Systematic review of therapy for neurogenic detrusor overactivity

Clare J. Fowler, FRCP

Institute of Neurology, University College London, UK; Consultant, National Hospital for Neurology & Neurosurgery, London, UK

Cite as: *Can Urol Assoc J* 2011;5(5Suppl2):S146-S148; DOI:10.5489/cuaj.11187

Abstract

While many neurologic diseases predispose patients to neurogenic detrusor overactivity (NDO), the only populations that have been systematically studied are adults with multiple sclerosis (MS), adults with spinal cord injury (SCI) and children and young adults with myelodysplasia. First-line pharmacotherapy for NDO is an antimuscarinic drug. However, the evidence base for these agents in this indication is poor. There is some high-quality evidence for the efficacy of detrusor injections of botulinum toxin A in the treatment of NDO, with significant reduction in urgency incontinence episodes, improved urodynamic parameters, and improved quality of life. While few adverse events have been reported with this therapy, there is a need for intermittent self-catheterization in these groups.

Neurogenic detrusor overactivity (NDO) can be seen with various neurological diseases. At present, however, the only such populations that have been systematically studied are adults with multiple sclerosis (MS) and spinal cord injury (SCI) and children and young adults with myelodysplasia. There have yet to be any randomized, controlled studies evaluating therapy for NDO in Parkinson's Disease or dementia. This review will, therefore, focus on the available treatment evidence from the above-mentioned conditions.

Antimuscarinic therapy for neurogenic detrusor overactivity

The first-line, mainstay treatment of NDO is the antimuscarinic drugs. This practice is not, however, based on a great deal of high quality research. Indeed, the body of evidence for their efficacy based on randomized controlled trials (RCTs) is surprisingly poor. In total, there are only five Grade-A studies in adults.¹⁻⁵ These studies, which spanned from 1985 to 2007, examined the effect of oral propiverine, oxybutynin, trospium or propantheline or intravesical

atropine. The research in MS has also been reviewed in a systematic fashion in a Cochrane review published in 2009.⁶ In children with myelodysplasia, there are two RCTs^{7,8} and 11 observational studies.⁹⁻¹⁹

Looking at all this evidence, propiverine, trospium, oxybutynin, propantheline and tolterodine have all been shown to produce clinical and some evidence of urodynamic improvement in NDO. Although this evidence is sufficient to conclude that "antimuscarinics are effective in NDO," prescribing more recently introduced antimuscarinics is not evidence-based. Rather, there is an assumption that their demonstrated efficacy in non-neurogenic DO is "carried over" to the NDO group. Indeed, everyday clinical experience does seem to bear that assumption out and even suggests that antimuscarinics may in fact be more efficacious in NDO than in idiopathic DO and that their benefits are longer lasting.

Other oral therapies for neurogenic detrusor overactivity

Desmopressin

The evidence for efficacy of desmopressin in MS for treatment of nocturia and daytime frequency is level 1, based on the results of a meta-analysis published in 2005.²⁰ However, desmopressin does carry the risk of hyponatremia, particularly in older patients. The recommendation for patients over 65 years of age is to check serum Na levels at baseline and again at 3 days and 7 days after commencing treatment or changing dose.

Cannabinoids

Two studies have looked at the efficacy of cannabinoids on urinary problems in MS and evidence of limited efficacy was found. In one study with orally administered Δ^9 -tetrahydrocannabinol extract, researchers observed a reduction in incontinence episodes,²¹ while in another

study using oral nabiximols (Sativex), there were significant reductions in the number of episodes of nocturia, overall bladder control, number of voids/day and Patient's Global Impression of Change relative to placebo.²² Notably, in this latter study, the beneficial effects in reducing nocturia was related to severity of baseline episodes (Fig. 1).

Other oral therapies

To date, there are no data available for α -adrenoreceptor antagonists or phosphodiesterase inhibitors, nor the recently introduced β -adrenoreceptor antagonists in the neurogenic population.

Neurotoxins for neurogenic detrusor overactivity

Intravesical vanilloids

There is some lesser grade evidence for the use of intravesical vanilloids to treat NDO but no such preparations are currently licensed.^{23,24}

Botulinum toxin

Despite its relatively recent introduction, there is high-quality evidence for the efficacy of detrusor injections of Botulinum toxin A in the treatment of NDO in MS and SCI in adults and myelodysplasia in children and young people. There are three RCTs in adults which provide evidence for improvement in daily frequency of incontinence episodes and specific quality of life (QoL), and six observational longer-term studies show benefit is sustained. Eleven prospective observational studies in children show comparable efficacy.²⁵⁻³⁶

Moreover, the results of pivotal licensing studies of onabotulinumtoxin A in NDO are currently being presented in abstract form and are showing a significant reduction in urgency incontinence episodes, improved urodynamic parameters, and improved QoL.³⁷⁻⁴⁰ In the registration study presented at the European Association of Urology meeting in March 2011, a total of 154 patients with multiple sclerosis and 121 with spinal cord injury were randomized to receive onabotulinumtoxin A 200 U or 300 U or placebo.^{25,26} The researchers showed that both doses of onabotulinumtoxin A were associated with significant improvements vs. placebo in episodes of urgency incontinence, maximum cystometric capacity (MCC), maximum detrusor pressure (MDP), and quality of life.

Few adverse events have been reported, but the need for intermittent self-catheterization (ISC) in these groups of patients is an important consideration. In the registration study described above, 30% of the 200 U group and 42%

Fig. 1. Treatment of neurogenic detrusor overactivity with cannabinoid therapy: reduction in number of nocturia episodes related to severity of baseline episodes.

of the 300 U group required intermittent self-catheterization, compared to 12% of the placebo group.

Conclusions

The evidence base for antimuscarinics to treat NDO is poor despite these medications being those most commonly used in clinical practice in this group. Few other drugs have had demonstrated efficacy and, with the exception of desmopressin, are rarely prescribed. The evidence for the efficacy of detrusor injections of Botulinum toxin A is already at level 1. Emerging licensing studies make a strong case for this being a highly effective treatment for NDO but with a risk of the need for intermittent self-catheterization.

Competing interests: Dr. Fowler has received speaker fees from Allergan and Astellas, and an educational grant from Allergan.

This paper has been peer-reviewed.

References

- Gajewski JB, Awad SA. Oxybutynin versus propantheline in patients with multiple sclerosis and detrusor hyperreflexia. *J Urol* 1986;135:966-8.
- Madersbacher H, Stohrer M, Richter R, et al. Trospium chloride versus oxybutynin: A randomized, double-blind, multicentre trial in the treatment of detrusor hyper-reflexia. *Br J Urol* 1995;75:452-6.
- Stohrer M, Madersbacher H, Richter R, et al. Efficacy and safety of propiverine in SCI-patients suffering from detrusor hyperreflexia - A double-blind, placebo-controlled clinical trial. *Spinal Cord* 1999;37:196-200.
- Fader M, Glickman S, Haggard V, et al. Intravesical atropine compared to oral oxybutynin for neurogenic detrusor overactivity: a double-blind, randomized crossover trial. *J Urol* 2007;177:208-13.
- Stohrer M, Murtz G, Kramer G, et al. Propiverine compared to oxybutynin in neurogenic detrusor overactivity-results of a randomized, double-blind, multicenter clinical study. *Eur Urol* 2007;51:235-42.

6. Nicholas RS, Friede T, Hollis S, et al. Anticholinergics for urinary symptoms in multiple sclerosis. *Cochrane Database Syst Rev* 2009;1:CD004193.
7. Hehir M, Fitzpatrick JM. Oxybutynin and the prevention of urinary incontinence in spina bifida. *Eur Urol* 1985;11:254-6.
8. Kaplinsky R, Greenfield S, Wan J, et al. Expanded follow up of intravesical oxybutynin chloride use in children with neurogenic bladder. *J Urol* 1996;156(2:Pt 2):753-6.
9. Goessl C, Knispel HH, Fiedler U, et al. Urodynamic effects of oral oxybutynin chloride in children with myelomeningocele and detrusor hyperreflexia. *Urology* 1998;51:94-8.
10. Amark P, Bussman G, Eksborg S. Follow-up of long-time treatment with intravesical oxybutynin for neurogenic bladder in children. *Eur Urol* 1998;34:148-53.
11. Baskin LS, Kogan BA, Benard F. Treatment of infants with neurogenic bladder dysfunction using anticholinergic drugs and intermittent catheterisation. *Br J Urol* 1990;66:532-4.
12. Connor JP, Betrus G, Fleming P, et al. Early cystometrograms can predict the response to intravesical instillation of oxybutynin chloride in myelomeningocele patients. *J Urol* 1994;151:1045-7.
13. Painter KA, Vates TS, Bukowski TP, et al. Long-term intravesical oxybutynin chloride therapy in children with myelodysplasia. *J Urol* 1996;156:1459-62.
14. Palmer LS, Zebold K, Firlit CF, et al. Complications of intravesical oxybutynin chloride therapy in the pediatric myelomeningocele population. *J Urol* 1997;157:638-40.
15. Ferrara P, D'Aleo CM, Tarquini E, et al. Side-effects of oral or intravesical oxybutynin chloride in children with spina bifida. *BJU Int* 2001;87:674-7.
16. Franco I, Horowitz M, Grady R, et al. Efficacy and safety of oxybutynin in children with detrusor hyperreflexia secondary to neurogenic bladder dysfunction. *J Urol* 2005;173:221-5.
17. Schulte-Baukloh H, Murtz G, Henne T, et al. Urodynamic effects of propiverine hydrochloride in children with neurogenic detrusor overactivity: a prospective analysis. *BJU Int* 2006;97:355-8.
18. Reddy PP, Borgstein NG, Nijman RJ, et al. Long-term efficacy and safety of tolterodine in children with neurogenic detrusor overactivity. *J Pediatr Urol* 2008;4:428-33.
19. Madersbacher H, Murtz G, Alloussi S, et al. Propiverine vs oxybutynin for treating neurogenic detrusor overactivity in children and adolescents: results of a multicentre observational cohort study. *BJU Int* 2009;103:776-81.
20. Bosma R, Wynia K, Havliková E, et al. Efficacy of desmopressin in patients with multiple sclerosis suffering from bladder dysfunction: a meta-analysis. *Acta Neural Scand* 2005;112:1-5.
21. Freeman RM, Adeganmi O, Waterfield MR, et al. The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial (CAMS-LUTS). *Int Urogynecol J Pelvic Floor Dysfunct* 2006;17:636-41.
22. Kavia RB, De Ridder D, Constantinescu CS, et al. Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis. *Mult Scler* 2010;16:1349-59.
23. de Sèze M, Wiart L, Ferrière J, et al. Intravesical instillation of capsaicin in urology: A review of the literature. *Eur Urol* 1999;36:267-77.
24. MacDonald R, Monga M, Fink HA, et al. Neurotoxin treatments for urinary incontinence in subjects with spinal cord injury or multiple sclerosis: a systematic review of effectiveness and adverse effects. *J Spinal Cord Med* 2008;31:157-65.
25. Neel KF, Saliman S, Salem M, et al. Botulinum-A toxin: solo treatment for neuropathic noncompliant bladder. *J Urology* 2007; 178(6):2593-7., et al. Repeated botulinum-A toxin injections in treatment of children with neurogenic detrusor overactivity. *Urology* 2005; 66(4):865-70.
26. Schulte-Baukloh H, Knispel HH, et al. Repeated botulinum-A toxin injections in treatment of children with neurogenic detrusor overactivity. *Urology* 2005;66:865-70.
27. Altaaweel W, Jednack R, Bilodeau C, et al. Repeated intradetrusor botulinum toxin type A in children with neurogenic bladder due to myelomeningocele. *J Urology* 2006;175:1102-5.
28. Akbar M, Abel R, Seyler TM, et al. Repeated botulinum-A toxin injections in the treatment of myelodysplastic children and patients with spinal cord injuries with neurogenic bladder dysfunction. *BJU Int* 2007;100:639-45. Erratum in: *BJU Int* 2007;100:719. Bedke, Jens [added]; Haferkamp, Axel [added].
29. Deshpande AV, Sampang R, Smith GH. Study of botulinum toxin A in neurogenic bladder due to spina bifida in children. *ANZ J Surgery* 2010;80:250-3.
30. Do N, Audry G, Forin V. Botulinum toxin type A for neurogenic detrusor overactivity due to spinal cord lesions in children: a retrospective study of seven cases. *J Pediatric Urology* 2009;5:430-6.
31. Kajbafzadeh AM, Moosavi S, Tajik P, et al. Intravesical injection of botulinum toxin type A: management of neuropathic bladder and bowel dysfunction in children with myelomeningocele. *Urology* 2006;68:1091-6.
32. Riccabona M, Koen M, Schindler M, et al. Botulinum-A toxin injection into the detrusor: a safe alternative in the treatment of children with myelomeningocele with detrusor hyperreflexia. *J Urology* 2004;171:845-8.
33. Schulte-Baukloh H, Knispel HH, Stolze T, et al. Repeated botulinum-A toxin injections in treatment of children with neurogenic detrusor overactivity. *Urology* 2005;66:865-70.
34. Schulte-Baukloh H, Michael Th, Sturzebecher B, et al. Botulinum-A toxin detrusor injection as a novel approach in the treatment of bladder spasticity in children with neurogenic bladder. *Eur Urology* 2003;44:139-43.
35. Schulte-Baukloh T, Scobert J, Stolze, et al. Efficacy of Botulinum-A toxin in children with detrusor hyperreflexia due to myelomeningocele: preliminary results. *Urology* 2002;59:325-7.
36. Schurch B, Schulte-Baukloh H. Botulinum toxin in the treatment of neurogenic bladder in adults and children. *European Urology, Supplements* 2006;5:679-84.
37. Cruz F, Herschorn S, Heesakkers, et al. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity [abstract]. Presented at the 2011 Annual Meeting of the European Association of Urology.
38. Ginsberg D, Gousse A, Keppenne V, et al. Phase 3 Efficacy and Safety Study of OnabotulinumtoxinA in Patients With Urinary Incontinence Due to Neurogenic Detrusor Overactivity [abstract]. Presented at the 2011 Annual Meeting of the American Urological Association.
39. Mengheang L, Hairston J, Smith C. Efficacy of OnabotulinumtoxinA in Patients with Neurogenic Bladder and Decreased Bladder Compliance [abstract]. Presented at the 2011 Annual Meeting of the American Urological Association.
40. Chancellor M, Patel V, Leng W, et al. OnabotulinumtoxinA in Patients With Urinary Incontinence Due to Neurogenic Detrusor Overactivity: Effects on Health-Related Quality of Life [abstract]. Presented at the 2011 Annual Meeting of the American Urological Association.

Correspondence: Dr. Clare J. Fowler, F.R.C.P., Institute of Neurology and Institute of Urology, UCL, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK, England WC1N 3BG; c.fowler@ion.ucl.ac.uk