The Role of Antimuscarinics in the Treatment of Neurogenic Detrusor Overactivity in Patients with Stroke, Spinal Cord Injury and Parkinson's Disease

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ABSTRACT

Voiding dysfunction with nocturia, frequency, and urgency with or without incontinence are common clinical manifestations in patients with cerebrovascular accident, Parkinson's disease and spinal cord injury. Neurogenic overactive bladder (OAB) is usually associated with detrusor overactivity (DO) with or without sphincter dysfunction and is caused by various diseases or events affecting central and peripheral nervous system control of the lower urinary tract. The International Continence Society (ICS) (2002) defined neurogenic detrusor overactivity (NDO) as "a urodynamic observation characterized by involuntary detrusor contractions during the filling stage, which may be spontaneous or provoked." A diagnosis of neurogenic detrusor overactivity depends on a detailed history, physical examination and urodynamic studies. Urodynamic study is the best tool to assess and classify detrusor activity. The goals of treatment are reduction of both intravesical pressure and the postvoid residual in order to restore urinary continence and lower urinary tract function, to prevent upper tract damage and to improve the patient's quality of life. Treatment strategy is based on whether the patient has urinary storage failure, impaired emptying function or a combination of both problems. Flexible doses of antimuscarinics, with additional clean intermittent catheterization (CIC), are effective in symptom relief and prevention of deterioration of upper tract function. Close monitoring of the postvoid residual is recommended among patients with NDO and impaired contraction. This article will review the pathogenesis of NDO and discuss the role of antimuscarinics in its optimal treatment. *Key words:* cerebrovascular accident, neurogenic detrusor overactivity, overactive bladder, Parkinson's disease, spinal cord injury, urinary incontinence.

INTRODUCTION

Overactive bladder (OAB) is a syndrome consisting of urinary urgency, usually with frequency and nocturia, with or without urge incontinence. OAB is a common lower urinary tract dysfunction affecting both men and women [1]. Neurogenic overactive bladder is a subgroup of OAB syndrome resulting from a variety of neurologic injuries or diseases. Neurogenic OAB is usually associated with detrusor overactivity (DO) with or without sphincter dysfunction. The term "neurogenic detrusor overactivity (NDO)" has replaced "detrusor hyperreflexia" according to International Continence Society (ICS) terminology standardization in 2002 [2]. The ICS defined NDO as "a urodynamic observation characterized by involuntary detrusor contractions during the filling stage, which may be spontaneous or provoked." Patients with NDO usually have urgency, frequency, nocturia or incontinence. Urodynamic study is the best tool to assess and classify detrusor activity. Acetylcholine is the main neurotransmitter during detrusor muscle contraction. Antimuscarinics have been used extensively as competitive antagonists with acetylcholine in muscarinic receptors to treat OAB or DO in daily clinical practice. Their main effect depends on competitive inhibition of muscarinic receptors, mainly M_2 and M_3 with acetylcholine binding over the neuromuscular junctions on the detrusor muscle of urinary bladder [3]. Patients with NDO treated with antimuscarinics are usually a challenge for clinicians because of poor effectiveness and interpersonal variations [4]. The pathogenesis of NDO and the role of antimuscarinic in its optimal treatment will be discussed in this mini-review.

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The central & peripheral nervous systems and urinary bladder function

The functions of the urinary bladder, including storage and voiding, are closely regulated by the central and peripheral nervous systems. Normal storage function depends on intact coordination of both autonomic (S_2-S_4 parasympathetic nerves & T_{10}-L_2 sympathetic nerves) and somatic innervations (S_2-S_4 pudendal nerve) of the urinary bladder and urethra. The afferent signals generated from urinary bladder distension are conveyed to the spinal micturition center (S_2-S_4) via the pelvic and hypogastric nerves [5]. These signals are then conveyed to the higher central nervous system (CNS) including the pons and cortex. During the storage phase, there is an inhibition of parasympathetic impulse and activation of both the smooth and striated urethral sphincters in response to stimulated afferent signals conveyed from the pelvic nerves. This inhibition control during the storage phase may result from modulation of pontine micturition center (PMC) activity via inhibitory impulses from the higher central nervous centers, including the cortical and brain stem areas. During the voiding phase, abolition of these inhibitory impulses triggers efferent impulses from the cortex and pontine micturition center to the sacral parasympathetic nucleus (S_2-S_4). Detrusor muscle contraction is then initiated via release of acetyl-

choline and nonadrenergic noncholinergic transmitters (mostly adenosine triphosphate, ATP) [6-8].

Common causes of neurogenic detrusor overactivity

The process of bladder control is highly complex and depends on the integrity of both the central and peripheral nervous systems. NDO can be caused by various diseases or events affecting central and peripheral nervous system control of the lower urinary tract (Table 1).

Cerebrovascular accident (CVA), Parkinson's disease (PD) and spinal cord injuries (SCI) are common causes of NDO. The incidence of urinary incontinence after CVA ranges from 38% to 60% [9,10]. Urinary incontinence presenting after an acute stroke is associated with a high mortality rate and is the best single indicator of disability [11,12]. Stroke patients with urinary incontinence usually have large infarcts, aphasia, cognition impairment and functional disability. The possible underlying mechanisms for the development of post-stroke urinary incontinence include disruption of the neuro-micturition pathway, stroke-related cognition or speech deficits, concurrent neuropathy and medication use [13,14].

In a recent survey, patients with PD also had a higher prevalence of urinary symptoms than normal controls (39.3% vs 10.8%). Most urinary symptoms were irritative, and the most common symptom was nocturia (63.9%), followed by frequency (36.1%), urgency (32.8%) and incomplete emptying (18.0%) [15]. The degree of LUTS in PD patients is correlated with the severity of PD rather than the duration of PD or age [16].

Voiding dysfunction is also a common clinical manifestation in patients with SCI. The pattern of voiding dysfunction is significantly associated with the level of injury. In a retrospective review, suprasacral injuries resulted in hyperreflexia in 94.9% of patients, low compliance (<12.5 mL/cm of water) and /or detrusor sphincter dyssynergia (DSD) in 41.8% and a high detrusor leak point pressure (>40 cm of water) in 40.3%. For patients with sacral injuries, 85.7% had areflexia, 78.6% had poor compliance and 85.7% had a high detrusor leak point pressure [17].

Table 1. Common causes of neurogenic urinary tract dysfunction

Peripheral neuropathy
• Diabetic neuropathy
• Alcohol abuse
• Pelvis plexus injury (surgery or trauma)
• Genital herpes zoster infection
Central neuropathy - spinal cord
• Spinal cord injury
• Herniated intervertebral disc disease
• Multiple sclerosis
• Poliomyelitis
• Transverse myelitis
• Myelomeningocele
• Spinal bifida
• Tethered cord syndrome
• Guillain-Barre syndrome
Central neuropathy - brain
• Cerebrovascular accident
• Parkinson's disease
• Frontal brain tumors
• Dementia
• Cerebral palsy
• Multiple system atrophy

Diagnosis of neurogenic detrusor overactivity

The diagnosis of neurogenic detrusor overactivity depends on a detailed history, physical examination and urodynamic studies. Noninvasive image studies such as renal ultrasonography or bladder ultrasonography are helpful in evaluating the condition of the upper and lower urinary tracts, respectively. Sonography can evaluate the kidney size, diameter of the renal parenchyma, bladder wall outline and the presence of hydronephrosis or stones, bladder trabeculation and diverticulum. In selective cases, radiologic image studies may be needed for confirmation of reflux, urolithiasis, spinal anomalies, bladder neck abnormalities and urethral anomalies [18]. Questions about neurological and congenital abnormalities, frequency of urinary tract infection and relevant surgery should be asked and clarified. The detailed history should also include assessment of urinary, menstrual, sexual and bowel function and an obstetric history. Urinary history should include LUTS, previous voiding pattern, urinary incontinence, bladder sensation and type/mode of voiding. A complete neurological examination should be done including S_2-S_5 sensation, reflexes, anal tone, pelvic floor voluntary contractions, prostate palpation and descensus of pelvic organs [18]. Basic urodynamic studies such as cystometry and uroflowmetry in combination with electromyography are helpful in assessing detrusor activity, compliance, sensation, capacity and the status of coordination in the external sphincter and striated pelvic floor muscles. A detrusor leak point pressure over 40 cm of water increases the risk of upper tract deterioration in patients with neurogenic voiding dysfunction [19].

Goals of treatment for neurogenic detrusor overactivity

Neurogenic detrusor overactivity with a dyssynergic sphincter produces high intravesical pressures and large postvoid residuals, leading to progressive bladder trabeculation, vesicoureteral reflux and renal function impairment. Management should focus on restoration of normal detrusor activity and suppression of dyssynergia. The goals of treatment are reduction of both the intravesical pressure and postvoid residual in order to restore urinary continence and lower urinary tract function, to prevent upper tract damage and to improve the patient's quality of life [4]. Many treatments of choice including surgical and non-surgical methods can be used to achieve these goals. Treatment strategy is based on whether the patient has urinary storage failure, impaired emptying function or a combination of both problems [20]. Clean intermittent catheterization (CIC) and antimuscarinics are still the main treatment choices for patients with emptying impairment and NDO, respectively. But each treatment should also be individualized with regard to the range of disability, the patient's mental and physical condition and the status of urinary tract function [21]. Only antimuscarinics will be discussed in this mini-review.

THE ROLE OF ANTIMUSCARINICS IN THE TREATMENT OF NEUROGENIC DETRUSOR OVERACTIVITY

Muscarinic receptors and neurogenic detrusor overactivity

Antimuscarinics inhibit the binding of acetylcholine to muscarinic receptors in the detrusor muscle, resulting in a reduction of involuntary

detrusor contractions and an increase in bladder capacity. The other possible mechanism may involve blocking acetylcholine to muscarinic receptors in the bladder mucosa and submucosa to suppress sensory pathways [8,22,23]. Five distinct genes encoding muscarinic receptor subtypes (M_{1-5}) have been identified pharmacologically [24]. The muscarinic receptors found in the human detrusor are of the M_2 and M_3 subtypes. The M_2 receptors predominate in number over M_3 receptors, but the M_3 receptors are responsible for detrusor muscle contractions [3,23]. Blocking of the M_2 or M_3 receptors in the urothelium may affect bladder afferent impulses and reduce overactive bladder symptoms [8,25,26].

Antimuscarinics in the treatment of neurogenic detrusor overactivity

Antimuscarinics have been used to relieve overactive bladder symptoms for years. There are several antimuscarinics with different pharmacologic characteristics available in clinical practice (Table 2). These antimuscarinics can inhibit involuntary detrusor contractions and increase the bladder capacity and compliance. In a systemic review of 32 clinical trials which included more than 6,800 participants with OAB, antimuscarinics effectively lessened incontinence episodes (0.6, 95%CI 0.4-0.8), number of voids in 24 hours (0.6, 95%CI 0.4-0.8) and increased maximum cystometric capacity (54 mL, 95%CI 43-66). The observed difference in treatment effectiveness between antimuscarinics and placebos was of a lesser magnitude than expected from clinical experience [27]. The use of antimuscarinics is also hindered by their anticholinergic side effects such as dry mouth, constipation, headache, dizziness, somnolence and abnormal vision [3]. The search for the "ideal" antimuscarinic is underway but improvements in formulation with the use of oral extended-release, intravesical solution, patch and gel forms have substantially decreased the incidence of anticholinergic side effects with comparative effectiveness [28].

Muscarinic receptors and cognition function

The other neglected issue in antimuscarinic treatment for elderly NDO patients is the influence on CNS functions, especially cognition function. Patients with NDO present a subgroup of patients with poorer responses to antimuscarinics. The treatment response might be further compromised by cognition impairment from antimuscarinics and disabilities from underlying neurological diseases. Cognition function had been linked to muscarinic receptors, especially M_1 and M_2 receptors, in the CNS. Post-stroke urinary incontinence with impaired awareness usually indicates greater brain damage and a poorer prognosis than urge urinary incontinence alone [14]. Ideal antimuscarinics should have limited CNS penetration and higher selectivity for M_3 over M_1 and M_2 receptors [29].

Antimuscarinics and urinary retention

Higher doses of antimuscarinics have been used to treat patients with NDO who are refractory to ordinary antimuscarinic therapy. In a prospective study, about 74.4% of patients with NDO requested higher doses for symptom relief [30]. The major safety concern with higher doses is compromise in detrusor contraction resulting in urinary retention. Antimuscarinics are contraindicated in patients with urinary retention, gastric retention, other severe decreased gastrointestinal mobility conditions, and uncontrolled narrow-angle glaucoma, and in patients who are at risk for these conditions. Patients with neurogenic detrusor hyperactivity are also susceptible to impaired contractile function (DHIC). In a retrospective study, about 18% of PD patients and 15% of patients with spinal cord lesions had DHIC [31,32]. Antimuscarinics should be used very carefully in NDO patients with residual urine. Flexible doses of antimuscarinics in combination with CIC or intravesical antimuscarinic instillation has been suggested to achieve optimal efficacy and tolerability and reduce anticholinergic adverse effects [30,33-35]. Combined use of alpha blockers and antimuscarinics has also been reported in the treatment of neurogenic voiding dysfunction. The possible mechanism may be related to reduction of bladder outlet resistance and increase bladder capacity [36]. But further large-scale clinical studies are needed to confirm the effectiveness and safety profiles before recommendations for extensive usage in clinical practice.

CONCLUSIONS

Voiding dysfunction with nocturia, frequency, and urgency with or without incontinence are common clinical manifestations among patients with CVA, PD and SCI. The majority of these patients have detrusor overactivity diagnosed by urodynamic studies. The presence of neurogenic detrusor overactivity (NDO) has been associated with the prognosis of stroke and severity of PD. NDO with a high bladder leak point pressure (>40 cm of water) may further compromise renal function. The goal of treatment is reduction of both intravesical pressure and the postvoid residual in order to restore urinary continence and lower urinary tract function, to prevent upper tract damage and to improve the

Table 2. Antimuscarinics with different pharmacokinetic characters

	Molecular weigh/structure	Metabolizing enzymes	Active metabolite	Half-life (hours)
Oxybutynin IR/ER	357.5/tertiary amines	CYP3A4	N-Desethyloxybutynin	2/13
Tolterodine IR/ER	475.6/tertiary amines	CYP3A4 CYP2D6	5-hydroxy-methyl-Tolterodine	2/8
Propiverine IR/ER	403.9/tertiary amines	CYP3A4 CYP2D6	Propiverine N-oxide	15-20
Solifenacin	408.5/tertiary amines	CYP3A4	None	45-68
Darifenacin	507.5/tertiary amines	CYP3A4 CYP2D6	None	12
Trospium	427.9/quaternary amines	Ester hydrolysis	None	20
Oxybutynin transdermal	357.5/tertiary amines	CYP3A4	N-Desethyloxybutynin	7-8

patient's quality of life. Flexible doses of antimuscarinics, with CIC are effective in symptom relief and prevention of upper tract function deterioration. Close monitoring of the postvoid residual is recommended in NDO patients with impaired contraction. The influence of antimuscarinics on cognition function should take into consideration when prescribing antimuscarinics in the geriatric population with NDO.

REFERENCES

1. Wein AJ, Rovner ES: Definition and epidemiology of overactive bladder. Urology 2002; **60**:7-12.
2. Abrams P, Cardozo L, Fall M, et al: The standardisation of terminology of lower urinary tract function: Report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002; **21**:167-178.
3. Abrams P, Andersson K-E: Muscarinic receptor antagonists for overactive bladder. BJU Int 2007; **100**:987-1006.
4. Chancellor MB, Anderson RU, Boone TB: Pharmacotherapy for neurogenic detrusor overactivity. Am J Phys Med Rehabil 2006; **85**: 536-545.
5. Andersson K-E, Pehrson R: CNS involvement in overactive bladder: Pathophysiology and opportunities for pharmacological intervention. Drugs 2003; **63**:2595-2611.
6. De Groat WC: Anatomy of the central neural pathways controlling the lower urinary tract. Eur Urol 1998; **34(Suppl 1)**:2-5.
7. Podnar S: Neurophysiology of the neurogenic lower urinary tract disorders. Clin Neurophysiol 2007; **118**:1423-1437.
8. Yoshimura N: Lower urinary tract symptoms (LUTS) and bladder afferent activity. Neurourol Urodyn 2007; **26**:908-913.
9. Brocklehurst JC, Andrews K, Richards B, Laycock PJ: Incidence and correlates of incontinence in stroke patients. J Am Geriatr Soc 1985; **33**:540-542.
10. Borrie MJ, Campbell AJ, Caradoc-Davies TH, Spears GF: Urinary incontinence after stroke: A prospective study. Age Ageing 1986; **15**:177-1781.
11. Marinkovic S, Badlani G: Voiding and sexual dysfunction after cerebrovascular accidents. J Urol 2001; **165**:359-370.
12. Taub NA, Wolfe CD, Richardson E, Burney PG: Predicting the disability of first-time stroke sufferers at 1 year. 12-month follow-up of a population-based cohort in southeast England. Stroke 1994; **25**: 352-357.
13. Gelber DA, Good DC, Laven LJ, Verhulst SJ: Causes of urinary incontinence after acute hemispheric stroke. Stroke 1993; **24**:378-382.
14. Pettersen R, Stien R, Wyller TB: Post-stroke urinary incontinence with impaired awareness of the need to void: Clinical and urodynamic features. BJU Int 2007; **99**:1073-1077.
15. Campos-Sousa RN, Quagliato E, da Silva BB, de Carvalho RM, Jr., Ribeiro SC, de Carvalho DFM: Urinary symptoms in Parkinson's disease: Prevalence and associated factors. Arq Neuropsiquiatr 2003; **61**:359-363.
16. Araki I, Kuno S: Assessment of voiding dysfunction in Parkinson's disease by the international prostate symptom score. J Neurol Neurosurg Psychiatry 2000; **68**:429-433.
17. Weld KJ, Dmochowski RR: Association of level of injury and bladder behavior in patients with post-traumatic spinal cord injury. Urology 2000; **55**:490-494.
18. Stohrer M, Goepel M, Kondo A, et al: The standardization of terminology in neurogenic lower urinary tract dysfunction: With suggestions for diagnostic procedures. International Continence Society Standardization Committee. Neurourol Urodyn 1999; **18**:139-158.
19. McGuire EJ, Cespedes RD, O'Connell HE: Leak point-point pressures. Urol Clin North Am 1996; **23**:253-262.
20. Jamil F: Towards a catheter free status in neurogenic bladder dysfunction: A review of bladder management options in spinal cord injury (SCI). Spinal Cord 2001; **39**:355-361.
21. Wyndaele JJ, Madersbacher H, Kovindha A. Conservative treatment of the neuropathic bladder in spinal cord injured patients. Spinal Cord 2001; **39**:294-300.
22. Hawthorn MH, Chapple CR, Cock M, Chess-Williams R: Urothelium-derived inhibitory factor(s) influences on detrusor muscle contractility in vitro. Br J Pharmacol 2000; **129**:416-419.
23. Andersson KE, Yoshida M: Antimuscarinics and the overactive detrusor--which is the main mechanism of action? Eur Urol 2003; **43**: 1-5.
24. Caulfield MP, Birdsall NJ: International Union of Pharmacology. XVII. Classification of muscarinic acetylcholine receptors. Pharmacol Rev 1998; **50**:79-90.
25. Andersson K-E: Bladder activation: Afferent mechanisms. Urology 2002; **59**:43-50.
26. Iijima K, De Wachter S, Wyndaele J-J: Effects of the M_3 receptor selective muscarinic antagonist darifenacin on bladder afferent activity of the rat pelvic nerve. Eur Urol 2007; **52**:842-847.
27. Herbison P, Hay-Smith J, Ellis G, Moore K: Effectiveness of anticholinergic drugs compared with placebo in the treatment of overactive bladder: Systematic review. BMJ 2003; **326**:841-844.
28. Ouslander JG: Management of overactive bladder. N Engl J Med 2004; **350**:786-799.
29. Kay GG, Abou-Donia MB, Messer WS, Jr., Murphy DG, Tsao JW, Ouslander JG: Antimuscarinic drugs for overactive bladder and their potential effects on cognitive function in older patients. J Am Geriatr Soc 2005; **53**:2195-2201.
30. Bennett N, O'Leary M, Patel AS, Xavier M, Erickson JR, Chancellor MB: Can higher doses of oxybutynin improve efficacy in neurogenic bladder? J Urol 2004; **171**:749-751.
31. Resnick NM, Yalla SV: Detrusor hyperactivity with impaired contractile function. An unrecognized but common cause of incontinence in elderly patients. JAMA 1987; **257**:3076-3081.
32. Yamamoto T, Sakakibara R, Uchiyama T, et al: Neurological diseases that cause detrusor hyperactivity with impaired contractile function. Neurourol Urodyn 2006; **25**:356-360.
33. Tyagi P, Tyagi S, Kaufman J, Huang L, de Miguel F: Local drug delivery to bladder using technology innovations. Urol Clin North Am 2006; **33**:519-530.
34. Reitz A, Schurch B: Intravesical therapy options for neurogenic detrusor overactivity. Spinal Cord 2004; **42**:267-272.
35. Horstmann M, Schaefer T, Aguilar Y, Stenzl A, Sievert KD: Neurogenic bladder treatment by doubling the recommended antimuscarinic dosage. Neurourol Urodyn 2006; **25**:441-445.
36. Ruggieri MR Sr, Braverman AS, Pontari MA: Combined use of α-adrenergic and muscarinic antagonists for the treatment of voiding dysfunction. J Urol 2005; **174**:1743-1748.