Intravesical Treatment for Overactive Bladder Refractory to Antimuscarinics

Hann-Chorng Kuo, M.D.

Department of Urology, Buddhist Tzu Chi General Hospital and Tzu Chi University, Hualien, Taiwan

ABSTRACT

Overactive bladder (OAB) is a symptom syndrome characterized by urgency frequency with or without urgency incontinence. The pathophysiology of OAB may involve parasympathetic efferent activity or afferent nerves which cause detrusor overactivity (DO) and sensory urgency. The traditional medication for OAB is antimuscarinic agents which target the muscarinic receptors not only on detrusor muscles but also on the sensory afferent nerves of the bladder. Intravesical treatment to inhibit abnormal receptor expression or transmitter release in the sensory nerve terminals in the suburothelial space might provide good therapeutic effects in the treatment of refractory OAB. Intravesical administration of antimuscarinics such as oxybutynin and tolterodine has been shown effective in increasing bladder capacity and decreasing incontinence episodes in patients with OAB. However, the need of daily intermittent transurethral catheterization and short therapeutic duration limited its wide application. Intravesical resiniferatoxin (RTX) instillation and intravesical botulinum toxin A (BTX-A) injection are two treatment alternatives for refractory OAB and have been demonstrated to have long-term effects. RTX at low concentrations can decrease sensory urgency without influencing detrusor contractility. BTX-A, however, has a substantial effect on detrusor contractility resulting in a large postvoid residual after injections.

Key words: overactive bladder, intravesical treatment, urodynamics

INTRODUCTION

Overactive bladder (OAB) is a symptom syndrome characterized by urgency frequency with or without urgency incontinence [1]. The prevalence of OAB has been estimated to be present in 16% of people in Europe and is highly prevalent in women [2]. In Taiwan, about 10% of men and women have symptoms suggestive of OAB [3]. The pathophysiology of OAB may involve parasympathetic efferent activity or afferent nerves which cause detrusor overactivity (DO) and sensory urgency. Patients may have spontaneous or provoked detrusor contractions during bladder filling phase or before bladder capacity is reached.

The traditional treatment for OAB is medication by an antimuscarinic agent such as oxybutynin, tolterodine, propiverine, tropspium, solifenacin or duloxetin which targets the muscarinic receptors. Despite the development of new antimuscarinic agents, many patients are refractory to oral therapy [4] or cannot tolerate the oral antimuscarinics [5]. Recent investigations have revealed that muscarinic receptors, mAChRs, are present in the urothelium and suburothelial sensory fibers as well as in the detrusor [6]. Acetylcholine (ACh) may mediate both sensory input as well as detrusor contractility. Activation of mAChRs located near the luminal surface of the bladder affects voiding functions via mechanisms involving adenosine triphosphate (ATP) and nitric oxide (NO) release, presumably from the urothelium, which in turn could act on bladder C-fiber afferent nerves to alter their firing properties. These findings suggest that urothelial-afferent nerve interactions can influence reflex voiding function [6]. The blockade of muscarinic receptors, possibly mediated by muscarinic 2 (M_2) receptors residing in the urothelium, has been shown to affect bladder afferent fibers, challenging the traditional concept that antimuscarinic therapy involves M_3 receptor-mediated effects on detrusor smooth muscle [7].

Received: November 16, 2008 Accepted: December 9, 2008
Address correspondence to: Dr. Hann-Chorng Kuo, Department of Urology, Buddhist Tzu Chi General Hospital, 707, Section 3, Chung Yang Road, Hualien, Taiwan
E-mail: hck@tzuchi.com.tw

PATHOPHYSIOLOGY OF OAB

Patients with neurogenic detrusor overactivity (NDO) or idiopathic DO (IDO) were found to have increased suburothelial expression of the vanilloid receptor, transient receptor potential vanilloid receptor subtype 1 (TRPV1) [8], purinergic receptor $P2X_3$ [9], sensory neuropeptides substance P and calcitonin gene-related peptide (CGRP) [10]. Increased density of suburothelial substance P and CGRP immunoreactive fibers aere also found in women with IDO compared to controls [11]. The urothelial release of neurotransmitters such as ACh, ATP and the neuropeptide substance P, and the expression of TRPV1 and $P2X_3$ receptors strongly imply a role for the urothelium in human bladder mechanosensation [12-14]. Recent investigations also discovered a suburothelial nexus of myofibroblasts or interstitial cells may be the substrate for a stretch-receptor organ. These cells are extensively linked by gap junctions and may respond to ATP in a mode similar to the activation of ATP-gated P2Y receptors [15,16]. The urothelial release of ACh and ATP on bladder filling increases with ageing [12], implicating an abnormal release of these neurotransmitters in the pathophysiology of DO. In treatment of IDO with intravesical injections of botulinum toxin type A (BTX-A), decreased immunoreactivity of $P2X_3$ expression in suburothelial fibers was noted, which correlated with improvement in patients' sensation of urgency [11].

Based on results from recent investigations, OAB might have a pathophysiology in the abnormality of expression of sensory receptors or release of transmitters in the suburothelial nerves or interstitial cells [17]. In this regard, intravesical treatment to inhibit receptor expression or transmitter release in the sensory nerve terminals in the suburothelial space might provide good therapeutic effects in the treatment of sensory urgency and DO.

Intravesical agents for OAB have long been used in treatment of patients with neurogenic voiding dysfunction (NVD). Patients with severe NDO might develop large postvoid residual (PVR) after intravesical treatment and clean intermittent self-catheterization (CISC) might be necessary although they could regain continence or decrease epi-

sodes of urinary incontinence. Nevertheless, intravesical treatment has emerging an attractive alternative therapeutic modality for OAB refractory to conventional antimuscarinic agents.

INTRAVESICAL ANTIMUSCARINICS OR LOCAL ANESTHETICS

Current reported agents used for intravesical treatment of refractory OAB include oxybutynin, trospium, atropine and lidocaine and bupivacaine. Intravesical oxybutynin has some local anesthetic effect in addition to blocking cholinergic transmission [18]. Intravesical oxybutynin is an effective and relatively safe option of therapy for OAB [19]. Oxybutynin can be absorbed from the bladder after intravesical administration. The serum concentrations of oxybutynin after single 5 mg intravesical instillation are at least as high as those reported after oral drug intake, but the parent drug/metabolite ratio is much higher after intravesical administration. The elimination of oxybutynin as well as its metabolite is prolonged after intravesical administration [20].

Intravesical administration of tolterodine significantly increased bladder capacity in vehicle treated rats with cerebral infarction but had no effect on the bladder capacity in resiniferatoxin (RTX) treated rats with cerebral infarction. The study demonstrated that intravesical tolterodine exerts an inhibitory effect on C-fiber bladder afferent nerves [21]. Another study investigating intravesical antimuscarinics on sensory and motor effects of rat bladder also demonstrated that the effects of antimuscarinics on OAB not only by suppression of muscarinic-mediated detrusor muscle contractions, but also by blocking muscarinic receptors in bladder afferent pathways [22].

An interesting study investigated the effects of intravesical cyclooxygenase-2 (COX-2) inhibitor on the expression of inducible nitric oxide synthase (iNOS) and nerve growth factor (NGF) in cyclophosphamide (CYP) induced OAB. In the COX-2 inhibitor-treated rats the contraction interval and intercontractile interval were significantly longer than in the OAB rats. In the OAB rats NGF activity in the mucosa and submucosa were increased, and there was greater expression of iNOS in all layers and NGF in detrusor. In the COX-2 inhibitor-treated rats, the expression was less in all layers. The study demonstrated intravesical instillation with COX-2 inhibitors can reduce CYP-induced bladder hyperactivity and expression of iNOS and NGF. This study provides evidence that OAB might be a chronic inflammatory process involving COX-2 and iNOS pathway and, therefore, intravesical instillation with COX-2 inhibitors can be considered as a promising treatment for refractory OAB [23].

Intravesical atropine and local anesthetic agents have been demonstrated to increase bladder capacity. In a study comparing intravesical atropine and oral oxybutynin for NDO revealed no significant difference in the changes of incontinence events and voiding frequency between two arms, but the changes in total side effect and dry mouth scores were significantly better in the atropine treatment arm [24]. However, the effect of intravesical atropine or local anesthetic is short-lived and is not considered suitable for clinical use [25]. The necessity of daily CISC and administering the agent also limit their use in treating refractory OAB. Therefore, searching for intravesical agents which have long-term effect on refractory OAB seems mandatory.

INTRAVESICAL RESINIFERATOXIN

The vanilloid receptors TRPV1 participating in normal bladder function are essential for normal mechanically evoked purinergic signaling by the urothelium and is involved in ATP release [26]. In conditions of NDO and IDO, there is up-regulation of unmyelinated nerve fibers expressing vanilloid receptors [8]. Successful treatment with RTX for patients with DO depend on presence of over-expression of vanilloid receptors on the sensory fibers in the bladder [27]. Instillation of RTX can sensitize the vanilloid receptors on the sensitive fibers resulting in an acute excitatory response and the disappearance of spontaneous detrusor contractions during bladder filling later on [28]. In rat bladders pretreated with capsaicin to desensitize C-fiber afferent nerves, the excitatory effects of intravesical administration of the mAChR agonist oxotremorine methiodide, which were blocked by mAChR antagonist atropine methyl nitrate, were absent, suggesting that urothelialafferent nerve interactions can influence reflex voiding function and the mechanisms involving ATP and NO release presumably from the urothelium [6].

Previous investigations in intravesical vanilloid therapy were aimed at treating NDO due to spinal cord lesions. Patients can regain continence, increase of bladder capacity and decrease of urinary incontinence after capsaicin or RTX instillations [29-31]. Only a few investigations have used capsaicin or resiniferatoxin to treat IDO or bladder hypersensitivity from non-spinal cord lesions [28,32]. As evidenced by positive ice water test results, over-expression and hyperactivity of the vanilloid receptors in the urinary bladder have been identified in patients with DO due to various non-spinal lesions [33]. Therefore, use of intravesical vanilloid agonists such as capsaicin or resiniferatoxin to treat OAB refractory to anticholinergic agents might be effective. However, the dose of RTX and the treatment regimen remain to be determined.

Previous studies have shown that intravesical capsaicin therapy exerts an excellent effect in patients with incontinence due to multiple sclerosis or spinal cord injuries [34-36]. High dose of capsaicin instillation might induce severe adverse events such as autonomic dysreflexia, bladder pain and hematuria. Because of its irritative effect, patients with non-spinal lesions might not be able to tolerate capsaicin therapy. RTX, an ultrapotent capsaicin analog, has been shown to have a clinical effect similar to capsaicin but with less neuronal excitatory effects [37]. Thus, RTX treatment is more suitable than capsaicin for patients who have normal bladder sensation and OAB [38].

The clinical effect of intravesical RTX at a concentration of 100 nM has been demonstrated in treating DO due to non-spinal cord lesions in patients refractory to anticholinergic treatment [39]. The magnitude of the neurotoxic effect of RTX seems to depend on the dose of vanilloids. A high concentration of resiniferatoxin might cause acute desensitization but might also result in neurotoxicity in the A-delta fibers mediating detrusor contractions, whereas a lower concentration might have less neurotoxicity and less desensitization of C-fibers. In order to achieve a better desensitization of C-fibers without neurotoxicity in the A-delta fibers, repeat treatment with a lower concentration of RTX might be necessary.

We have conducted a randomized, double-blind, placebo-controlled study of therapeutic effect of RTX on OAB recently. The results showed that four repeated installations of RTX at a concentration of 10 nM were well tolerated and effective in about 50% of patients with re-

fractory DO compared to the control group at 3 months after instillations [40]. Repeated instillations might lead to greater desensitization of afferent C-fibers and can provide a satisfactory therapeutic outcome in the majority of OAB patients [39,40].

BTX-A INTRAVESICAL INJECTIONS

BTX-A was widely used in treatment of NDO due to spinal cord lesion and was reported to provide satisfactory results [41]. Detrusor underactivity developed after detrusor injection of 300 U of BTX-A and lasted for 9 months. Seventy-three percent of patients with neurogenic bladder resumed a continent condition after treatment [41]. Most of the patients treated with BTX-A for their neurogenic incontinence reported increase of quality of life and desired for repeated injection after the therapeutic effect had disappeared [42]. Achievement of urinary continence and an increase in bladder capacity seem promising, however, the results for patients with non-neurogenic DO were not as good as for those with NDO [43].

BTX-A can cause skeletal or smooth muscle paralysis by blocking ACh release at the neuromuscular junction [44]. Reduction of expression of $P2X_3$ and TRPV1 receptors on suburothelial sensory fibers has been observed in patients receiving detrusor BTX-A injections for DO and has been associated with reduction in the degree of urgency in patients with a successful therapeutic result [11]. An antinociceptive effect through a direct decrease in the amount of neuropeptides such as substance P and CGRP released from activated sensory neurons has been postulated to account for the clinical effectiveness of BTX-A in pain relief [44,45].

The dose of BTX-A in treatment of OAB or non-neurogenic DO has not been well established yet. In previous studies using BTX-A for IDO, most investigators used detrusor injections of 200 U or 300 U of Botox (Allergan, Irvine, USA). However, the reported therapeutic results varied greatly. Kessler et al treated 11 patients with IDO with detrusor injections of 300 U Botox and the maximal bladder capacity increased from 220 to 340 mL. However, four patients needed clean intermittent catheterization (CIC) due to large postvoid residuals [46]. Rajkumar et al treated 15 women with IDO with detrusor injections of 300 U Botox and 14 had improvement in urgency and frequency, the therapeutic effects lasted for 5-6 months [47]. Popat et al used 200 U Botox for 31 patients with IDO. Although significant improvement in bladder capacity was noted after treatment, 20% of the patients needed CIC [48]. Schulte-Baukloh et al used 300 U of Botox for detrusor and urethral injections in 7 women with OAB without DO. The bladder capacity increased by 20% and all patients could void without the need for CIC [49]. In the author's previous study, detrusor injections of 200 U Botox provided a 73% success rate in 30 IDO patients, with a mean therapeutic duration of 5.3 months [43]. Further study using suburothelial injections of Botox at a dose of 200 U revealed therapeutic results (85% success rate) as good as those achieved with 300 U Botox in other studies [50].

Although the original results of 200 U to 300 U of Botox for patients with IDO seems promising, high percentage of adverse events such as chronic urinary retention, large PVR, hematuria and urinary tract infection remain difficult problems to be solved [43,50]. Under this safety consideration, a dose reduction and mode of administration are necessary in order to achieve similar therapeutic effects and reduce adverse effects [50].

Recently, the dose of Botox for IDO was further reduced to 100 U by many investigators and a satisfactory outcome was still achieved. Werner et al treated 26 women with IDO with a 53% success rate [51]. Schmid et al treated 100 IDO patients with an 88% success rate [52]. However, the therapeutic effects of 100 U Botox need further clarification. A dose- related increase in adverse events has been found with increasing doses of BTX-A [53]. In a recent study report by the author, 35% of patients had urinary tract infection, 30% had a large PVR requiring CIC, and 75% had difficult urination after 100 U Botox injection [50]. This high incidence might prohibit patients receiving a second injection when their OAB symptomatic relapse. A 100 U dose of suburothelial Botox reduced the rates of urinary tract infection to 4.3%, a large PVR to 30.4%, and difficult urination to 56.5% [53]. Therefore, adjustment of the dose of BTX-A for patients with IDO seems mandatory to minimize de novo adverse events.

Because intravesical BTX-A injection might induce detrusor underactivity and cause undesired adverse events, limited injections of BTX-A at the bladder base and trigone instead of to the whole bladder has been suggested to achieve therapeutic effect and avoiding adverse events of difficult urination. The trigone and bladder base have been found to have abundant sensory fibers. The role of trigonal sensory fibers on bladder urgency sensation and DO has not yet been explored. Injections of BTX-A into these areas have been shown to have therapeutic effects on idiopathic urgency frequency syndrome and interstitial cystitis [54,55]. Although vesicoureteral reflux might be a potential complication after BTX-A in these areas, there is no evidence of it so far [55,56]. An advantage of bladder base and trigonal injections of BTX-A is that detrusor underactivity does not develop after treatment [55]. Therefore, bladder base and trigonal BTX-A injections might be used in treating patients who have OAB and impaired detrusor contractility.

CONCLUSIONS

Strategies for treating OAB are aiming at the parasympathetic efferent and sensory afferent nerves in the bladder. The use of antimuscarinics is the first line treatment for OAB. In patients with OAB symptoms refractory to antimuscarinic therapy, the pathogenesis of OAB may be due to abnormality of sensory receptor expression on the sensory afferent nerves, and intravesical treatment targeting the sensory nerves will be effective. Intravesical administration of antimuscarinics and local anesthetics is effective in increasing bladder capacity, but the short-lived effect has limited its clinical use. Intravesical RTX instillation and intravesical BTX-A injection can reduce sensory receptor expression and desensitize the sensory fibers with long-term effect on OAB. RTX at low concentrations can decrease sensory urgency without influencing detrusor contractility. BTX-A, however, has a great effect on detrusor contractility, resulting in a large PVR after injection. Careful adjustment of dose and administrating frequency may improve therapeutic effects and decrease adverse events. Although clinically effective, both RTX and BTX-A are still in clinical trial. Informed consent should be obtained before treatment.

REFERENCES

1. Abrams P, Kelleher CJ, Kerr LA, Rogers RG: Overactive bladder significantly affects quality of life. Am J Manag Care 2000; **6(Suppl 11)**:S580-S590.

2. Milson I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ: How widespread are the symptoms of an overactive bladder and how are they managed? A population based prevalence study. BJU Int 2001; **87**:760-766.
3. Chen GD, Lin TL, Hu SW, Chen YC, Lin LY: Prevalence and correlation of urinary incontinence and overactive bladder in Taiwanese women. Neurourol Urodyn 2003; **22**:109-117.
4. Chapple CR: Muscarinic receptor antagonist in the treatment of overactive bladder. Urology 2000; **55(Suppl 5A)**:33-50.
5. Yarker Y, Goa KL, Fitton A: Oxybutynin: A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in detrusor instability. Drugs Aging 1995; **6**:243-262.
6. Kullmann FA, Artim DE, Birder LA, de Groat WC: Activation of muscarinic receptors in rat bladder sensory pathways alters reflex bladder activity. J Neurosci 2008; **28**:1977-1987.
7. Yoshimura N: Lower urinary tract symptoms (LUTS) and bladder afferent activity. Neurourol Urodyn 2007; **26(Suppl 6)**:908-913.
8. Brady CM, Apostolidis AN, Harper M, et al: Parallel changes in bladder suburothelial vanilloid receptor TRPV1 (VR1) and pan-neuronal marker PGP9.5 immunoreactivity in patients with neurogenic detrusor overactivity after intravesical resiniferatoxin treatment. BJU Int 2004; **93**:770-776.
9. Brady C, Apostolidis A, Yiangou Y, et al: P2X3-immunoreactive nerve fibers in neurogenic detrusor overactivity and the effect of intravesical resiniferatoxin (RTX). Eur Urol 2004; **46**:247-253.
10. Smet PJ, Moore KH, Jonavicius J: Distribution and colocalization of calcitonin gene-related peptide, tachykinins, and vasoactive intestinal peptide in normal and indiopathic unstable human urinary bladder. Lab Invest 1997; **77**:37-49.
11. Apostolidis A, Popat R, Yiangou Y, et al: Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of Botulinum toxin for human detrusor overactivity. J Urol 2005; **174**:977-983.
12. Yoshida M, Miyamae K, Iwashida H, Otani M, Inadome A: Management of detrusor dysfunction in the elderly: Changes in acetylcholine and adenosine triphosphate release during ageing. Urology 2004; **63(3 Suppl 1)**:17-23.
13. Sun Y, Chai TC: Up-regulation of P2X3 receptor during stretch of bladder Urothelial cells from patients with interstitial cystitis. J Urol 2004; **171**:448-452.
14. Apostolidis A, Brady CM, Yiangou Y, Davis J, Fowler CJ, Anand P: Capsaicin receptor TRPV1 in urothelium of neurogenic human bladders and the effect of intravesical resiniferatoxin. Urology 2005; **65**: 400-405.
15. Wiseman OJ, Fowler CJ, Landon DN: The role of the human bladder lamina propria myofibroblasts. BJU Int 2003; **91**:89-93.
16. Sui GP, Rothery S, Dupont E, Fry CH, Severs NJ: Gap junctions and connexin expression in human suburothelial interstitial cells. BJU Int 2002; **90**:118-129.
17. Apostolidis A, Dasgupta P, Fowler CJ: Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. Eur Urol 2006; **49**:644-650.
18. Fowler CJ: Intravesical treatment of overactive bladder. Urology 2000; **55(Suppl 5A)**:60-64.
19. Saito M, Watanabe T, Tabuchi F, Otsubo K, Satoh K, Miyagawa I: Urodynamic effects and safety of modified intravesical oxybutynin chloride in patients with neurogenic detrusor overactivity: 3 years experience. Int J Urol 2004; **11**:592-596.
20. Lehtoranta K, Tainio H, Lukkari-Lax E, Hakonen T, Tammela TL: Pharmacokinetics, efficacy, and safety of intravesical formulation of oxybutynin in patients with detrusor overactivity. Scan J Urol Nephrol 2002; **36**:18-24.
21. Yokoyama O, Yusup A, Miwa Y, Oyama N, Aoki Y, Akino H: Effects of tolterodine on an overactive bladder depend on suppression of C-fiber bladder afferent activity in rats. J Urol 2005; **174**:2032-2036.
22. Kim Y, Yoshimura N, Masada H, de Miguel F, Chancellor MB: Antimuscarinic agents exhibit local inhibitory effects on muscarinic receptors in bladder-afferent pathways. Urology 2005; **65**:238-242.
23. Jang J, Park EY, Seo SI, Hwang TK, Kim JC: Effects of intravesical instillation of cyclooxygenase-2 inhibitor on the expression of inducible nitric oxide synthase and nerve growth factor in cyclophosphamide-induced overactive bladder. BJU Int 2006; **98**:435-439.
24. Fader M, Glickman S, Haggar V, Barton R, Brooks R, Malone-Lee J: Intravesical atropine compared to oral oxybutynin for neurogenic detrusor overactivity: A double-blind, randomized crossover trial. J Urol 2007; **177**:208-213.
25. Haferkamp A, Hohenfellner M: Intravesical treatment of overactive bladder syndrome. Urology A 2006; **45**:1283-1288.
26. Birder LA, Nakamura Y, Kiss S, et al: Altered urinary bladder function in mice lacking the vanilloid receptor TRPV1. Nat Neurosci 2002; **5**:856-860.
27. Liu HT, Kuo HC: Increased expression of transient receptor potential vanilloid subfamily 1 in the bladder predicts the response to intravesical instillations of resiniferatoxin in patients with refractory idiopathic detrusor overactivity. BJU Int 2007; **100**:1086-1090.
28. Kuo HC: Effectiveness of intravesical resiniferatoxin for anticholinergic treatment refractory detrusor overactivity due to nonspinal cord lesions. J Urol 2003; **170**:835-839.
29. Fowler CJ, Beck RO, Gerrard S, Betts CD, Fowler CG: Intravesical capsaicin for treatment of detrusor hyperreflexia. J Neurol Neurosurg Psychiatry 1994; **57**:169-173.
30. Cruz F, Guimaraes M, Silva C, Reis M: Suppression of bladder hyperreflexia by intravesical resiniferatoxin. Lancet 1997; **350**:640-641.
31. Silva C, Rio ME, Cruz F: Desensitization of bladder sensory fibers by intravesical resiniferatoxin, a capsaicin analog: Long-term results for the treatment of detrusor hyperreflexia. Eur Urol 2003; **38**: 444-452.
32. Lazzeri M, Beneforti P, Spinelli M, Zanollo A, Barbagli G, Turini D: Intravesical resiniferatoxin for the treatment of hypersensitive disorder: A randomized placebo controlled study. J Urol 2000; **164**: 676-679.
33. Chai TC, Gray ML, Steers W: The incidence of a positive ice water test in bladder outlet obstructed patients: Evidence for bladder neural plasticity. J Urol 1998; **160**:34-38.
34. Cruz F, Guimaraes M, Silva C, Rio ME, Coimbra A , Reis M: Desensitization of bladder sensory fibers by intravesical capsaicin has long lasting clinical and urodynamic effects in patients with hyperactive or hypersensitive bladder dysfunction. J Urol 1997; **157**:585-589.
35. De Seze M, Wiart L, Joseph PA, Dosquo JP, Mazaux JM, Barat M: Capsicin and neurogenic detrusor hyperreflexia: A double- blind placebo- controlled study in 20 patients with spinal cord lesions. Neurourol Urodyn 1998; **17**:513-523.
36. Igawa Y, Satoh T, Mizusawa H, et al: The role of capsaicin-sensitive afferents in autonomic dysreflexia in patients with spinal cord injury. BJU Int 2003; **91**:637-641.
37. Lazzeri M, Spinelli M, Beneforti P, Zanollo A, Turini D: Urodynamic assessment during intravesical infusion of capsaicin for the treatment of refractory detrusor hyperreflexia. Spinal Cord 1999; **37**:440-443.
38. Cruz F, Guimaraes M, Silva C, Reis M: Intravesical resiniferatoxin, a capsaicin analong, represses bladder hyperreflexia without evoking significant acute discomfort. Lancet 1997; **350**:640-641.
39. Kuo HC: Multiple intravesical instillation of low-dose resiniferatoxin is effective in the treatment of detrusor overactivity refractory to anticholinergics. BJU Int 2005; **95**:1023-1027.
40. Kuo HC, Liu HT, Yang WC: Therapeutic effect of multiple resiniferatoxin intravesical instillation in patients with refractory detrusor overactivity: A randomized double-blind, placebo controlled study. J Urol 2006; **176**:641-645.
41. Reitz A, Stohrer M, Kramer G, et al: European experience of 200

cases treated with botulinum-A toxin injections into the detrusor muscle for urinary incontinence due to neurogenic detrusor overactivity. Eur Urol 2004; **45**:510-515.
42. Kuo HC: Therapeutic satisfaction and dissatisfaction in patients with spinal cord lesions and detrusor sphincter dyssynergia who received detrusor botulinum toxin A injection. Urology 2008; **72**:1056-1060.
43. Kuo HC: Urodynamic evidence of effectiveness of botulinum A toxin injection in treatment of detrusor overactivity refractory to anticholinergic agents. Urology 2004; **63**:868-872.
44. Simpson LL: Kinetic studies on the interaction between botulinum toxin type A and the cholinergic neuromuscular junction. J Pharmacol Exp Ther 1980; **212**:16-21.
45. Aoki KR: Evidence for antinociceptive activity of botulinum toxin type A in pain management. Headache 2003; **(43 Suppl 1)**:S9-S15.
46. Kessler TM, Danuser H, Schumacher M, Studer UE, Burkhard FC: Botulinum A toxin injections into the detrusor: An effective treatment in idiopathic and neurogenic detrusor overactivity? Neurourol Urodyn 2005; **24**:231-236.
47. Rajkumar GN, Small DR, Mustafa AW, Conn G: A prospective study to evaluate the safety, tolerability, efficacy and durability of response of intravesical injection of botulinum toxin type A into detrusor muscle in patients with refractory idiopathic detrusor overactivity. BJU Int 2005; **96**:848-852.
48. Popat R, Apostolidis A, Kalsi V, Gonzales G, Fowler CJ, Dasgupta P: A comparison between the response of patients with idiopathic detrusor overactivity and neurogenic detrusor overactivity to the first intradetrusor injection of botulinum-A toxin. J Urol 2005; **174**:984-989.
49. Schulte-Baukloh H, Weiss C, Stolze T, Sturzebecher B, Knispel HH: Botulinum-A toxin for treatment of overactive bladder without detrusor overactivity: Urodynamic outcome and patient satisfaction. Urology 2005; **66**:82-87.
50. Kuo HC: Clinical effects of suburothelial injection of botulinum A toxin in patients with non-neurogenic detrusor overactivity refractory to anticholinergics. Urology 2005; **66**:94-98.
51. Werner M, Schmid DM, Schussler B: Efficacy of botulinum-A toxin in the treatment of detrusor overactivity incontinence: A prospective nonrandomized study. Am J Obstet Gynecol 2005; **192**:1735-1740.
52. Schmid DM, Sauermann P, Werner M, et al: Experience with 100 cases treated with botulinum-A toxin injections in the detrusor muscle for idiopathic overactive bladfder syndrome refractory to anticholinergics. J Urol 2006; **176**:177-185.
53. Kuo HC: Will suburothelial injection of small dose of botulinum A toxin have similar therapeutic effects and less adverse events for refractory detrusor overactivity? Urology 2006; **68**:993-998.
54. Zermann DH, Ishigooka M, Schubert J, Schmidt RA: Trigonum and bladder base injection of botulinum toxin A (BTX) in patients with severe urgency-frequency-syndrome refractory to conservative medical treatment and electrical stimulation. Neurourol Urodyn 2001; **20**:412-413.
55. Kuo HC: Comparison of effectiveness of detrusor, suburothelial and bladder base injections of botulinum toxin A for idiopathic detrusor overactivity. J Urol 2007; **178**:1359-1363.
56. Mascarenhas F, Cocuzza M, Gomes CM, Leao N: Trigonal injection of botulinum toxin-A does not cause vesicoureteral reflux in neurogenic patients. Neurourol Urodyn 2008; **27**:311-314.