each treatment group. Statistically significant decreases in pain, urgency and the O'Leary-Sant symptom score were observed in the liposome group. Decreased urgency in the liposome group had the most profound effect of the ordinal measures.

#### CONCLUSIONS:

Each glycosaminoglycan directed treatment seemed beneficial. Liposome intravesical instillation is safe for interstitial cystitis/painful bladder syndrome with potential improvement after 1 course of therapy for up to 8 weeks. Intravesical liposomes achieved efficacy similar to that of oral pentosanpolysulfate sodium. Further large-scale placebo controlled studies are needed. Intravesical liposomes appear to be a promising new treatment for interstitial cystitis/painful bladder syndrome.

BJU Int. 2009 Dec;104(11):1689-92. Epub 2009 Jul 7.

Instillation of liposomes vs dimethyl sulphoxide or pentosanpolysulphate for reducing bladder hyperactivity.

Tyagi P, Hsieh VC, Yoshimura N, Kaufman J, Chancellor MB.

#### Source

Department of Anaesthesiology, Stanford University School of Medicine, Stanford, CA, USA.

#### Abstract

#### OBJECTIVE:

To investigate the efficacy of intravesical liposomes against dimethyl sulphoxide (DMSO), and pentosanpolysulphate (PPS) in reducing chemically induced bladder hyperactivity in rats.

#### MATERIALS AND METHODS:

Bladder reflex activity of female Sprague-Dawley rats was evaluated by continuous cystometry under urethane anaesthesia (1.0 g/kg). After obtaining a control cystometrogram (CMG) with normal saline (0.04 mL/min) for 2 h, bladder hyperactivity was then induced by 1 h infusion of protamine sulphate (10 mg/mL) followed by a 1-h infusion of KCl (500 mm). Six rats each were then infused with KCl-based preparations containing either 50% DMSO, PPS (6 mg/mL), or liposomes (2 mg/mL) for 2 h. The variables measured included the intercontraction interval (ICI), pressure threshold (PT) and baseline pressure (BP).

#### RESULTS:

Sequential infusion of protamine sulphate/KCl induced hyperactive bladder with no significant difference in ICI, PT or BP among groups before initiating treatment. ICI was significantly increased after infusion of PPS (58.1% increase) and liposomes (156.8% increase) but there was no increase with DMSO. PT was not significantly affected by liposome infusion but slightly increased with PPS (12.4% increase).

There was a large and significant increase in PT and BP with DMSO (116.5% increase) and BP largely remained unchanged after instillation with liposomes or PPS.

#### CONCLUSIONS:

Intravesical liposomes and PPS have a beneficial effect in a bladder hyperactivity rat model, while acute instillation of DMSO does not. Intravesical liposomes were effective in doubling the ICI compared with PPS, and might be a new treatment option for bladder hyperactivity.

Urol. 2009 Aug;182(2):786-92. Epub 2009 Jun 18.

Urodynamic and immunohistochemical evaluation of intravesical botulinum toxin A delivery using liposomes.

Chuang YC, Tyagi P, Huang CC, Yoshimura N, Wu M, Kaufman J, Chancellor MB.

#### Source

Department of Urology, Chang Gung Memorial Hospital, Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan, Republic of China. [chuang82@ms26.hinet.net](mailto:chuang82@ms26.hinet.net)

#### Abstract

#### PURPOSE:

Botulinum toxin A (Allergan, Irvine, California) is a high molecular weight neurotoxin used to treat hypersensitive bladder by direct injection to pass the urothelial barrier. We investigated the feasibility of intravesical botulinum toxin A delivery using liposomes (Lipella Pharmaceuticals, Pittsburgh, Pennsylvania), which are phospholipid bilayered vesicles, and evaluated the urodynamic and immunohistochemical effect on acetic acid induced bladder hyperactivity in rats.

#### MATERIALS AND METHODS:

Liposomes (1 ml), botulinum toxin A (20 U/1 ml saline) or botulinum toxin A encapsulated in liposomes (lipotoxin, that is 20 U botulinum toxin A plus 1 ml liposomes) was administered in the bladder and retained for 1 hour on day 1 after baseline cystometrogram. Continuous cystometrogram was performed on day 1 by filling the bladder with saline and on day 8 by filling the bladder with saline, followed by 0.3% acetic acid. The bladder was then harvested. Cystometrogram parameters, histology, SNAP25 and calcitonin gene-related peptide expression were measured by Western blotting or immunostaining.

#### RESULTS:

The intercontraction interval was decreased 57.2% and 56.0% after intravesical acetic acid instillation in liposome and botulinum toxin A pretreated rats, respectively. However, rats that received lipotoxin showed a significantly decreased intercontraction interval response (21.1% decrease) to acetic acid instillation but without compromised voiding function. Also, lipotoxin pretreated rats had a better

decrease in the inflammatory reaction and SNAP-25 expression, and increase in calcitonin gene-related peptide immunoreactivity than those in liposome or botulinum toxin A pretreated rats.

#### CONCLUSIONS:

Intravesical lipotoxin administration cleaved SNAP-25, inhibited calcitonin gene-related peptide release from afferent nerve terminals and blocked the acetic acid induced hyperactive bladder. These results support liposomes as an efficient vehicle for delivering botulinum toxin A without injection.