Pharmacotherapy for Neurogenic Lower Urinary Tract Dysfunction

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Disclosures
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Topics
Pharmacotherapy for the

- Underactive Detrusor
- Underactive Sphincter
- Overactive Sphincter
- Overactive Detrusor

Suprapontine Lesion
Suprasacral Spinal Lesion
Sacral / Subsacral Spinal Lesion
Intrapelvic Lesion

Epiconal Lesion
Epiconal Lesion
Sphincter Overactivity only
Sphincter Underactivity only
Management of the underactive (acontractile) detrusor

- Behavioural therapy
- Pharmacotherapy
- Intermittent (self-) catheterization
- Indwelling transurethral / suprapubic catheter
- Surgery

*in incomplete lesions*

- Intravesical electrotherapy
- Sacral neuromodulation
PHARMACOTHERAPY
Cholinergics

• Receptor agonists such as bethechanol to stimulate detrusor muscarinic receptors
• Cholinesterase inhibitors such as distigmine to reduce the degradation of acetylcholine.

no randomized controlled studies

Cholinergics are not able to induce / increase detrusor contractions, but seem to increase the detrusor muscle-tone (sensation of full bladder earlier)

• Alpha blockers
PHARMACOTHERAPY
Underactive Detrusor

EAU 2011
• There is no drug with evidence of efficacy for underactive detrusor
• Decreasing bladder outlet resistance
  – alpha-blockers (non-selective and selective) have been partially successful for decreasing bladder outlet resistance, residual urine and autonomic dysreflexia

NICE 2012
• Alpha-blockers; Do not offer alpha-blockers to people as a treatment for bladder emptying problems caused by neurological disease.

ICI 2013
• For detrusor areflexia no effective drugs are available up to now; further research is needed.
FUTURE SOLUTIONS for Detrusor Underactivity

- TRPV1 agonists, other TRP channel activators, e.g. NK2 Receptor Agonists
- Selective neurostimulation
- Reinnervation procedures
- Bladder tissue engineering, cell therapy
Topics
Pharmacotherapy for the

- Underactive Detrusor
- Underactive Sphincter
- Overactive Sphincter
- Overactive Detrusor

Diagram:
- Suprapontine Lesion
- Suprasacral Spinal Lesion
- Sacral / Subsacral Spinal Lesion
- Intrapelvic Lesion
- Epiconal Lesion
- Epiconal Lesion
- Sphincter Overactivity only
- Sphincter Underactivity only
Management of neurogenic sphincter weakness

• Pharmacotherapy

• Operative treatment
  Suburethral Injections („Bulking Agents")
  Slings - for women
  Artificial sphincter

• Condom Catheter / Pads
Management of neurogenic sphincter weakness

Pharmacotherapy

– Alpha-adrenergics

*no controlled trials proving efficacy*

– Duloxetin

*Serootonin – Noradrenalin re-uptake inhibitor should work in incomplete lesion by stimulating the Nucleus Onuf, not proved through studies*
Topics

Pharmacotherapy for the

- Underactive Detrusor
- Underactive Sphincter
- **Overactive Sphincter**
- Overactive Detrusor
Neurogenic Sphincter Overactivity
Detrusor-Sphincter-Dyssynergia

To be expected when the detrusor reflex
*bladder - brain stem - bladder*
is interrupted/lesioned.

Brain stem lesions  Suprasacral spinal cord lesions
Pharmacotherapy of the striated overactive sphincter

• Relaxation of the striated sphincter
  
  *Baclofen*® - only effective in dosages not tolerable for the patient, no clinical relevance for the treatment of detrusor–sphincter ext.–dyssynergia

  *Alpha Blockers*

• Botulinum toxine A injection into the striated sphincter

• NO-donors to inhibit striated sphincter contraction
Pharmacotherapy
the overactive (spastic) sphincter

**EAU 2011**

- Decreasing bladder outlet resistance
  - **Alpha-blockers** (non-selective and selective) have been partially successful for decreasing bladder outlet resistance, residual urine and autonomic dysreflexia

**NICE 2012**

- **Alpha-blockers**: Do not offer alpha-blockers to people as a treatment for bladder emptying problems caused by neurological disease.
Pharmacotherapy of the striated overactive sphincter

• Relaxation of the striated sphincter
  
  *Baclofen®* - only effective in dosages not tolerable for the patient, no clinical relevance for the treatment of *detrusor–sphincter ext.–dyssynergia*

  *Alpha Blockers*

  

• Botulinum toxine A injection into the striated sphincter

• NO-donors to inhibit striated sphincter contraction
Oral Nitric Oxide Donors: A New Pharmacological Approach to Detrusor-Sphincter Dyssynergia in Spinal Cord Injured Patients?

André Reitz\textsuperscript{a,*}, Peter A. Knapp\textsuperscript{a}, Michael Müntener\textsuperscript{b}, Brigitte Schurch\textsuperscript{a}

\textsuperscript{a}Neuro-Urology, Swiss Paraplegic Center, Balgrist University Hospital, Forchstrasse 340, 8008 Zurich, Switzerland

\textsuperscript{b}Department of Urology, University Hospital, Zurich, Switzerland

Accepted 4 November 2003

Published online 26 November 2003
Efficacy of NO on resting sphincter pressure after sublingual application of 10mg Isosorbiddinitrat (Isoket®)
DSD without vs. with NO

Baseline

20 min after 10 mg Isoket®
Discussion

• NO significantly decreases the resting pressure of the striated urethral sphincter.

• NO significantly reduces the contractility of the striated urethral sphincter during DSD.

• No effect on the detrusor pressure.

• Bladder emptying is improved and post-void residual urine decreases significantly.
Topics

Pharmacotherapy for the

- Underactive Detrusor
- Underactive Sphincter
- Overactive Sphincter
- **Overactive Detrusor**
Neurogenic Detrusor Overactivity

- Cerebral
  - Suprapontine
  - Pontine
- Spinal
  - Suprasacral
- Peripheral

Different symptoms, different risk profiles, different treatment strategies
Suprapontine lesion

PMC

Tumors
Encephalitis
CVA
Head injury
Degenerative disease
Parkinsonism

Detrusor Overactivity
Coordinated Voiding
Voiding right - timing wrong*
Intravesical pressure situation during storage and voiding normal
Suprapontine Detrusor Overactivity

How to regain control over the bladder?

Management

Behavioural therapy

Bladder retraining programmes
  * if mentally impaired - toileting / prompted voiding
  * if mentally fit - micturition training

and

Pharmacotherapy

Primary aim: to improve urgency / urge incontinence

• Antimuscarinics (=Anticholinergics)
• Botulinum Toxin A

  if functional bladder capacity is reduced

Basis: Voiding Diary
Pontine lesion

Multiple Sclerosis
Multi-System-Athrophy
Parkinson’s disease
Tumors

Detrusor Overactivity
Detrusor Underactivity
Uncoordinated Voiding
Detrusor-External Sphincter-Dyssynergia (DSD)

post-void residual urine
High intravesical pressure situation possible
How to regain control over the bladder?

Management

Behavioural therapy

Bladder retraining programmes as with suprapontine detrusor overactivity

Pharmacotherapy

• Antimuscarinics (=Anticholinergics)
• Botulinum Toxin A

Check post-void residual urine – DSD?

Aim of therapy: to reduce detrusor overactivity and to normalize an increased intravesical pressure situation
DO/OAB – Pharmacological Treatment

Antimuscarinics = first line treatment

<table>
<thead>
<tr>
<th></th>
<th>Tertiary ¹</th>
<th>Quarternary ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Tolterodin</td>
<td>x</td>
<td></td>
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<tr>
<td>Propiverin</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Trosépiumchlorid</td>
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<td>x</td>
</tr>
<tr>
<td>Solifenacín</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Darifenacín</td>
<td>x</td>
<td></td>
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<tr>
<td>Fesoterodine</td>
<td>x</td>
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</tbody>
</table>

Efficacy proved for above AMs
Level of Evidence 1, Grade of Recommendation A

International Consultation on Incontinence 2012
Long-Term Antimuscarinic Treatment

- Neurogenic Bladder patients with NDO
  - SCI
  - Myelodysplasia („Spina bifida“)
  - Multiple sclerosis

- Elderly with OAB
  - due to degenerative processes
  - brain, bladder
Pharmacotherapy with Antimuscarinics

What do we want?

• High and long-term efficacy
• Tolerability and safety
• No drug-to-drug interactions
Antimuscarinics for NDO

• Recently published reviews on antimuscarinics (AM) focus on idiopathic detrusor overactivity (IDO) and overactive bladder (OAB)
  
  *Chapple 2008*

• Studies on neurogenic detrusor overactivity (NDO) were either not included or not analysed separately
  
  *Chapple 2008*

• The aim of AM treatment in NDO is different compared to IDO as detrusor pressure in the storage and emptying phase is crucial for these patients
Passed away only recently after surgery.

I would like to inform you that some of the charts of this lecture have been designed by Gerd Mürtz for a lecture he wanted to give in the Department of Uro-Neurology at the National Hospital for Neurology and Neurosurgery, Queen Square, London.
Reviews of antimuscarinics in adults with NDO

Anticholinergic Drugs for Adult Neurogenic Detrusor Overactivity: A Systematic Review and Meta-analysis

Priya Madhuvrata, Manju Singh, Zaid Hasafa, Mohamed Abdel-Fattah

Sheffield Teaching Hospital NHS Foundation Trust, Sheffield, UK; Obstetrics and Gynaecology Department, Grampian NHS, Aberdeen, UK; University of Aberdeen, Aberdeen, UK

Neurogenic detrusor overactivity in adults: a review on efficacy, tolerability and safety of oral antimuscarinics

H Madersbacher, G Mürtz and M Stöhrer
Antimuscarinics in adults with NDO

Body of evidence

Madersbacher et al., Spinal Cord 2013, 51, 432-441
## Placebo-controlled studies – study characteristics

<table>
<thead>
<tr>
<th>Author</th>
<th>L.E</th>
<th>Study Design</th>
<th>Treatment duration (weeks)</th>
<th>Treatment groups</th>
<th>Patient number (N)</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Diagnosis¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stöhrer (1990)</td>
<td>1b</td>
<td>Prospective, randomised, parallel group, double-blind, placebo-controlled, multicentre (2)</td>
<td>3</td>
<td>3 x 1 Placebo, 3 x 5 mg Oxy IR</td>
<td>60</td>
<td>n. a.</td>
<td>n. a.</td>
<td>Detrusor hyperreflexia in spinal cord injured patients and upper motor neuron lesion</td>
</tr>
<tr>
<td>Stöhrer (1991)</td>
<td>1b</td>
<td>Prospective, randomised, parallel group, double-blind, placebo-controlled, multicentre (3)</td>
<td>3</td>
<td>Placebo (N=32), 2x20 mg TC IR (N=28)</td>
<td>61 enrolled, 55 analysed</td>
<td>30 male, 25 female</td>
<td>32.3 (TC) 34.2 (Plac.)</td>
<td>Spinal cord injury with consecutive detrusor hyperreflexia</td>
</tr>
<tr>
<td>Stöhrer (1999)</td>
<td>1b</td>
<td>Prospective, randomised, parallel group, prospective, double-blind, multicentre (4)</td>
<td>2</td>
<td>3 x 1 Placebo, 3 x 15 mg Prop IR</td>
<td>113</td>
<td>69 male, 44 female</td>
<td>30 ± 11.7 (Prop.) 29.2 ± 10.9 (Plac.)</td>
<td>Detrusor hyperreflexia and suprasacral spinal cord injury</td>
</tr>
<tr>
<td>Ethans (2004)</td>
<td>1b</td>
<td>prospective, randomised, cross-over, double-blind, monocentre</td>
<td>2 weeks for each cross-over period, intermediate 4-day-washout period</td>
<td>Placebo (N=10), 2 x 2 mg Tolt IR (N=10)</td>
<td>14 enrolled, 10 completed</td>
<td>9 male, 1 female</td>
<td>40.5 (range 21-63)</td>
<td>NDO due to SCI (7), MS (2), spina bifida (1)</td>
</tr>
<tr>
<td>Amarenco (2012)</td>
<td>1b</td>
<td>prospective, randomised, double-blind, multicentre (n.a.)</td>
<td>4</td>
<td>Placebo (N=40), Solifenacin 10 mg (N=51)</td>
<td>n. a.</td>
<td>n. a.</td>
<td>18 - 65</td>
<td>NDO due to SCI (81) or MS (95)</td>
</tr>
</tbody>
</table>

¹ Terminology used by the original study authors has been retained

n.a. = not applicable  Oxy = Oxybutynin  Tolt = Tolterodine  TC = Trospium chloride

*Madersbacher Spinal Cord 2013, 51: 432-441*
## Placebo-controlled studies – efficacy outcomes

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<tbody>
<tr>
<td></td>
<td>Oxy IR 3 x 5 mg</td>
<td>Placebo 2 x 20 mg</td>
<td>Prop IR 3 x 15 mg</td>
<td>Tolt IR 2 x 2 mg</td>
</tr>
<tr>
<td>N</td>
<td>60 overall</td>
<td>29</td>
<td>60</td>
<td>14 overall</td>
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<tr>
<td>Urodynamic parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max. cystometric</td>
<td>pre</td>
<td>post</td>
<td>post-pre</td>
<td></td>
</tr>
<tr>
<td>bladder capacity (mL)</td>
<td>175</td>
<td>240</td>
<td>171</td>
<td>262</td>
</tr>
<tr>
<td>Max. detrusor pressure</td>
<td>Pre</td>
<td>post</td>
<td>post-pre</td>
<td></td>
</tr>
<tr>
<td>(cmH₂O)</td>
<td>90</td>
<td>85</td>
<td>101</td>
<td>81</td>
</tr>
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</table>

The study of Amarenco (EAU 2012) is not included in this table, because detailed results are not given.

n.a. not applicable  Oxy = Oxybutynin  Prop = Propiverine  Tolt = Tolterodine  TC = Trospium chloride

Madersbacher Spinal Cord 2013, 51: 432-441
## Active-controlled studies – efficacy outcomes

<table>
<thead>
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<tr>
<td></td>
<td>Oxy IR 3x5 mg</td>
<td>Propantheline IR 3x15 mg</td>
<td>Oxy IR 3x5 mg</td>
<td>TC IR 2x20 mg</td>
<td>Prop IR 3x15 mg</td>
</tr>
<tr>
<td>N</td>
<td>19</td>
<td>15</td>
<td>43</td>
<td>52</td>
<td>45</td>
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<tr>
<td><strong>Urodynamic parameters</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Max. cystometric bladder capacity (mL)</strong></td>
<td>Pre post</td>
<td>post-pre</td>
<td>138</td>
<td>198</td>
<td>188</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>282</td>
<td>198</td>
<td>351</td>
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<td></td>
<td></td>
<td></td>
<td>+ 144</td>
<td>+ 35</td>
<td>+ 166</td>
</tr>
<tr>
<td><strong>Max. detrusor pressure (cmH\textsubscript{2}O)</strong></td>
<td>Pre post</td>
<td>post-pre</td>
<td>82</td>
<td>82</td>
<td>69</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>44</td>
<td>53</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-38</td>
<td>-29</td>
<td>-26</td>
</tr>
</tbody>
</table>

n.a. not applicable  Oxy = Oxybutynin  Prop = Propiverine  Tolt = Tolterodine  TC = Trospium chloride

Madersbacher Spinal Cord 2013, 51: 432-441
Oxybutynin: studies in NDO

• Placebo-controlled dose-finding study: NONE CONDUCTED

• Placebo-controlled study (N=60; SCI)
  Stöhrer American Spinal Cord Association 1990

• Active-controlled studies (conducted mostly by competitors):
  vs. propiverine (N=131) Stöhrer Eur Urol 2007
  vs. trospium chloride (N=88) Madersbacher BJU Int 1995
  vs. tolterodine (N=14) Ethans J Spinal Cord Medicine 2004

• Open-label studies: Bennett J Urol 2004
  Pannek Urol 2000

• SmPC: Licensed for NDO: ...unstable bladder, whether due to neurogenic bladder disorders (detrusor hyperreflexia) in conditions such as MS and spina bifida or to idiopathic....
Trospium chloride: studies in NDO

• Placebo-controlled dose-finding study (N=66): Stöhrer IMSOP 1998

• Placebo-/Active-controlled studies:
  Placebo (N=61)  Stöhrer Urol Int 1990
  Oxybutynin IR (N=113)  Madersbacher BJU Int 1995

• Open-label studies: Combination with another antimuscarinic and/or dose titrations:
  Menarini Int J Clin Pharmacol 2006
  Horstmann Neurol Urodyn 2006
  Amend Eur Urol 2008

• SmPC: Licensed for NDO  ...overactive bladder (e.g. idiopathic or neurological detrusor overactivity) www.medicines.org.uk accessed 16.8.2014
Tolterodine: studies in NDO

• Placebo-controlled dose-finding study (N=76):
  van Kerrebroeck Neurourol Urodyn 1998

• Placebo- / Active-controlled study (N=14 cross-over). Urodynamic parameters assessed to a limited extent. Double dose of tolterodine (8 mg) compared to oxybutynin required
  Ethans J Spinal Cord Medicine 2004

• Open-label studies: Combination with another antimuscarinic and / or dose titrations
  Ethans J Spinal Cord Medicine
  Horstmann Neurourol Urodyn 2006
  Amend Eur Urol 2008

• SmPC: Not licensed for NDO
  Cave: Even in the EAU guidelines of NDO tolterodine is falsely cited as antimuscarinic licensed in NDO
  Stöhrer Eur Urol 2009
Fesoterodine: studies in NDO

• Dose-finding study: NONE CONDUCTED

• Placebo-/Active-controlled studies: NONE CONDUCTED

• Open-label studies: MS long term study over 22 months with fesoterodine 4 mg (n=29) Proietti Eur Assoc Urol 2012

• SmPC: Not licensed for NDO.

Special warnings and precautions for use:
Safety and efficacy have not yet been established in patients with a neurogenic cause for detrusor overactivity.

www.medicines.org.uk
Solifenacin: studies in NDO

• Dose-finding study: NONE CONDUCTED

• Placebo / Active-controlled study (N=176: Sol 5 mg N=46, Sol 10 mg N=51, oxy 15 mg N=39, plac N=40; SCI + MS): Only the results solifenacin vs placebo reported, solifenacin vs. oxybutynin not reported Amarenco, Abstract EAU 2012

• Open-label studies:
  Multiple sclerosis (N=30) van Rey & Heesakkers Adv Urol 2011
  NDO (N=41) Spinelli Eur Assoc Urol 2007

• SmPC: Not licensed for NDO.

Special warnings and precautions for use:
Safety and efficacy have not yet been established in patients with a neurogenic cause for detrusor overactivity. www.medicines.org.uk
Darifenacin: studies in NDO

• Dose-finding study: NONE CONDUCTED
• Placebo- / Active-controlled studies: NONE CONDUCTED
• Open-label studies:
  MS Carl & Laschke Urology 2006
  SCI intravenous (!) darifenacin  Bycroft ICS 2003
• SmPC: Not licensed for NDO

Special warnings and precautions for use:
Safety and efficacy have not yet been established in patients with a neurogenic cause for detrusor overactivity. www.medicines.org.uk
Mirabegron (beta-3-receptor-antagonist): studies in NDO

- Dose-finding study: **NONE CONDUCTED**
- Placebo-/Active-controlled studies: **NONE CONDUCTED**
- Open-label studies: **NONE CONDUCTED**
- SmPC: Not licensed for NDO.

However, no respective comment in the “special warnings and precautions” section of the SmPC. [www.medicines.org.uk](http://www.medicines.org.uk)
Propiverine IR / ER: studies in NDO

• Dose-finding study: Mazur Urologe A 1994

• Placebo-controlled study (N=113, SCI) Stöhrer Spinal Cord 1999

• Active-controlled studies:
  vs. oxybutynin IR 3 x 5 mg (N=88) Madersbacher BJU Int 1995
  propiverine IR 3 x 15 mg vs. propiverine ER 45 mg once daily
  Stöhrer Spinal Cord 2013

• Open-label studies: Long-term 39 patients 12 months Mazur Kontinenz 1994

• SmPC: Licensed for NDO: ...neurogenic detrusor overactivity (detrusor hyperreflexia) from spinal cord transverse lesion paraplegia
Propiverine IR vs. placebo in NDO

Max. hyperreflexic detrusor contraction

Max. cystometric capacity

Stöhrer Spinal Cord 1999  37: 196-200
Propiverine IR 15 mg t.i.d. vs. ER 45 mg s.i.d. in NDO - Primary efficacy outcome reflex volume

Reflex volume

Stöhrer ICS 2009, Spinal Cord 2013 51: 419-423
Propiverine is even effective in patients non-responsive to other antimuscarinics

- 73 patients (median age 71 years) with OAB symptoms non-responsive to solifenacin, tolterodine or imidafenacin
- 21/73 patients (28.8%) withdrew prematurely
- Only in 9/21 patients withdrawl due to adverse events.
- 52/73 patients (71.2%) completed the 12-week-treatment with propiverine
  
  The OABSS as well as the scores of OAB symptoms improved significantly; no increase of PVR

- Key message
  - not to restrict propiverine to patients non-responsive to other antimuscarinics
  - even in patients non-responsive to other antimuscarinics propiverine is effective and well tolerated

- Consecutively, also a first-line approach with propiverine, due to its dual mode of action, might be more promising compared to “antimuscarinics only”.

Masumori et al., Advances in Urology, 2011
Effects of propiverine on rabbit bladder

Study design: rabbit – detrusor in vitro

Clinical significance of a combined (“dual”) mode of action

- A significant degree of atropine resistance may exist in morphologically and / or functionally changed bladders

- It has been reported to occur in
  - hypertrophic bladders (Sjögren 1982)
  - interstitial cystitis (Palea 1993)
  - neurogenic bladders (Wammack 1995)
  - ageing bladder (Yoshida 2001)

- The importance of NANC component to detrusor contraction remains to be established

  Andersson et al., International Consultation on Incontinence, Paris, 2009 & 2013
Tolerability

Propiverine IR 15 mg t.i.d.

vs.

Oxybutynin IR 5 mg b.i.d

Severity Gradings

Dry Mouth Incidence

Propiverine

Oxybutynin

N

0
5
10
15
20
25
30
35
40
45

Propiverine

Oxybutynin

47.1 %

67.2 %

33 / 70

41 / 61

1 Madersbacher et al., BJU International 1999 (84), 646-651
2 Stöhrer et al., Eur Urol 2007 (51), 235-242
Tolerability
Propiverine vs. Solifenacin

Solifenacin 10 mg caused more dry mouth (P = 0.012) and occurrence of constipation (P = 0.004) than propiverine 20 mg."

Yamaguchi et al., Brit J Urology 2007, 579-587
Dry mouth not only bothers the patient but causes dental problems especially in the elderly

- Caries of the tooth roots
- Difficulties with tooth prosthesis – no suction effect from the dry mucosa – the prosthesis doesn’t stick
- Pressure ulcers on the dry mucosa by tooth prosthesis
Propiverine and CNS Studies

26th Annual Meeting of the ICS, Athens 1996
EFFECT OF PROPIVERINE ON PSYCHOMOTOR PERFORMANCE
Kluge A et al.

35th Annual Meeting of the ICS, Montreal 2005
THE EFFECTS OF ANTI-CHOLINERGIC DRUGS FOR OVERACTIVE BLADDER ON COGNITIVE IMPAIRMENT, MENTAL DYSFUNCTION AND MOTOR DYSFUNCTION ON PATIENTS WITH NEUROLOGICAL DISEASES.
Uchiyama T et al.

HOW TO MANAGE OVERACTIVE BLADDER IN ELDERLY INDIVIDUALS WITH DEMENTIA? A COMBINED USE OF DONEPEZIL, A CENTRAL ACETYLCHOLINESTERASE INHIBITOR, AND PROPIVERINE, A PERIPHERAL MUSCARINE RECEPTOR ANTAGONIST.
Sakakibara R et al.

43rd Annual Meeting of the ICS, Barcelona 2013
INFLUENCE OF PROPIVERINE ER 30 MG ONCE DAILY ON COGNITIVE FUNCTION IN ELDERLY FEMALE AND MALE PATIENTS WITH OVERACTIVE BLADDER: A NON-INTERVENTIONAL STUDY TO ASSESS REAL LIFE DATA
Oelke M et al.

Courtesy of Helmut Madersbacher
OAB and memory disorders increase

Decline in delayed memory recall relative to age 20–29 (%)\textsuperscript{1}

OAB prevalence (%)\textsuperscript{2}

\textsuperscript{1}Crook TH, et al. Dev Neuropsychol 1993;9:103–13

\textsuperscript{2}Milsom I, et al. BJU Int 2001;87:760–6
**THE EFFECTS OF ANTI-CHOLINERGIC DRUGS FOR OVERACTIVE BLADDER ON COGNITIVE IMPAIRMENT, MENTAL DYSFUNCTION AND MOTOR DYSFUNCTION ON PATIENTS WITH NEUROLOGICAL DISEASES.**

Uchiyama T, Sakakibara R, Liu Z, Yamamoto T, Hattori T

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital Study</strong></td>
<td>With</td>
</tr>
<tr>
<td>n=18</td>
<td>• Multiple cerebral infarction n=8</td>
</tr>
<tr>
<td>age 71 ± 8.2 ys</td>
<td>• Multiple cerebral infarction + Parkinson's n=6</td>
</tr>
<tr>
<td>male:female = 13:5</td>
<td>• Multiple cerebral infarction + Alzheimer's n=6</td>
</tr>
<tr>
<td></td>
<td>• Parkinson's Disease n= 3</td>
</tr>
<tr>
<td><strong>Nursing Home Study</strong></td>
<td>With severe dementia including</td>
</tr>
<tr>
<td>n=14</td>
<td>• Alzheimer's Disease n=7</td>
</tr>
<tr>
<td>age 82 ± 4.5 ys</td>
<td>• Frontotemporal dementia n=1</td>
</tr>
<tr>
<td>male:female = 5:9</td>
<td>• Mixed dementia n=4</td>
</tr>
<tr>
<td></td>
<td>• un-differential dementia n=2</td>
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Propiverine
THE EFFECTS OF ANTI-CHOLINERGIC DRUGS FOR OVERACTIVE BLADDER ON COGNITIVE IMPAIRMENT, MENTAL DYSFUNCTION AND MOTOR DYSFUNCTION ON PATIENTS WITH NEUROLOGICAL DISEASES.

Uchiyama T, Sakakibara R, Liu Z, Yamamoto T, Hattori T

**Interpretation of the results/ concluding message**

The results suggest that propiverine has no significant effect on cognitive impairment, mental function and motor dysfunction in patients with neurological diseases, even in aged patients with dementia and motor dysfunction such as parkinsonism.

Therefore, propiverine could be used safely in patients with neurological diseases and OAB.
HOW TO MANAGE OVERACTIVE BLADDER IN ELDERLY INDIVIDUALS WITH DEMENTIA? A COMBINED USE OF DONEPEZIL, A CENTRAL ACETYLCHOLINESTERASE INHIBITOR, AND PROPIVERINE, A PERIPHERAL MUSCARINE RECEPTOR ANTAGONIST.

R. Sakakibara¹, T. Ogata², T. Uchiyama ¹ et al.
¹ Chiba University, Chiba, Japan; ² Toho University, Sakura, Japan

<table>
<thead>
<tr>
<th>Study design</th>
<th>Diagnosis</th>
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| n = 26 cognitively impaired older individuals  
mean age 78 ys  
male:female = 7:19 | With severe dementia including  
• Alzheimer's Disease n=7  
• Multiple Cerebral Infarction n=5  
• AD + Multiple Cerebral Infarction n=8  
• Frontotemporal dementia n=1  
• DLB n=5 |
| Already taking 5mg of donepezil per day for 7 months (range 3-20 months)  
All have OAB – therefore propiverine 20mg was added | |

Methods

- Bladder diary
- MMSE (Mini-mental State Examination, 0-30 scale)
- ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive subscale, 0-70 scale)

Were completed before and three months after the additional intake of propiverine
HOW TO MANAGE OVERACTIVE BLADDER IN ELDERLY INDIVIDUALS WITH DEMENTIA? A COMBINED USE OF DONEPEZIL, A CENTRAL ACETYLCHOLINESTERASE INHIBITOR, AND PROPIVERINE, A PERIPHERAL MUSCARINE RECEPTOR ANTAGONIST.

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Conclusions

The addition of 20mg propiverine per day to 5mg donepezil improved OAB without any cognitive change. This is in contrast to reports with tolterodine 4mg per day when given to patients on donepezil (5mg or 10mg) or on rivastigmine (6mg).

All patients developed delusion and agitation after starting with tolterodine therapy.

This combination therapy, AChE-Inhibitor + propiverine, could become an option in patients who suffer from dementia and OAB together.
The Dilemma with Antimuscarinics in OAB Patients treated with Cholinesterase-Inhibitors for Cognitive Impairment

Recommendation for the urologist

• Prefer antimuscarinics, which do not cross the BBB and/or bind less to M1 receptors close follow-up,
• Trospium does not cross the BBB, Darifenacin and Solifenacin are less bound to M1 receptors
• Studies with Propiverine and Trospium prove that they do not change cognitive function and that they can safely be added to cholinesterase inhibitors
• Avoid oral Oxybutynin
NDO & Antimuscarinics
Conclusions (1)

• Contrary to IDO and OAB, in NDO no remarkable placebo effects were demonstrated following placebo treatment.

• Only oxybutynin, propiverine and trospium chloride were evaluated in large placebo-controlled studies, demonstrating:
  - maximum detrusor pressure ↓ by 30% - 40%
  - maximum cystometric capacity ↑ by 30% - 40%

• Self-selected dosing of AM exceeding the recommended doses improved efficacy.
NDO & Antimuscarinics

Conclusions (2)

• Despite the fact that most patients with NDO are on AM medication life-long, long-term data were primarily assessed for IDO

• The effects of AM on quality of life should be investigated further

• Future studies should aim at incorporating not only urodynamic, but also the crucial clinical parameters, e.g. achievement of continence between catheterisations
Pharmacotherapy for Neurogenic LUT Dysfunction
Summary (1)

For the underactive detrusor
- no effective drug available

For the underactive sphincter
- no good studies for alpha-adrenergics
- no studies with duloxetine (which may work in incomplete lesions)

For the overactive sphincter
- Baclofen® may work but only in intolerably high dosages
- Alpha-blockers not recommended by NICE guidelines
- NO donors effective, but only in the acute experiment
For the overactive detrusor

- AM are the first-line treatment, adequately powered RCT-studies only with propiverine, trospium and oxybutynin
- Propiverine much better tolerated than oxybutynin
- CNS studies in neurologic patients favour (1) propiverine and (2) trospium
- No studies in NDO with Mirabegron