W2: Where are we with intravesical therapeutics in 2018?

Workshop Chair: Rufus Cartwright, United Kingdom
28 August 2018 09:00 - 10:30

Start	End	Topic	Speakers
09:00	09:15	Introduction, Overview of Workshop and Intravesical Therapy	Rufus Cartwright
09:15	09:35	Overview of currently licensed options for IC/BPS	Mauro Cervigni
09:35	09:55	Future options under current investigation including lipophilic drug delivery	Pradeep Tyagi
09:55	10:05	Best practices in intravesical instillation	Angie Rantell
10:05	10:30	Hands-on practice with intravesical instillation	Mauro Cervigni Pradeep Tyagi Angie Rantell Rufus Cartwright Heidi Brown

Aims of Workshop

In this 90 minute workshop, delegates will learn about current and potential future applications of intravesical therapeutics and will gain hands-on experience with intravesical instillation. Speakers will cover:

1) Welcome, overview of the workshop, why intravesical therapeutics are exciting (15 min).
2) Overview of currently licensed options for IC/BPS (20 min).
3) Future options under current investigation (20 min).
4) Best practices in catheterisation for intravesical therapeutics instillation (10 min).

Hands-on practice with Uropharma's system for bladder instillations will follow these presentations (25 min).

Learning Objectives

1: To understand how current intravesical therapeutics work.
2: To understand how potential future intravesical therapeutics might work .
3: To be familiar with best practices in catheterisation for intravesical drug delivery.

Learning Outcomes

After completing this workshop, the delegate will:
~ Be able to name one current intravesical therapeutic agent.
~ Be able to name one potential future intravesical therapeutic agent.
~ Be able to perform intravesical therapeutics instillation using best practices.

Target Audience

Delegates interested in learning more about current and potential applications of intravesical therapeutics and gaining hands-on experience with intravesical instillations

Advanced/Basic

Basic

Conditions for Learning

This course will offer 4 brief presentations followed by hands-on practice with an existing catheter instillation technology. It is restricted to 50 delegates to ensure that the speakers can pay adequate attention to delegates during the hands-on portion.

Suggested Reading (not expected prior to workshop)

Advances in intravesical therapy for urinary tract disorders.
Tyagi P, Kashyap M, Hensley H, Yoshimura N.
Expert Opin Drug Deliv. 2016;13(1):71-84. doi: 10.1517/17425247.2016.1100166. Epub 2015 Oct 19. Review.

Minimum standards for continence care in the UK.
Rantell A, Dolan L, Bonner L, Knight S, Ramage C, Toozs-Hobson P.
Neurourol Urodyn. 2016 Mar;35(3):400-6. doi: 10.1002/nau.22717. Epub 2015 Jan 16. Review.

American Urological Association (AUA) and Society of Urologic Nurses and Associates (SUNA) Policy Statement. Intravesical Administration of Therapeutic Medication. (http://www.auanet.org/guidelines/intravesical-administration-of-therapeutic-medication)

A randomized, open-label, multicenter study of the efficacy and safety of intravesical hyaluronic acid and chondroitin sulfate versus dimethyl sulfoxide in women with bladder pain syndrome/interstitial cystitis.

Cervigni M, Sommariva M, Tenaglia R, Porru D, Ostardo E, Giammò A, Trevisan S, Frangione V, Ciani O, Tarricone R, Pappagallo GL.
Neurourol Urodyn. 2017 Apr;36(4):1178-1186. doi: 10.1002/nau.23091. Epub 2016 Sep 21.

Urinary incontinence in women.
Aoki Y, Brown HW, Brubaker L, Cornu JN, Daly JO, Cartwright R.
Nat Rev Dis Primers. 2017 Jul 6;3:17042. doi: 10.1038/nrdp.2017.42. Review. Erratum in: Nat Rev Dis Primers. 2017 Nov 16;3:17097.

Introduction, Overview of Workshop and Intravesical Therapy

Rufus Cartwright

Early theories of the pathophysiology of detrusor overactivity were anatomically centered on the spine and parasympathetic motor supply to the bladder (the neurogenic hypothesis). Much work in the early 2000's focused on the detrusor muscle itself (the myogenic hypothesis), with the recognition that both bladder strips and individual detrusor cells from patients with detrusor overactivity would display heightened contractile responses. However, more recent attention has focused on the urotheliogenic hypothesis. In both rodent and porcine models the mucosal layer of the bladder is seen to augment detrusor function, either through release of a variety of neurotransmitters, or through its own spontaneous electrical activity.

The urothelium is not just a passive barrier, but is a responsive structure, able to detect thermal, mechanical and chemical stimuli. With the recognition of the urothelium as a mediator of bladder function, much recent attention has been concentrated on the role of urothelial inflammation and infection in the aetiology of urgency incontinence, and bladder pain syndrome. This new understanding has led to renewed interest in intravesical drug delivery that can directly target the urothelium. Intravesical therapies not only have theoretical advantages in directly accessing the urothelium, but can avoid systemic absorption, minimising adverse effects. Many of the currently used drugs for functional bladder conditions, including overactive bladder, bladder pain syndrome, and recurrent UTI have common side effects when administered by mouth that limit compliance.

While intravesical therapies have been available for decades, the evidence base has lagged behind that of equivalent oral drugs, and clinical adoption has been slow. This workshop aims to bring participants up to date with the latest evidence for use of intravesical therapies, discuss future directions for research, and provide hands on training in delivering intravesical instillations.

Overview of currently licensed intravesical options for IC/BPS

Mauro Cervigni

Intravesical administration of therapeutics to improve symptoms of bladder pain syndrome / interstitial cystitis (BPS/IC) have been of great interest for decades. A 2007 Cochrane review included trials of six different types of intravesical instillation: Resiniferatoxin, Dimethyl sulfoxide (DMSO), BCG, pentosan polysulphate, oxybutin, and alkalinisation of urine pH, concluding that the evidence base was limited for most of these therapies, and that the most promising evidence was available for bacillus calmette geurin (BCG) and oxybutin (1). In the last decade, focus has shifted more towards DMSO and a new therapeutic option: combination hyaluronic acid plus chondroitin sulphate (HA/CS). The theory behind this combination is that reconstruction of the glycosaminoglycan layer plays a role in the successful treatment of BPS/IC. To date, there have been four randomized trials including DMSO: two comparing it with BCG, one with sterile saline, and one with HA/CS (2, 3).

Intravesical instillation of HA/CS in women with BPS/IC has shown promising results. In a randomized, open-label, multicentre study involving 110 women with BPS/IC, intravesical HA/CS (Ialuril®, IBSA) was compared with DMSO. In this study, the allocation ratio (HA/CS: DMSO) was 2:1. Thirteen weekly instillations of HA (1.6%)/CS (2.0%) or 50% DMSO were given. Patients were evaluated at 3 (end-of-treatment) and 6 months. Primary endpoint was reduction in pain intensity at 6 months by visual analogue scale (VAS) versus baseline. Secondary efficacy measurements were quality of life and economic analyses. A significant reduction in pain intensity was observed at 6 months in both treatment groups versus baseline ($P < 0.0001$) in the intention-to-treat population.

Treatment with HA/CS resulted in a greater reduction in pain intensity at 6 months compared with DMSO for the per-protocol population (mean VAS reduction 44.77 ± 25.07 vs. 28.89 ± 31.14, respectively; $P = 0.0186$). There were no significant differences between treatment groups in secondary outcomes. At least one adverse event was reported in 14.86% and 30.56% of patients in the HA/CS and DMSO groups, respectively. There were significantly fewer treatment-related adverse events for HA/CS versus DMSO (1.35% vs. 22.22%; $P = 0.001$). Considering direct healthcare costs, the incremental cost-effectiveness ratio of HA/CS versus DMSO fell between 3735€/quality-adjusted life years (QALY) and 8003€/QALY. Thus, treatment with HA/CS appears to be as effective as DMSO with a potentially more favorable safety profile. Both treatments increased health-related quality of life, while HA/CS showed a more acceptable cost-effectiveness profile. In a prior pilot study of 12 patients who underwent HA/CS instillation, there was sustained improvement of the symptomatology, up to 3 years, in patients with BPS/IC refractory to previous treatments (4).

1. Dawson TE, Jamison J. Intravesical treatments for painful bladder syndrome/ interstitial cystitis. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD006113.

2. Rawls WF, Cox L, Rovner ES. Dimethyl sulfoxide (DMSO) as intravesical therapy for interstitial cystitis/bladder pain syndrome: A review. Neurourol Urodyn. 2017 Sep;36(7):1677-1684. doi: 10.1002/nau.23204. Epub 2017 Feb 21.

3. Cervigni M, Sommariva M, Tenaglia R, Porru D, Ostardo E, Giammò A, Trevisan S, Frangione V, Ciani O, Tarricone R, Pappagallo GL. A randomized, open-label, multicenter study of the efficacy and safety of intravesical hyaluronic acid and chondroitin sulfate versus dimethyl sulfoxide in women with bladder pain syndrome/interstitial cystitis. Neurourol Urodyn. 2017 Apr;36(4):1178-1186. doi: 10.1002/nau.23091. Epub 2016 Sep 21.

4. Cervigni M, Natale F, Nasta L, Mako A. Intravesical hyaluronic acid and chondroitin sulphate for bladder pain syndrome/interstitial cystitis: long-term treatment results. Int Urogynecol J. 2012 Sep;23(9):1187-92. doi: 10.1007/s00192-012-1742-y. Epub 2012 May 9.

Future options under current investigation
Pradeep Tyagi

There are various platforms for delivery of therapeutics in the management of interstitial cystitis/ painful bladder syndrome (IC/PBS) and treatment refractory OAB (1). The intravesical route mitigates the adverse effects encountered with the conventional routes of administration by limiting the systemic uptake, avoiding first pass metabolism and obtaining a local effect for the drug within the bladder. These characteristics can ensure maximal therapeutic benefit to occur at desirable site with potential and real benefits for patients having morbid adverse effects from oral administration. Intravesical Elmiron works faster than oral delivery in IC/PBS patients. As illustrated in a patient with refractory radiation cystitis (2), intravesical tacrolimus resolved the gross hematuria without inducing the nephrotoxicity associated with oral or systemic administration of Tacrolimus. Intravesical Tacrolimus also obviated the need of formalin instillation or cystectomy or diversion in the severely affected patient (2).

However, poor bladder uptake of instilled macromolecules such as onabotulinumtoxin A or DNA with molecular weight >400 Daltons presents a challenge, which is currently met by intradetrusor injection instead of instillation (3). Several drug delivery methods using physical and chemical approaches have been tried to make a liquid instillation of onabotulinumtoxin A. Physical approaches include application of electromotive drug administration, ultrasound or low energy shock wave to assist the bladder wall uptake of instilled onabotulinumtoxin A. Chemical based approaches include, urothelial denudation with protamine sulfate or dimethyl sulfoxide (DMSO). Compared to physical and chemical approaches, the drug delivery platform of liposomes relies on endocytosis of vesicles bound to the urothelial cell membrane for increasing the permeability of bound (complexed) drugs. Liposome complexed onabotulinumtoxin A enhances activity of the metalloprotease (toxin) while reducing its degradation. In a multi-center, placebo controlled study, liposome complexed onabotulinumtoxin A successfully reduced the urinary frequency and urgency, but did not significantly reduce the urge urinary incontinence episodes.

The usefulness of intravesical delivery can be limited by vehicle (carrier) toxicity as shown by RTX or short duration of action. Preclinical studies with thermosensitive hydrogel reported at the turn of this century to extend the drug exposure in urothelium beyond the first voiding of urine after instillation were recently tested on 15 severely symptomatic IC/PBS patients. Single instillation of hydrogel entrapped with botulinum toxin reduced the symptom scores at the 12- week follow-up from baseline. The mean number of voids per night at baseline decreased for 6 weeks and then returned to baseline level at week 12 (4). Likewise, elastomeric polymers were used to fabricate a continuous lidocaine-releasing intravesical system (LiRIS) for a period of 2 weeks in 16 IC/PBS patients. We recently checked the potential utility of MRI technique to image the 5mm thick human bladder wall and 0.5mm thick rat bladder wall uptake of instilled agents using novel contrast mixture as a proxy for drugs (5). Recent advances in intravesical drug delivery can be a potential option for patients refractory to drugs administered from other routes.

References

1. Tyagi P, Kashyap M, Hensley H, Yoshimura N. Advances in intravesical therapy for urinary tract disorders. Expert Opin Drug Deliv. 2016;13(1):71-84
2. Dave CN1, Chaus F1, Chancellor MB2, Lajness M1, Peters KM1. Innovative use of intravesical tacrolimus for hemorrhagic radiation cystitis. Int Urol Nephrol. 2015 Oct;47(10):1679-81.
3. Tyagi P, Kashyap M, Yoshimura N, Chancellor M, Chermansky CJ. Past, Present and Future of Chemodenervation with Botulinum Toxin in the Treatment of Overactive Bladder. J Urol. 2017 Apr: 197:982-90.
4. Rappaport YH, Zisman A, Jeshurun-Gutshtat M, Gerassi T, Hakim G, Vinshtok Y, Stav K. Safety and Feasibility of Intravesical Instillation of Botulinum Toxin-A in Hydrogel-based Slow-release Delivery System in Patients With Interstitial Cystitis-Bladder Pain Syndrome: A Pilot Study. Urology. 2018 Jan 4. pii: S0090-4295(18)30004-9.
5. Tyagi P, Janicki J, Moon CH, Kaufman J, Chermansky C. Novel contrast mixture achieves contrast resolution of human bladder wall suitable for T1 mapping: applications in interstitial cystitis and beyond. Int Urol Nephrol. 2018;50(3):401-409.

Best practices in intravesical instillation

Angie Rantell

According to the National Institute for Health and Care Excellence (NICE) (2015), intermittent catherisation (ISC) is the gold standard for urine drainage. It is performed by the patient independently or by carer or healthcare provider and involves using a catheter to drain the bladder, after which the catheter is removed. There are several reasons why patients may have to perform ISC. It can be used as a short-term or long-term management system. In the short-term, it may be used to manage immediate postoperative complications, such as incomplete emptying following intra-vesical injections of Botox or immediately post-surgery for stress urinary incontinence, for instillation of medication directly into the bladder or for postpartum retention (Rantell, 2012).

Nélaton is the collective term used to describe intermittent catheters. Unlike Foley catheters, Nélaton devices do not have a balloon and so are not are designed to remain in the bladder (Davis 2018). A range of catheters are available for ISC, which can be single-use or reusable. Research shows almost exclusive use of single-use catheters in the UK (Prieto et al, 2015), and these can be broken down into three subgroups: hydrophilic coated catheters, prelubricated catheters and uncoated catheters. These groups can be subdivided further:

(a) Hydrophilic coated:
- Activated system, ready to use
- Not activated: sterile water provided for activation
- Not activated: water added by user.

(b) Prelubricated:
- Prelubricated, closed system with integrated collection bag
- Prelubricated, with protective sleeve for no-touch insertion.

(c) Uncoated:
- Non-lubricated: water-soluble gel added by user (Prieto et al, 2015).

Hydrophilic coated catheters are used to reduce surface friction and enhance lubricity. This style of catheter has a dehydrated hydrophilic coating, which can be felt when touching it. The catheters need to be soaked in water for about 30 seconds to activate the coating, lubricating it and making it ready for use. They usually come packaged with a sachet of sterile water that activates the coating when pressed (Nazarko, 2013). Due to the nature of the coating, these catheters should be discarded after use. There is some evidence to suggest that using hydrophilic coated catheters reduces the risk of UTI, however, for various reasons the trials performed were methodologically weak so this is yet to be demonstrated convincingly in the research (Prieto et al 2015; Bermingham et al, 2013).

This presentation will focus on the use of intermittent catheterisation for the instillation of a therapeutic substance into the bladder. It will discuss the different catheters available and best practice amongst instillation techniques. Models of service delivery will also be considered including teaching patients to self-catheterise and self-administer their medication at home versus patients attending weekly clinics for a health care professional to provide the treatment. Patient education, counselling and trouble-shooting will be recommended.

References

1. Bermingham SL, Hodgkinson S, Wright S, Hayter E, Spinks J, Pellowe C. Intermittent self catheterisation with hydrophilic, gel reservoir, and non-coated catheters: a systematic review and cost effectiveness analysis. BMJ 2013; 346:e8639. Httpa://doi.org/10.1136/bmj.e8639
2. Davis C & Rantell A, 2018, Selecting an intermittent self catheter: key considerations. British Journal of Nursing ISC supplement. In press.
3. National Institute for Health and Care Excellence. Urinary Incontinence in Women: Management [CG171]. London: NICE; 2015
4. Nazarko L. Intermittent self-catheterisation: past, present and future. Br J Community Nurs 2013; 17(9): 408–12
5. Prieto JA, Murphy C, Moore KN, Fader MJ. Intermittent catheterisation for long-term bladder management (abridged Cochrane review). Neurourol Urodyn. 2015; 34(7): 648–53
6. Rantell A. Intermittent self-catheterisation in women. Nurs Stand. 2012; 26(42): 61–8

Intravesical Therapy: Introduction and overview of workshop

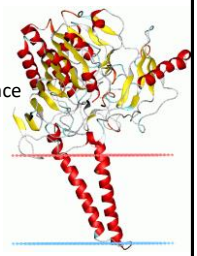
Rufus Cartwright

Department of Urogynaecology, Oxford University Hospitals NHS Trust, UK

No relevant financial conflicts of interest

My Background

- MD degree on transdermal oxybutynin
  - Learned just a little about pharmacokinetics
  - Learned quite a lot about oral anticholinergics
- PhD in genomics of urinary incontinence
  - SULF2 risk gene for UUI
  - Removes 6-O-sulfate groups from heparan sulfate
  - Heparan sulfate is a key component of bladder glycosaminoglycan layer
- Now a urogynae trainee
  - Patients with functional bladder conditions who do not respond to conventional oral treatments



Scope

- Intravesical agents are widely used for management of bladder cancer

Scope

- ~~Intravesical agents are widely used for management of bladder cancer~~

Scope

- ~~Intravesical agents are widely used for management of bladder cancer~~
- Here we will mainly address three "functional" conditions
  - Bladder Pain Syndrome / Interstitial Cystitis
  - Overactive Bladder / Detrusor Overactivity
  - Recurrent UTI

Definitions

- Overactive bladder syndrome: urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology

Haylen et al, Int Urogyn J/Neurourol Urodyn 2010

Neurourology and Urodynamics

REVIEW ARTICLE

An International Urogynecological Association (IUGA)/International Continence Society (ICS) Joint Report on the Terminology for Female Pelvic Floor Dysfunction

Definitions

- EAU criteria: Recurrent UTI is defined at least three episodes of uncomplicated cystitis in the past year, with clinical symptoms and/or positive culture for each episode (a positive culture being defined as the isolation of $>10^3$ colony-forming units of a uropathogen per milliliter of urine)

Naber KG et al. EAU guidelines for the management of urinary and male genital tract infections

Definitions

- ICS: Painful bladder syndrome is the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology

Haylen et al, Int Urogyn J/Neurourol Urodyn 2010

- European Society for the Study of Interstitial Cystitis/Painful Bladder Syndrome (ESSIC) defined BPS as chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder and accompanied by at least one other urinary symptom such as persistent urge to void or urinary frequency, in the absence of infection or other pathology

van de Merwe et al Eur Urol, 2008

Current Intravesical Therapies: IC/BPS

- Dimethylsulfoxide (DMSO)
- Heparin
- Hyaluronic acid & Chondroitin Sulphate (IALURIL)
- Alkalinized lidocaine
- 8.4% sodium bicarbonate
- Pentosan polysulfate
- Bacillus Calmette–Guérin (BCG)

Current Intravesical Therapies: rUTI

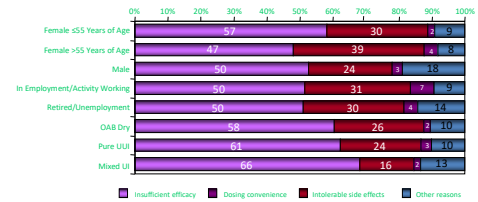
- Hyaluronic acid and Chondroitin Sulphate (IALURIL)
- Heparin
- Gentamycin
- Other antibiotics (neomycin/polymyxin)

Current Intravesical Therapies: OAB / DO

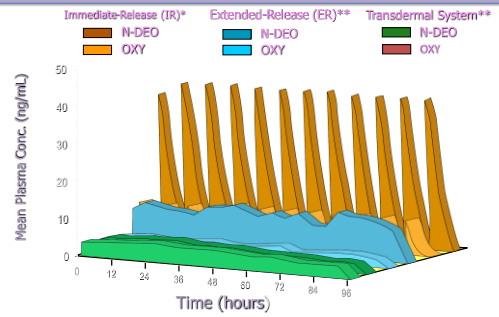
- Atropine
- Oxybutynin

Advantages: Tolerability and Efficacy

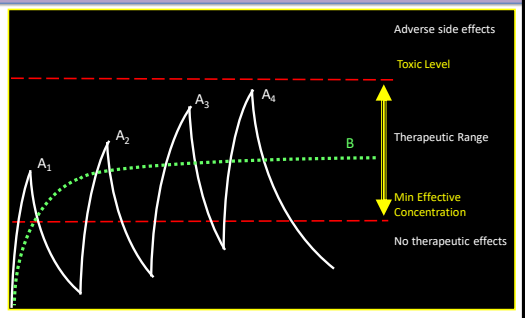
Lack of Efficacy is the major reason for failure of first-line antimuscarinic therapy:



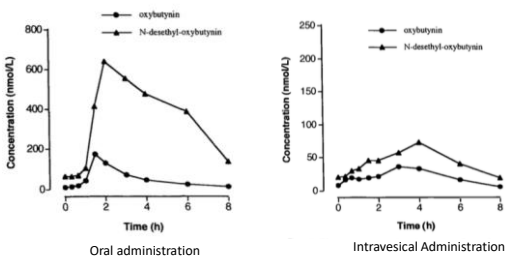
Relative Drug Plasma Concentrations



Drug Concentration Profile



Drug Concentrations



Oral administration

Intravesical Administration

Buyse et al, J Urol 1998

The Urothelium

- The urothelium is not merely a barrier
- The urothelium plays an important sensory role
- Has a key role in detrusor functioning
- Damage to the urothelium or its glycosaminoglycan coating may be central to bladder pain and recurrent UTI

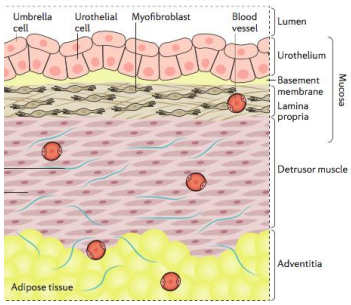
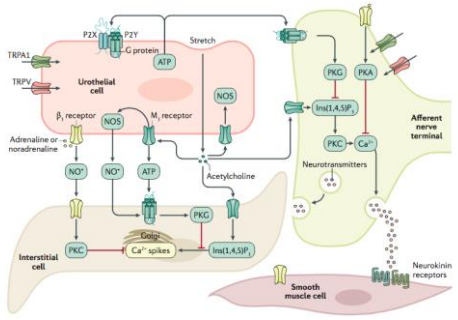
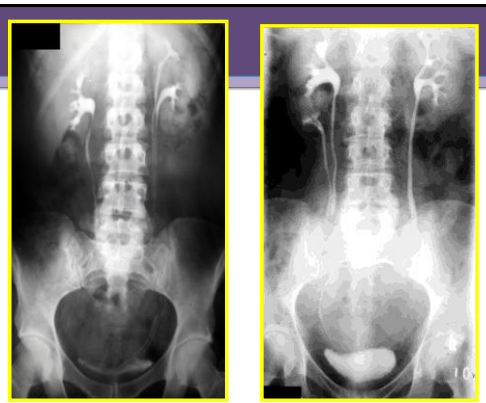


Figure from Aoki et al, Nature Primers 2017

Which receptors can an intravesical drug act on?

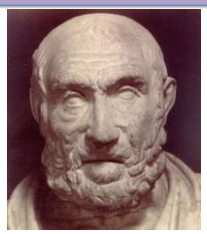


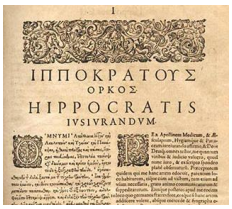


Disadvantages

- Some drugs do not cross the urothelium
- Can have a short duration of action / need for frequent administration
- Discomfort and costs
- Risk of infection

Disadvantages





Primum non nocere

- For many of these medicines there remain a severe lack of high quality RCTs
- Harms of these medicines are not well understood

Disadvantages

- iAluril is licensed as a medical device
- Other instillations including heparin and antibiotics remain unlicensed
- The method of delivery – the catheter-- is also unlicensed
- May open clinicians up to liability in the event of complications

Workshop Outline

- Mauro Cervigni will address the evidence for instillations for bladder pain
- Pradeep Tyagi will address future developments in the field
- Angie Rantell will address practical considerations for delivering an intravesical instillation service
- Hands on portion – try out current options and future devices

Future Options Under Current Investigation

Pradeep Tyagi PhD
University of Pittsburgh

Affiliations to disclose†:

- Consultant for Venisca Inc.
- Co-Inventor of Intravesical Liposome technology Licensed by University of Pittsburgh

† All financial ties (over the last year) that you may have with any business organization with respect to the subjects mentioned during your presentation

Funding for speaker to attend:

- [x] Self-funded
- [ ] Institution (non-industry) funded
- [ ] Sponsored by:

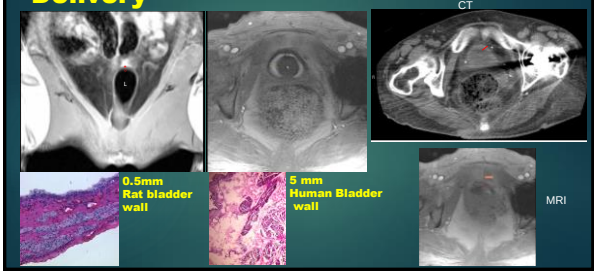
Outline of My talk

- Brief history of intravesical drug delivery
- Target of intravesical drug delivery
- Physiochemical Properties impacting Intravesical drug delivery
- Future options like polymers, liposomes, hydrogel peptides

Intravesical Drug Delivery

- **1903**: Instillation of $AgNO_3$ for bladder cancer - Herring H. BMJ
- **1967**: DMSO for IC –Stewart J Urol
- **1976**: BCG- Morales; approved by FDA in 1990
- **1988**: Capsaicin – Fowler & de Groat Lancet
- 2013: Botox injection approved for OAB

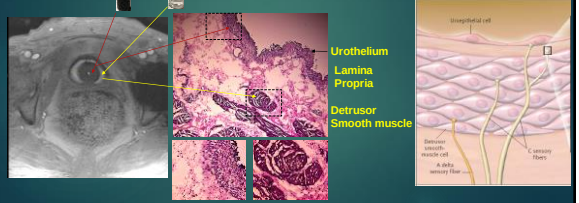
Target of Intravesical Drug Delivery



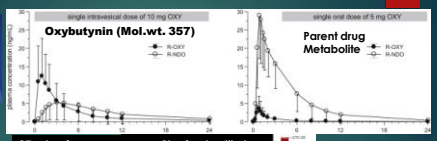
Intravesical Delivery of Contrast Agents

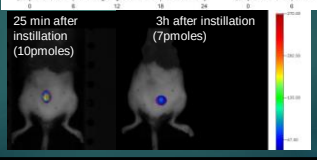
Mol wt. Ferumoxytol
750 Kda

Mol wt. Gadobutrol
604.71



Systemic Uptake Depends on Mol. Weight

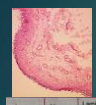


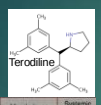


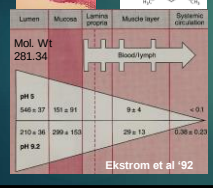
Lipid and dye (Mol. wt ~1000)

J. Urology, 190(5), 2013, 1791–1797

Intravesical Drug Delivery



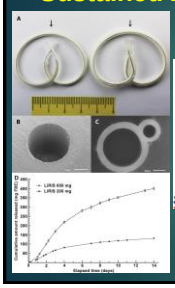


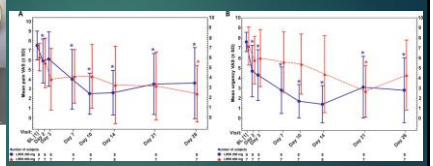


Ekstrom et al '92

- Low exchange rate into plasma
- Current options better suited for water soluble and small molecular weight drugs
- Delivering water insoluble drugs, large molecular weight proteins is a challenge
- Duration of drug exposure is short lived, first voiding washes out

Sustained Intravesical Drug Delivery

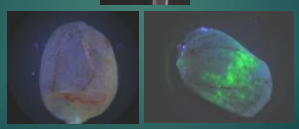




J. Curtis Nickel et al., Sci Transl Med 2012;4:143ra100

Thermosensitive Hydrogel To Extend Exposure

FITC

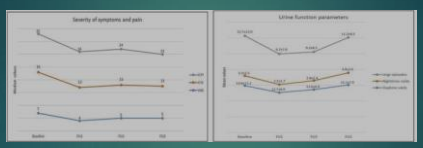


Hydrogel +FITC

24h after instillation

Tyagi P; Pharm Res. 2004;21(5):832-7.

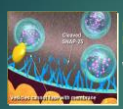
Clinical Trial on Hydrogel + OnabotulinumtoxinA



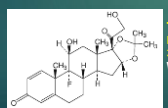
- Study on 15 (M/F=4/11, age 24-76) PBS/IC patients (ICSI range 12-19, ICPI range 12-16, median VAS=7) follow-up at 2,6,12 weeks
- Study on OAB patients ongoing in US and Europe

Stav et al J. Urol., 193(4) Suppl. 2015, Page e398

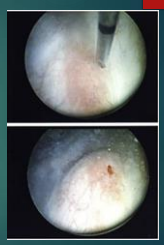
Injection vs Instillation



Botulinum Toxin
Mol. weight
150 kilo Daltons
Water soluble

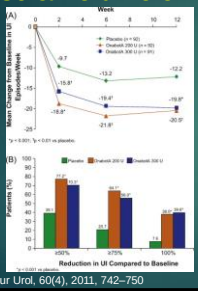


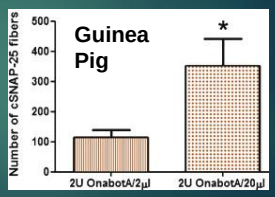
Triamcinolone
Mol. weight
394 Daltons
Water insoluble



Funaro et al Urology. 2018 May 18.
Giannantoni et al., J Urol, **185:** e319, 2011

Dose & Volume of Injection





Cruz et al. Eur Urol, 60(4), 2011, 742–750

Coelho et al Eur Urol, 61(6), 2012, 1178–1184

Injection- Drawbacks

- Potency sensitive to volume and depth of injection
- Different diffusion of toxin preparations
- Increased PVR and risk of retention
- Risk of hesitancy and difficulty in urination
- Need for clean intermittent catheterization
- Risk of toxin migration ?
- Transient trunk muscle weakness

Injection-Free Future Options

Challenges

- Toxin degradation by proteases and proteinases in urine
- Toxin dilution in urine
- Poor bladder uptake of large macromolecules across urothelium

Attempted Approaches

- Increase urothelial permeability by Protamine sulfate
- By TAT peptide
- DMSO
- Liposomes
- Hydrogel, Hyaluronan-PE
- Physical Approaches
  - Iontophoresis
  - Low Energy Shock wave

Hyaluronan-phosphatidylethanolamine Gel

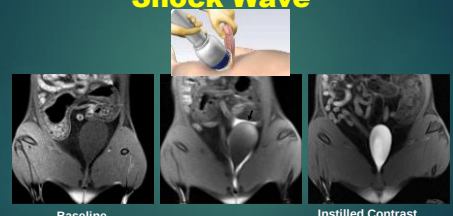
J Pediatr Urol. 2018;14(2):172.e1-172.e6.

Iontophoresis + AbobotulinumtoxinA

- 24 children (3-16) with myelomeningocele and refractory neurogenic detrusor overactivity instilled once with 10 IU/kg
- Subjects followed for 6 years
- 10mA delivered for 20 min via indwelling catheter and two dispersive electrodes
- Dry between 2 consecutive CIC defined as response, which tapered from 75% at 1 year to 29.15 at 6yr
- Skin erythema and burning sensation

Seyedian et al Urology. 2018 ;114:167-174.
Ahmadi et al J. Urol., 183(4) Suppl. 2010, Page e291

Botox and Low energy Shock Wave



Chuang & Tyagi et al J Urol. 2016 ;196(2):599-608

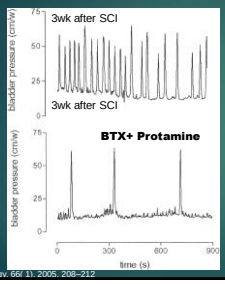
DMSO + Botox

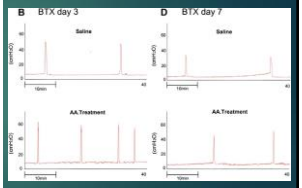
Measure	Baseline	1 month	3 month	p value 1month	p value 3month
PVR(mL)	8 (0–24)	19 (0–32)	24 (9–65)	0.24	0.033
Urine culture (negative; positive)	16; 5	16; 5	13; 8	>.99	0.25
24h pad weight (g)	135 (6–259)	46 (9–183)	55 (11–318)	0.21	0.43
24h UI episodes	4 (2–9)	2 (0–5)	4 (2–6)	0.004	0.81
Daily pad Use	4 (2–7)	3 (1–5)	3 (2–5)	0.24	0.14
Urgency (IUSS)	0;2;8;11	0;13; 7; 1	0; 11; 7; 3	<.001	0.004
UDI-6 (0–18)	10 (8–12)	5 (4–9)	6 (4–8)	0.003	0.001
Bothersome (0–10)	9 (8–10)	5 (3–8)	5 (2–7)	0.001	<.001
IIQ-7 (0–21)	13 (10–18)	7 (2–11)	6 (2–12)	0.007	0.002

IUSS- Indevus Urgency Severity Scale -Number of patients with none; mild; moderate severe
UDI-6- Urogenital Distress Inventory
IIQ-7 -Incontinence Impact Questionnaire-short form

Petrou et al Mayo Clin Proc. 2009;84(8):702-6.

Botox + Protamine

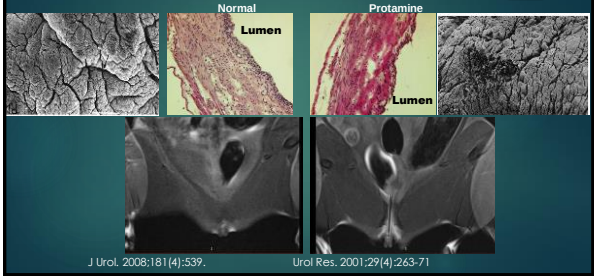




Khera et al Urology. 66(1): 2005. 208–212

Chuang et al J Urol. 2004;172(4 Pt 1):1529-32.

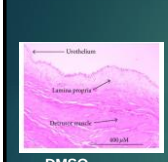
Effect of Protamine



J Urol. 2008;181(4):539.

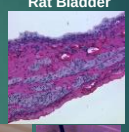
Urol Res. 2001;29(4):263-71

Urothelium Denudation Or Liposomes



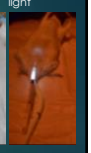
Protamine Rat Bladder

Liposomes Rat Bladder

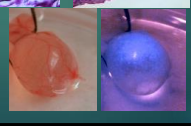


Visible light

Near-infra red light



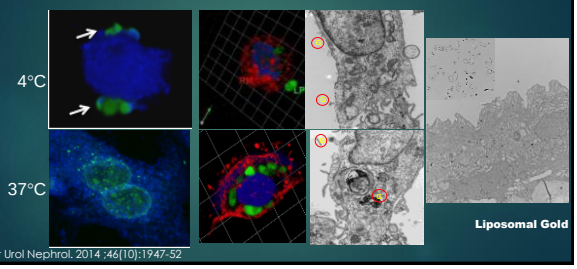
DMSO Pig bladder



Biomed Res Int. 2014;2014:347616.

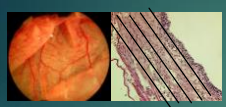
J Urol. 2008;181(4):539

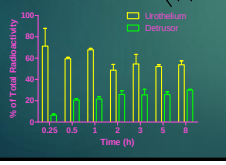
Endocytosis of Liposomes by Rat Urothelium Cells- Confocal & TEM



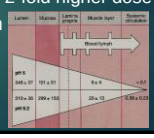
Int Urol Nephrol. 2014 ;46(10):1947-52

How Far the Liposomes Penetrate ?





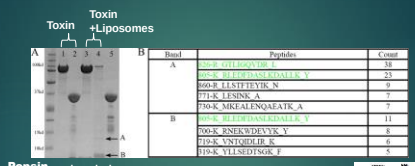
- Harvested bladder serially sectioned and radioactivity measured after instillation of labelled liposomes
- Urothelium has 2-fold higher dose fraction upto 8h



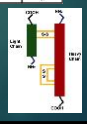
Liposomes+ Botox

+ OnabotulinumtoxinA

Protection of Botulinum Toxin



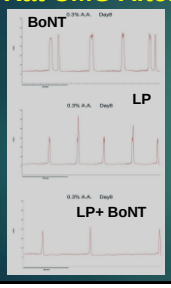
Band	Peptides	Count
A	256-R_GTLSQVDR_L	38
	605-K_ILTFDPIASEDALIK_Y	23
	660-R_LSTITEYIK_N	9
	771-K_LESINK_A	7
	730-K_MKEALENQAEATK_A	7
B	605-K_ILTFDPIASLKDALIK_Y	11
	700-K_RNEKWDEVYK_Y	8
	719-K_YNTQIDLIK_K	6
	719-K_YLLSEDTSGK_F	5

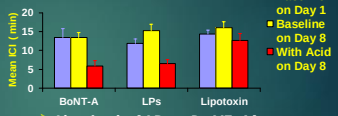


Liposomes protect LC-HC peptides from cleavage by Pepsin

Darren J. Mushrush et al. J. Biol. Chem. 2011; 286:27011-27018

Rat CMG After Lipotoxin Instillation

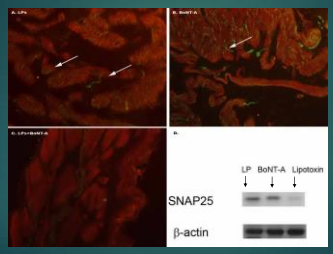




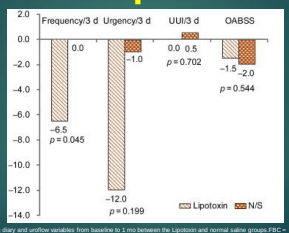
- Lipotoxin (LPs + BoNT-A) pretreatment blunted the AA induced decrease in ICI of only 21.1 % compared to ~50% in other groups

Chuang YC, Tyagi P, J Urol. 2009;182(2):786-92.

Effect on SNAP25



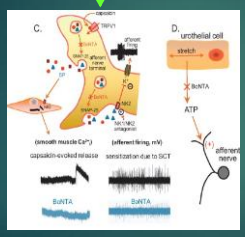
Clinical Data- Lipotoxin 4 weeks Followup

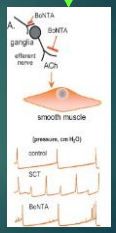


Median changes of voiding diary and uroflow variables from baseline to 1 mo between the Lipotoxin and normal saline groups.FBC = functional bladder capacity; N/S = normal saline; OABSS = Overactive Bladder Symptom Score; PVR = postvoid residual volume;...

Kuo et al European Urology, Volume 65, Issue 6, 2014, 1117–1124

Instilled Botox Likely Impairs Only Afferent & Not Efferent

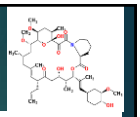


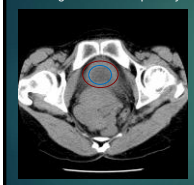


Ikeda et al. Eur Urol. **62:** 1157, 2012

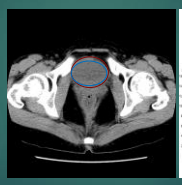
Tacrolimus For IC

- Combined oral therapy of IC/BPS patient with 10 mg of prednisolone and 2 mg of tacrolimus per day reduced bladder wall thickness





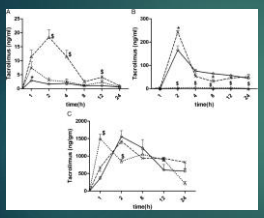
Pre



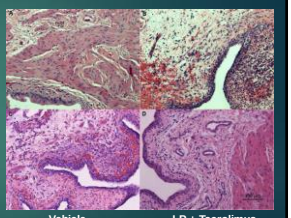
Post

Kaneko et al Can Urol Assoc J. 2012; 6(2): E46–E49

Intravesical Tacrolimus For Cystitis



Neurourol Urodyn. 2011;30(3):421-7
J Urol. 2013;189(4):1553-8.



Vehicle LP + Tacrolimus

Int Urol Nephrol. 2015 ;47(10):1679-81.

Summary

- Future options are necessary for the delivery of large molecular weight drugs
- Chemical approaches for increasing the bladder permeability include protamine and DMSO, protein transduction, iontophoresis and LESW
- Liposomes rely on endocytosis and have been tested in controlled clinical studies
- Hydrogel and polymeric devices are being tested to extend the exposure of instilled drugs

Acknowledgements

- Dr. Leaf Huang
- Dr. Naoki Yoshimura
- Dr. Yao chi Chuang
- Dr. Hann Chorng Kuo
- Dr. Anthony Kanai
- Dr. Matthew Fraser
- Dr. Lori Birder
- Dr. Harvey Henseley
- Dr. T. Kevin Hitchens
- Dr. Michael Chancellor
- Dr. Chris Chermansky
- Dr. Jonathan Kaufman
- Dr. Mahendra Kashyap
- Dr. Nirmal Jayabalan
- Dr. Bharathi Raja

Funding support from NIH, DOD, ICA

Best Practices in Intravesical Instillations

Angie Rantell
Lead Nurse, Urogynaecology
King's College Hospital, London

Angie Rantell

ICS 2018 PHILADELPHIA

Affiliations to disclose†:

I have received honoraria for lectures from Allergan, Astellas, Cogentix, Coloplast, Hollister and Mediplus.

† All financial ties (over the last year) that you may have with any business organization with respect to the subjects mentioned during your presentation

Funding for speaker to attend:

- [ ] Self-funded
- [ ] Institution (non-industry) funded
- [x] Sponsored by: *Pfizer Research Grant*

Bladder Instillations

- Intravesical instillation is a procedure by which fluids are slowly introduced into the bladder and allowed to remain there for a specific length of time before being drained, voided or withdrawn. It is performed to expose the tissues of a given area to the solution
- Only best practice guidelines for bladder Ca (EAUN Guidelines 2015)

Pre Procedure

- Explain procedure to patient
- Highlight potential risks or complications
- Explain dosing schedule
- Identify any individual patient requirements that may affect the efficacy of treatment
- ? Written or verbal informed consent

Preparation of bladder instillation

- Dependent on individual product and preparations sourced
- Clean area
- Follow manufacturers instructions (SMP)
- Appropriate PPE


Medications Pre Procedure

- Anticholinergics
- Analgesics
- Alkalising agents
- Antibiotics
- Diuretics


Administration considerations

- Positioning of the patient
- Cleaning of the meatus
- Catheter type and size
  - Luer lock maintain closed system
  - Intermittent Vs foley
  - ? hydrophilic
- Use of a lubricant / LA

Dwell Time + Removal

- According to SPC / manufacturers?
- As long as pt can hold?
- ? Change patient positions
- ? Restrict fluids / promote fluids
- ? Void to empty / drain bladder
- ? Flush twice

Documentation

- Medication and dose
- Expiry
- ? What prepared with
- Catheter size / aseptic or clean / volume instilled
- Dwell time and how expelled
- Adverse events
- If and when next dose due

Staff education for instillations

Knowledge	Rationale
Recurrent UTI, BPS / bladder cancer pathway	To ensure other elements of treatment / investigation take place as required
Indication for treatment	To ensure the patient meets the requirements for treatment
Data supporting it use	To help the patient understand the benefits of treatment
Importance of counselling the patient regarding the treatment	To help ensure concordance and compliance
Pharmacokinetics and pharmacodynamics of the agent being used	To help the patient understand how the treatment works and how it affects their disease

Staff education for instillations

Knowledge	Rationale
Contraindication of treaments	To maintain patient safety
Potential physical and health hazards of agents being used	To ensure the patient / nurse / environment safety
Competence in urethral catheterisation	To ensure safe and effective administration of the treatment and reduce risk of side effects
Awareness of side effects	To help patients manage side effects / cousel patients appropriately
Dose / scheldule	To ensure the treatment is administered in a timely fashion

Service delivery models

- Nurse led
- Weekly / daily clinics
- Outpatient / ambulatory care
  VS
- Self Instillation at home

Aetiology of CAUTI

- Source
  - Patients colonic or perineal flora
  - Bacteria on hands of staff / carer / patients

- How do microbes enter the bladder?
  - Extraluminal around the external surface
  - Intraluminal inside the catheter
- Daily risk of bacturiuria with catheterisation 3-10%
  - By day 30 – 100%

Maki 2001

Risk factors for CAUTI

- Insertion technique
- Maintenance technique
- A history of previous catheter use
- Length of stay in hospital prior to catheter insertion
- Location of catheter insertion e.g. on ward, A&E, theatre
- Female gender
- Increasing age
- General debilitation / impaired immunity

Education and training in catheter care of staff and carers

Conclusions

- Always follow manufacturers recommendations
- Ensure patients are fully informed prior to starting a course of therapy
- Lack of research and best practice guidelines for instillations