Future Therapy for Neurogenic Bladder Dysfunction: Drugs, Devices and Tissue Engineering

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Disclosures

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Learning Objectives

At the conclusion of this activity, the participant will be able to:

• A. Describe medications under development to treat neurogenic bladder dysfunction
• B. Realize the hazards of tube drainage and some future prospects for safer drainage
• C. Describe the possibilities for tissue regeneration for bladder augmentation
Obtaining CME Credit

• If you would like to receive CME credit for this activity, please visit:

  http://www.pesgce.com/PVAsummit2011/

• This information can also be found in the Summit 2011 Program on page 8.
Overview

• Drug Therapy
  – Conventional Antimuscarinics (Oxybutynin)
  – Clinical Trials (beta-3 agonists)
  – Future medications (ATP antagonists)

• Tube drainage
  – Conventional (urethral and suprapubic tubes)
  – Biofilm dispersants, inhibitors, modified surfaces

• Tissue Engineering and Stem Cells
Neurogenic Bladder

- Ongoing Functional Obstruction from DESD
- Refractory Neurogenic Overactivity and Incontinence
- Loss of Bladder Compliance from Denervation
Price Paid - Severe Hydronephrosis, Renal Damage from SCI/NGB and Unsafe Storage of Urine
Detrusor Sphincter Dyssynergia with Obstruction

Ongoing Functional Obstruction
Neurogenic Bladder - Reasons for Urodynamic Testing - Mandatory

- **Baseline Evaluation**
  - Measure Compliance
  - Diagnose Obstruction

- **Plan Management**
  - Find the “Danger Zone”

- **Measure Outcomes**
  - Pharmacological Therapy
  - Surgical Therapy
Storage Pressure - Compliance

- Compliance: $\Delta V/\Delta P$
- Ability to accommodate more volume with little rise in pressure – “Good”
- Small volume increase leads to big rise in pressure – “Bad”

Graph showing the relationship between volume change and pressure change, with “Bad” and “Good” landmarks.
The Problem

- Refractory Neurogenic Detrusor Overactivity (NDO) remains a real problem
- Current medications have very limited efficacy in this population with significant intolerable side effects
- Although Botulinum Toxin injection has helped, we still face refractory NDO (why?) in some patients and botox injection is costly and must be repeated
- New drugs and treatments with novel mechanisms of action are essential
Pharmacologic Therapy for NGB

• Selective Agents
  – Sensory (afferent) approaches
    • Capsaicin/Resiniferatoxin (RTX)
    • ATP receptor (P2X$_3$) antagonist(s)
    • Neurokinin receptor (NK1)
    • Sodium Channel blocker (Na$_v$ 1.8)
    • Cannabinoid receptor (CB1)
    • Endothelin receptor (ET$_A$)
  – Myogenic (efferent) approaches
    • Antimuscarinic Agents
    • $\beta$3 Agonist(s)
    • PDE Inhibitors (PDE4)
Afferents

Spinal cord S2-S4

Efferents

Bladder

Afferent Drugs

Atropine
Oxybutynin
Tolterodine
The Micturition Cycle: Old and New

Storage Phase

Bladder filling

First sensation to void

Emptying Phase

Normal desire to void

Bladder filling

Old Science

Anti-Cholinergics

“urgency incontinence”

Bladder pressure

Anticholinergic Medications

- Oxybutynin
- Ditropan
- Detrol/Toviaz
- Vesicare
- Enablex
- Sanctura
Inhibitory effect of Anticholinergics

\[ \text{Beta-\ adrenergic receptor} \]
\[ \text{M}_2 \text{ receptor} \]
\[ \text{M}_3 \text{ receptor} \]

\[ \text{Adenylyl Cyclase} \]
\[ \text{cAMP} \]
\[ \text{ATP} \]

Detrusor Contraction

\[ \text{Inhibitory effect of PDE Inhibitor} \]
\[ \text{PDE} \]
\[ \text{(+)} \]
\[ \text{hydrolysis} \]

Detrusor Relaxation

Bladder Smooth Muscle

• Oxybutynin
• Tolterodine
• Solifenacin
• Fesoterodine
• Trospium Cl
• Darifenacin

Acetylcholine
Compliance With Oral Therapies is POOR! Even worse with SCI Patient Polypharmacy

Data on File, Watson Pharma, Inc.
IMS HEALTH Rx.
Beta-3 Adrenoceptor Agonists

- Beta-3 adrenoceptor activation is the main bladder relaxation mechanism
- Human bladder contains 3 beta adrenoceptors and 97% are Beta-3 adrenoceptors
- Beta-3 adrenoceptors also located in urothelium and afferent nerves
- Phase II and III studies with Beta-3 receptor agonist (mirebegron) for OAB are promising
- No significant studies in NGB dysfunction, yet
Inhibitory effect of Anticholinergics

Beta-adrenergic receptor

$M_2$ receptor

$M_3$ receptor

Detrusor Contraction

Inhibitory effect of PDE Inhibitor

Sympathetic Input

Adenylyl Cyclase

ATP → CAMP

PDE → hydrolysis

Detrusor relaxation
Inhibitory effect of Anticholinergics

Beta-adrenergic receptor

\( M_2 \) receptor

\( M_3 \) receptor

Detrusor Contraction

Inhibitory effect of PDE Inhibitor

Beta 3 Agonist

Adenylyl Cyclase

\( + \)

\( - \)

ATP

CAMP

PDE

(+)

hydrolysis

Detrusor Relaxation
Beta-3 Adrenoceptor Agonist Applied to Spinal Cord

Beta-3 receptors also located in the Spinal Cord and located mainly in the ventral horn
Fullhase et al., NUU (2011)
Future Drug Action

Afferents

Spinal cord S2-S4

Efferents

Capsaicin RTX

Bladder

Atropine Oxybutynin Tolterodine

Afferent Drugs
Neurogenic Theories

Decreased capacity to handle afferent information

Decreased suprapontine inhibition

Increased afferent activity

Increased sensitivity to released contraction – mediating transmitter(s)

Our Lab data shows a 6.5x Increase in basal urothelial ATP release after SCI
“Neuro” urothelium

Stretch

ATP

Nitric Oxide

Smooth Muscle

Purine Receptors (P2X)

Sensation
Urothelial ATP Release

- Overactivity (OAB and LUTS)
- Neurogenic Overactivity (SCI)
- Pain
ATP

$P2X_{3,2/3}$

$A_\delta$ Afferent

VR1

Parasympathetic Efferent

$P2X_1$

C-fiber Afferent

"Silent"
Normal Rats

Recording activity from the Sensory Spinal Cord

Recording Electrode

A
Saline

B
Intravesical ATP

C
AF-353 (10 mg/kg)

D
AF-353 (20 mg/kg)

E
Suramin (100 mg/kg)
Future: Novel Afferent – Directed Agents

Afferents → Spinal Cord S2-S4 → Efferents

P2X Receptor Antagonists

ATP

Anticholinergic Medications
Targeting Gene Therapy for Neurogenic Bladder Dysfunction

HSV-GAD Vector Injection Or Ab-NGF

C-Fiber Afferent neurons

Bladder

PMC

L6-S1 spinal cord

Efferent output

GAD – synthesizing enzyme for GABA (inhibitory transmitter)
Ab – NGF - Antibody to Nerve Growth Factor
Existing ‘Native Bladder’ Drainage Technologies

- Foley Urethral Catheter
- Suprapubic Tube
- Intermittent Catheterization

Problems with “Indwelling” Tubes

- ‘Open Access’-skin microbes migrate on external catheter surface
- 100% have colonized urine.
- No hope of eliminating microbes
- Antibiotics select ‘resistant microbes
- Leakage and odors are frequent
- Bladder stones and Skin Problems
- Infection of adjacent organs
Catheterization = Ancient Technology
“Little Change” since Franklin & Foley

Fredric Foley, MD
Balloon catheter; 1935

Ben Franklin
1st antimicrobial catheter;
1st ‘self-catheterization’
1752; “before microbes!!”
Catheter Associated UTI
Incidence of microbe colonization

- ~5%/day colonized w/o Coating.
- ~3%/day colonized w/Coating

After 5 weeks→100% colonized; those on antibiotics commonly have resistant organisms. i.e. NO HOPE of STERILIZING URINE w/ OPEN ACCESS TUBES
Microbes become resistant by forming Biofilms

Microbes attach to all non-biologic surfaces.

Microbes reproduce to 10 million/ml in 36 hrs.

Microbes secrete peptides and sugars and ‘slimy’ biofilm on all surfaces.

Antibiotics do not penetrate biofilm, but do kill floating microbes.

Microbes within biofilms are X1000 X10,000+ more resistant to antibiotics.

Sterile urine cultures [catheterized patients]→ May not identify microbes existing within biofilms
Etiology of Catheter Infections

• #1 - “Open Access” Tube Drainage Systems: Skin Microbes migrate in surface moisture on the “outer” catheter surfaces. Bladder urine is constantly ‘seeded’ with skin microbes from the skin & perineum

• #2 - Catheter surfaces provide ‘sanctuary’ for growth and survival of microbes
3 Evolving Future Technologies

- **#1** - “Closed Access” Tube Drainage Systems: Prevent microbial access to bladder urine by skin & perineal microbes
- **#2** - Biofilm Blocking and Dispersive Agents: Prevent “biofilm sanctuaries” for skin & perineal microbes; increase microbial sensitivity to drugs
- **#3** - Surface topology prevents microbial migration
Antimicrobial topology
Surface modification of urinary tubes

Representative SEM micrographs from artificial urine media assay after 24 hours of exposure

Microbes grow & migrate slower Over selected topographic surfaces
Catheter Migration Studies

Sharklet Topography Greatly Slows Microbe Migration

No Microbial Migration

Sharklet surface Silicone Bridge

E. Coli Cultures

Smooth surface Silicone Bridge

No Bridge

No Microbial Migration

Silicone Bridge

Migration
New Technologies
Biofilm Blocking/Dispersive Molecules

None Commercialized

J. Am. Chem. Soc. 2007, 129, 6966


Chem. Commun., 2008, 14, 1698
ChemBioChem 2008, 9, 1267

Bladder Augmentation with Bowel 

Problems and Complications
- Mucus
- Bowel obstruction
- Cancer
Urinary Bladder Regeneration
Organ Regeneration Technology Platform

- Construct catalyses regenerative process
- As scaffold degrades, bladder wall is regenerating
- Developed from bladder biopsy, technology advancing to obtain cells from fat biopsy

*Oberpenning et al, Nature Biotechnology, 1999
Tissue-Engineered Autologous Augmentation Cystoplasty

Atala et al. Lancet 2006; 367:1241-46
Morphological Analysis - 31 months after Augmentation Cystoplasty

Atala et al. Lancet 2006; 367:1241-46
• **Beta 3 Adrenergic Agonist** (Mirabegron - Astellas, Solabegron) – alter intracellular second messenger levels in smooth muscle and urothelium to promote relaxation.

• **Purinergic Receptor Blockers** – still in the laboratory, but promising

• **Intravesicular Botox (no injection) and Targeted Botox**

• **Improvements in permanent tube drainage**

• **Advancements in Regenerative Tissue and Stem cell research**

• **Targeted Gene Therapy, siRNA or other SCI therapies improving bladder function**
Thank you
RNAIII Inhibiting Peptide [isolated from mutant S. Epidermidis]: Blocks biofilm by all Staphylococcal species [including MRSA]; Enhances antimicrobials targeting Staphylococci.

Dis-B, a protein isolated from Actinobacillus actinomycetemcomitans: It prevents and disperses biofilms formed by Staph epidermidis E. Coli, and Candida Albicans. Enhances antimicrobials targeting most Gram [+] and Gram [-] species.

All BIDA ‘block’ &/or ‘disperse’ microbe adhesion and all increase sensitivity of microbes to traditional antimicrobial drugs by X1000-100,00X
SCI Bladder: Alternatives

-\eservoir vs onduit:
  Native vs. Augmented vs. Tissue-Engineered

-\rainage:
  Intermittent vs. Continuous Tube Drainage

-\ptimum
  Native, 300+ ml capacity, odor free, leak-proof, low pressure, cosmetic, cost-effective, renewable, w/ Sterile Urine; Functional in bed or in wheelchair & user-friendly for care-giver and patient.
Clinical Development to Date
Tengion, Inc.

2 Phase 2 studies

–SB (pediatric): poster April 28
–SCI (adult): in progress

Open-label, single-arm

–Primary endpoint:
  • Urodynamic improvement at 12 months

–Secondary endpoints:
  • Safety
  • Urodynamic improvement at 6, 9 months
  • Incontinence
Bladder – Sphincter Dyssynergia
Detrusor – Sphincter Dyssynergia