An urodynamic study of solifenacin in female and male patients with symptomatic overactive bladder

Jianguo Wen[#1,2,3], Chuanchuan Ren[1,2], Yan Chen[1,2], Jinsheng Li[1,2], Ruili Zhang[1], Qingjun Meng[1], Weixing Zhang[1], Baoping Qiao[1], Jinxing Wei[1], Shengjun Zhang[3], Yrjö T. Konttinen[4,5,6]

[1]Department of Urology, [2]Urodynamic Center, [3]Institute of Clinical Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, China
[4]Department of Medicine/Invärtes medicin, Helsinki University Central Hospital, Finland
[5]ORTON Orthopaedic Hospital of the Invalid Foundation, Finland
[6]COXA Hospital for Joint Replacement, 00029, Finland
Email: wenjg@hotmail.com

Abstract: Purpose To investigate the effects of solifenacin on the detrusor function in OAB patients without any LUT pathology. **Methods** A total of 64 out-patients (29 females, 35 males) with symptomatic OAB of 1-5 year duration entered the study. Solifenacin 5 mg q.d. was administered orally for 12 weeks. Before and after medication, filling cystometry, 3-day voiding diary, OABSS, PPBC and AE were recorded. **Results** Before and after treatment, the number of patients showing detrusor overactivity (DO) was 38 vs. 27, respectively. The average number of DO wave peaks decreased in women (2.4±2.0 vs. 0.9±1.1, P<0.05) and in men (2.4±2.0 vs. 0.6±1.3, P<0.001). DO disappeared in 11 patients (4 females, 7 males). FDV increased in women (108.0±67.0 ml vs. 178.0±79.0 ml, P<0.001) and in men (98.0±66.0 ml vs. 198.0±89.0 ml, P<0.05). MCC increased in women (189.0±131.0 ml vs. 297.0±86.0 ml, P<0.01) and in men (178.0±127.0 ml vs. 289.0±79.0 ml, P<0.001). BC (DV/DP) and PQmax did not change (P>0.05). Three-day diaries disclosed improvements of urgencies (27.3±9.7 vs. 17.6±12.8, P <0.05) and voiding volumes (127.0±58.9 vs. 289.0±157.9, P<0.001). All patients improved in OABSS (12.4±2.6 vs. 8.6±4.3, P<0.01) and PPBC (5.5±0.5 vs. 2.9±1.6, P<0.001). Mild and moderate dry mouth developed in 29.7% and 35.9% of patients, respectively. **Conclusions** Solifenacin urodynamically decreases the overactivity of detrusor, increases bladder capacity and improves life quality in symptomatic OAB patients. Minor patients without improvement may try to modulate mechanosensory pathways of micturition reflexes.

[Jianguo Wen, Chuanchuan Ren, Yan Chen, Jinsheng Li, Ruili Zhang, Qingjun Meng, Weixing Zhang, Baoping Qiao, Jinxing Wei, Shengjun Zhang, Yrjö T. Konttinen. **An urodynamic study of solifenacin in female and male patients with symptomatic overactive bladder.** *Life Sci J* 2013; 10(3): 7-12]. (ISSN: 1097-8135). http://www.lifesciencesite.com 2

Key Words overactive bladder; OAB; detrusor; urodynamics

Introduction

International Continence Society (ICS) defines overactive bladder (OAB) as a syndrome comprising the symptoms of urgency, with or without urge incontinence, usually accompanied by frequency and nocturia [1]. Epidemiological surveys have shown that the prevalence of OAB is 16.6% in Europeans [2] aged over 40 years and 16.6% in American adults [3]. An epidemiological survey of 1581 Chinese women in Taiwan has demonstrated that OAB affects 18.6%, [4] and, thus, its prevalence rate is similar to that of Western populations.

In pharmacological management of OAB antimuscarinic agents remain the mainstay of therapy [5]. However, despite their proven efficacy, the tolerability of some of these agents may be limited by adverse events (AEs) due to their non-selective effects on muscarinic acetylcholine receptors in various organs. Solifenacin is a once-daily oral muscarinic receptor antagonist, especially effective towards muscarinic-3 receptor (M3R) [6]. Furthermore, in vitro and in vivo studies solifenacin showed relative selectivity to M3 receptor in the bladder compared with salivary gland tissue [7]. Phase 3 trials of solifenacin for OAB showed significant improvement of the symptoms compared with placebo and had an acceptable level of anticholinergic side effects, most frequently dry mouth [8]. Furthermore, two reports have thus far investigated urodynamic effects of solifenacin. One Italian study dealt with male patients with OAB concomitant with urodynamic evidence of detrusor underactivity (a voiding disorder) [9]. The other study was performed in Japan and analyzed its effects on untreated female patients with OAB and some obvious neurogenic lower urinary tract (LUT) pathology [10]. LUT pathology includes OAB symptoms and voiding symptoms. Voiding symptoms are more prevalent in men with detrusor underactivity (DUA) or bladder outlet obstruction (BOO). Although the effects of solifenacin on the detrusor function both in male and female patients with OAB and with accompanying obvious LUT pathology have been reported using symptom scales [9,10], the effects of solifenacin on the detrusor function in OAB patient without significant LUT

pathology have not been reported. Therefore, the aim of the present study was to investigate the effects of solifenacin on the detrusor function of both female and male patients with symptomatic OAB but without LUT pathology.

Material and Methods

Patients

The study was conducted from March to November in 2010, enrolled 64 out-patients in the hospital. All patients underwent a detailed clinical evaluation including full history recording, physical examination (general, abdominal, rectal and neurological), bladder diary and various questionnaires, urinalysis with culture when necessary and cytology with suspected carcinoma. The inclusion criteria for the study were: 1) OAB symptoms (including urinary frequency, urgency, or urge incontinence) for at least 3 months; 2) ＞8 micturition per 24 hours; 3) ＞3 urgency or＞3 incontinence episodes during the last three days; 4) man or woman over 18 years. Exclusion criteria for the study were: 1) Urodynamically outflow obstruction as flow and detrusor pressure (Pdet) are measured; 2) post-void residual volume (PVR) >200 ml; 3) persistent or recurrent urinary tract infection; 4) bladder stones; 5) chronic interstitial cystitis; 6) previous pelvic irradiation; 7) previous or current malignant disease of the pelvic organs; 8) any medical condition contraindicating the use of anticholinergic medication (including narrow-angle glaucoma and urinary or gastric retention); 9) use of any urinary medication during the month preceding the current study; 10) pregnancy or breast feeding; 11) intention to become pregnant during the study period. Women who were not using a reliable method of contraception were excluded.

Study design

Patients were given 5 mg solifenacin *q.d.* for 12 weeks. Before and at the end of the treatment period, the overactive bladder symptom score (OABSS) was determined by using a self-administered questionnaire. Urodynamic filling cystometry was carried out and adverse events (AEs) were recorded.

Urodynamic tests

Urodynamic tests were done using DUET Logic urodynamic instrument (Medtronic, Skovlunde, Denmark), in accordance with the methods recommended by ICS. Symptoms and urodynamic parameters were recorded using the standardized terminology of ICS [11]. The parameters measured were bladder compliance (BC = DV/DP), the number of involuntary detrusor contraction waves (detrusor overactivity, DO), bladder capacity at the first desire to void (FDV), maximum cystometric capacity (MCC) and detrusor pressure at maximum flow rate (Pdet at Qmax, P_{Qmax}).

The survey questionnaire

(1) Overactive bladder symptom score (OABSS) [12] contains four questions: 1) frequency of urination during the day: from getting up in the morning to falling asleep at night, how many times have you urinated? 2) Frequency of urination at night: after falling asleep at night to getting up the next morning, how many times have you urinated? 3) Urgency: how often do you have a strong, sudden urge to urinate? 4) Urge incontinence: when you have a sudden need to urinate, how often have you lost urine? The maximum total score is 15 points; the higher the score, the more severe are the symptoms.

(2) Patient perception of the bladder condition scale (PPBC) [13,14]. Patients evaluated the impact of the condition of their bladder on their daily life using PPBC scale. The impact was classified into none, very mild (no impact on daily life), mild (some impact on daily life), moderate (uncomfortable impact on daily life), or severe (intolerable impact, causing agony in daily life); the higher the score, the more severe are the symptoms.

AEs

All AEs were recorded. The degree of dry mouth was classified into none, mild (symptoms barely noticeable), moderate (treatment for symptoms was necessary, *e.g.* mouthwash), or severe (dry mouth caused severe discomfort).

Statistics

All values in the tables are expressed as mean ± deviation (SD). The mean values were statistically compared by paired t-test with the use of SPSS 17.0 software. Statistical difference was assumed at $P<0.05$, significant difference as $P<0.01$.

Ethics

The study protocol was approved by the institutional Medical Ethics Committee according to the Declaration of Helsinki (1983), and informed consent was obtained from the patients.

Results

Clinical findings

All the patients completed the study. The mean age of the patients (35 males, 29 females) was 42.9± 20.4 years (range 21-63), male (48.9± 22.7 years (range 27-63)), female (39.6± 17.5 years (range 21-52)). The mean duration of OAB was 2.1 ± 2.0 years (range 1-5). No other LUT symptoms except OAB were found. Six patients had hypertension and were taking losartan 50 mg/d and hydrochlorothiazide 12.5 mg/d with a good control of their blood pressure (129 ± 21 mmHg).

Urodynamic tests of the detrusor

Before and after treatment, the number of patients who had DO were 38 (21 male, 17 female) *vs.* 27 (15 male, 13 female), and the average number of DO wave peaks decreased both in females 2.4±2.0 *vs.* 0.9 ±

1.1, $P<0.05$ and males 2.4±2.0 *vs.* 0.6±1.3, $P<0.001$). Fig. 1 shows a representative pressure-flow study before and after treatment.

Before and after treatment, FDV increased both in females (108.0± 67.0 ml *vs.* 178.0±79.0 ml, $P<0.001$) and in males (98.0±66.0 ml *vs.* 198.0±89.0, $P<0.05$). MCC increased both in females (189.0±131.0 ml *vs.* 297.0±86.0 ml, $P<0.01$) and in males (178.0±127.0 ml *vs.* 289.0±79.0 ml, $P<0.001$). BC and P_{Qmax} did not change ($P>0.05$) (Table 1).

Three-day voiding dairy

After using solifenacin for 12 weeks, voiding times, nocturia, urinary incontinence, and pad quantity showed no differences ($P>0.05$), but the number of urgencies ($P<0.05$) and voiding volumes improved ($P<0.001$) (Table 2).

Questionnaire findings

The score in Day-time frequency, nocturia, urgency, urge incontinence and total of the OABSS decreased ($P<0.05$ or $P<0.001$), and PPBC score also decreased ($P<0.001$) (Table 3).

AEs

Only dry mouth was reported. Twenty-two patients had no AEs. Twenty-three patients (35.9 %) had mild dry mouth complaints. Nineteen patients (29.7 %) had moderate dry mouth and needed some care, such as mouthwash or drink more water. None of the patients gave up solifenacin treatment for AEs.

Discussion

OAB symptoms have a significant negative impact on health-related quality of life (HRQL), impairing several aspects of life [15]. Pathophysiology of OAB is now generally considered to damage the afferent and efferent neural pathways of the bladder leading to a reduction of the processing capability of the afferent information from the bladder [16]. However, the cause of OAB may be different in different patients. In addition, there are other theories about the causes and pathomechanisms and maybe the real mechanisms have not been discovered yet.

OAB symptoms are usually evaluated using bladder voiding diary, PPBC symptoms rating scale, quality of life scales and questionnaires of the major OAB symptoms. ICS recommends urinary bladder voiding diary as a method for assessment of the bladder function [17]. Such a 3-day voiding diary was used to assess the LUT symptoms: no differences were found in voiding times, nocturia, urinary incontinence or pad quantity ($P>0.05$), whereas the number of urgencies diminished ($P<0.001$).

Muscarinic receptor antagonists form the mainstay in OAB pharmacotherapy [18]. There are 5 different subtypes of muscarinic receptors, M1–M5 [19]. In the urinary bladder, normal bladder contraction is mainly mediated by stimulation of M3 receptors, which also form the target of antimuscarinic agents used for the treatment of OAB. By blocking the muscarinic receptors antimuscarinic agents inhibit the abnormal bladder contractions (detrusor overactivity) and subsequently reduce OAB symptoms. A recent placebo-controlled trial of bladder symptoms and quality of life in OAB showed that urinary frequency and incontinence were reduced at the same time as voiding volumes increased and the quality of life improved [20]. In this study, 64 OAB patients orally took daily 5 mg solifenacin for 12 weeks, which improved the OABSS scores of urgency, frequency, nocturia and urinary incontinence ($P<0.05$ or $P<0.001$). Improvement was also recorded in PPBC symptoms rating scale. The mean pre-treatment PPBC symptom score was 5.50, corresponding to a perception of "moderate to severe" bladder problems. At end of treatment, the PPBC symptom score had decreased to 2.9 ($P<0.001$), corresponding to a perception of "some minor problems" associated with the bladder. These results confirm and extend the effectiveness of solifenacin in OAB patients.

The most commonly reported AEs of solifenacin is dry mouth, but also other AEs, such as constipation and blurred vision have been reported. However, these AEs are dose-related. Michel and co-workers made a cardiovascular safety evaluation of solifenacin, and found no increase in heart rate or blood pressure [21]. In this study, only mild and moderate dry mouth was reported, but none of the patients gave up solifenacin treatment because of dry mouth. Patients with moderate dry mouth needed some care, such as mouthwashe or drinking more water. The increasing total voiding volume per day may explain why there were no changes of voiding times per day, while the voiding volume per time increased in 3-day voiding diaries as the result of the treatment.

Although there are some studies of using solifenacin in OAB, reports about the effects of solifenacin on the detrusor are rare [22]. Some papers have reported the effects of solifenacin on detrusor in OAB patients with some LUT pathogenesis, but there are no previous papers on the effects of the solifenacin on detrusor in OAB in patients without other LUT pathogenesis. In the past, it was believed that the OAB patients had spontaneous or induced DO. In fact, not all OAB patients have urodynamic DO and not all patients with DO have OAB symptoms [23]. An urodynamic study about solifenacin in 28 untreated female Japanese patients suffering from OAB and some suffering OAB and obvious neurogenic LUT pathology showed that DO disappeared in five patients and that the overall bladder capacity improved after 12-week treatment. However, this report excluded patients with a urinary tract infection, >200 ml PVR and the use of antimuscarinic drugs, but did not exclude any other

LUT pathology, such as chronic interstitial cystitis or previous pelvic irradiation. The current study included 29 Chinese female OAB patients without any other LUT pathology. When they took 5mg/d solifenacin orally for 12 weeks, the average number of DO wave peaks decreased. DO disappeared in 4 patients and FDV and MCC increased. This result suggests that solifenacin also inhibits involuntary contractions of the detrusor muscle during the storage phase.

Another study on the urodynamic effects of solifenacin treatment on male patients with OAB and concomitant detrusor underactivity in Italy, 15% of whom had prostatic hyperplasia and 2.2% with acute urinary retention [9]. It shows that solifenacin treatment seemed not to be of clinical significance in inducing the urodynamic parameter changes. The current solifenacin treatment study showed the diminished average number of the DO wave peaks, higher FD and MCC after medication, while P_{Qmax} had no difference. It also suggests that solifenacin decreases the overactivity of detrusor and increases bladder capacity in Chinese male patients with OAB but without significant LUT pathology.

It seems that solifenacin is more or less effective in most patients, however, there were 5 (3 male, 2 female) patients in this study, who did not show any improvement. They just reported side effects such as dry mouth of solifenacin. None of the parameters reflecting the urodynamics or OABSS showed any difference between the premedication and postmedication period. The pharmacological effect of solifenacin is that it inhibits binding of acetylcholine (ACh) to muscarinic 3 receptors (M3R) on the detrusor muscle, and reduces detrusor contractions. However, the OAB etiology may be multifactorial. The increased sensitivity to stimulation of the M3 receptor may be also responsible for OAB in some patients [24]. In addition, the urothelium may also play a role in OAB. The urothelium is innervated by afferent nerves that can act as luminal sensors, and once stimulated, these suburothelial afferent fibers may lead to urgency and unstable detrusor contractions [25]. Recent research highlights several potential targets for the treatment of OAB, particularly within the mechanosensory pathways [26].

In conclusion, solifenacin 5mg orally per day for 12 weeks both in female and male OAB patients decreases the overactivity of detrusor, increases bladder capacity and improves the quality of life while with few AEs in most of Chinese female and male patients without LUT pathology. However, the effects of solifinacin dosage and recurrence rates with different dosages after withdrawal of the medication should be evaluated further. Patients showing no response to this medicine may be future candidates to treatments modulating the mechanosensory pathways.

Table 1. Urodynamic parameters before and after 12-week treatment in female and male groups（mean±s.d.）

Parameters/Time	Before	treatment	After	treatment	*P*	
Gender	female	male	female	male	female	male
BC(mL/cmH2O)	60.8±28.4	59.1±29.6	53.5±26.1	52.8±26.8	>0.05	>0.05
Number of DO	2.38±1.95	2.35±1.95	0.86±1.13	0.64±1.33	<0.05	<0.001
FD(ml)	108.0±67.0	98.0±66.0	178.0±79.0	198.0±89.0	<0.001	<0.001
MCC(ml)	189.0±131.0	178.0±127.0	297.0±86.0	289.0±79.0	<0.05	<0.001
PQmax(cmH2O)	53.7±21.8	49.7±26.8	53.9±17.2	56.7±25.6	>0.05	>0.05

Table 2. Three-days voiding dairy before and after 12-week treatment in all OAB patients（mean±s.d.）

time/ project	voiding times	urgency times	nocturia times	incontinence times	pad quantity	Voided volume (ml)
Before treatment	45.13±14.81	27.25±9.71	12.00±5.27	10.88±13.12	1.88±4.59	127.0±58.9
After treatment	34.63±18.39	17.63±12.80	9.00±6.10	6.88±10.51	1.25±3.31	289.0±157.9
P	>0.05	<0.05	>0.05	>0.05	>0.05	<0.001

Table 3. Questionnaire parameters before and after 12-week treatment in all OAB patients（mean±s.d.）

Time/score	daytime frequency	nocturia	urgency	incontinence	Total	PPBC
Before treatment	1.25±0.46	2.88±0.35	5.00±0.00	3.25±2.12	12.38±2.56	5.50±0.53
After treatment	0.38±0.74	1.38±0.92	2.75±1.98	1.63±2.07	8.60±4.31	2.88±1.64
P	<0.001	<0.001	<0.001	<0.05	<0.01	<0.001

Figure 1 shows the uro-voiding cystometry before and after solifenacin treatment. It shows the change of urodynamic condition of the detrusor in a 43-year-old female patient, who had urinary urgency and frequency for 3 years, and took the urodynamic test before and after 12 weeks solifenacin medication.

(A) Before treatment, the urodynamic test showed several detrusor overactivity wave peaks during the infusion of bladder (Pdet> 15 cmH_2O during bladder infusion). Upon filling to 192 mL, the patient

cannot control and involuntarily gets into the voiding phase during which urine flowed out with the maximum detrusor pressure of 84 cmH_2O.

(B) After 12 weeks of medication, the urodynamic test showed that there is no detrusor overactivity wave peaks during the infusion of bladder (Pdet> 15 cmH_2O). The bladder capacity before a strong desire to void (also MCC) was 357 ml. Urine flowed out with the maximum detrusor pressure is 67 cmH_2O. P-Q figure showed no obstruction.

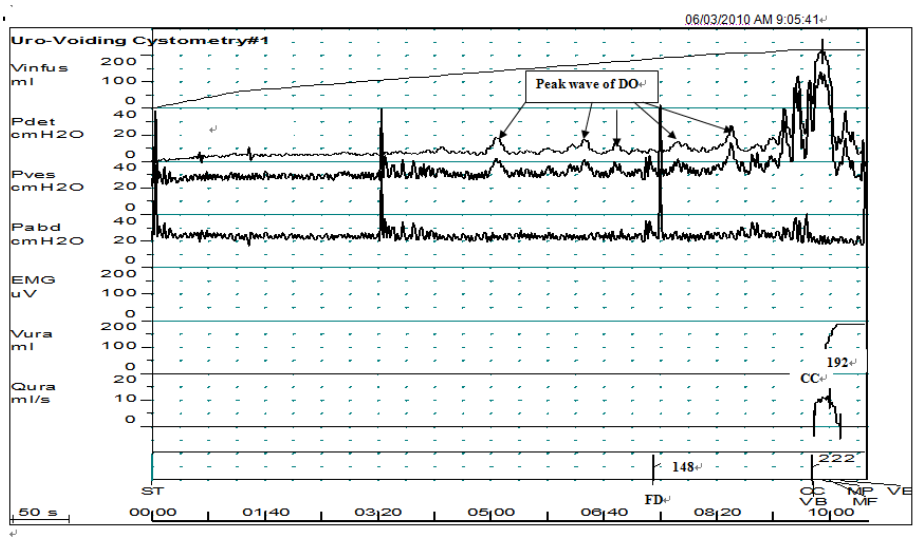

Figure 1 (A) The pressure-flow study before solifenacin treatment

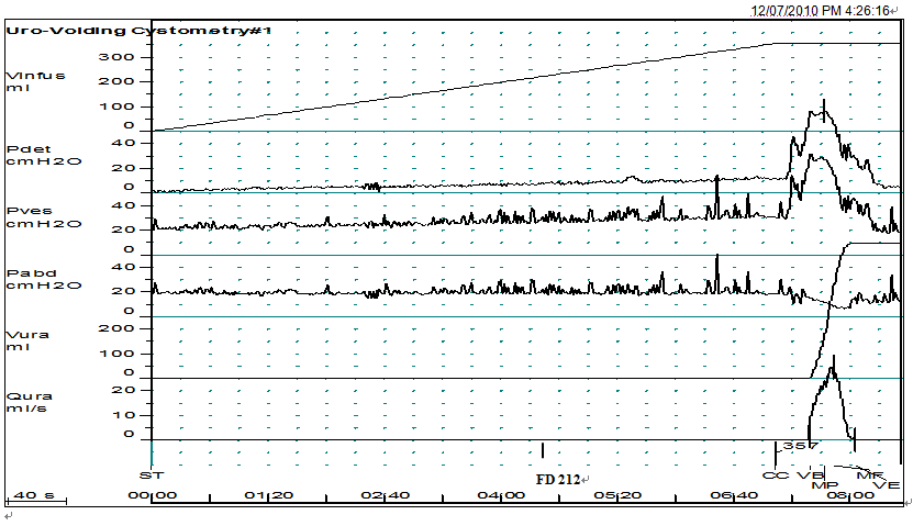

Figure 1 (B) The pressure- flowing study after solifenacin treatment

Declaration of interest:

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

#Corresponding author:

Jianguo Wen, MD (CHN), PhD (DK), Urologist, Prof. of Urology/incontinence, Head of Urodynamic Center, Chairman of Institute of Clinical Research, the First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, China. Email: wenjg@hotmail.com

References

[1] Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, Van Kerrebroeck P, Victor A, Wein A. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology, 2003;61(1):37-49.

[2] Milsom I, Abrams P, Cardozo L, Roberts RG, Thüroff 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(9): 760-766.

[3] Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, Hunt TL, Wein AJ. Prevalence and burden of overactive bladder in the United States. World J Urol, 2003;20(6):327-336.
[4] 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(2):109-117.
[5] Yamaguchi O, Marui E, Kakizaki H, Itoh N, Yokota T, Okada H, Ishizuka O, Ozono S, Gotoh M, Sugiyama T, Seki N, Yoshida M. Randomized, double-blind, placebo- and propiverine-controlled trial of the once-daily antimuscarinic agent solifenacin in Japanese patients with overactive bladder. BJU Int, 2007; 100(3):579-587.
[6] Suzuki M, Ohtake A, Yoshino T, Yuyama H, Hayashi A, Ukai M, Okutsu H, Noguchi Y, Sato S, Sasamata M. Effects of solifenacin succinate (YM905) on detrusor overactivity in consciouscerebral infarcted rats. Eur J Pharmacol, 2005;512(1):61-66.
[7] Ohtake A, Ukai M, Hatanaka T, Kobayashi S, Ikeda K, Sato S, Miyata K, Sasamata M. In vitro and in vivo tissue selectivity profile of solifenacin succinate (YM905) for urinary bladder over salivary gland in rats. Eur J Pharmacol, 2004;492(2-3):243-250.
[8] Ohtake A, Saitoh C, Yuyama H, Ukai M, Okutsu H, Noguchi Y, Hatanaka T, Suzuki M, Sato S, Sasamata M, Miyata K. Pharmacological characterization of a new antimuscarinic agent, solifenacin succinate, in comparison with other antimuscarinic agents. Biol Pharm Bull, 2007;30(1):54-58.
[9] Ronchi P, Gravina GL, Galatioto GP, Costa AM, Martella O, Vicentini C. Urodynamic parameters after solifenacin treatment in men with overactive bladder symptoms and detrusor underactivity. Neurourol Urodyn, 2009;28(1):52-57.
[10] Tanaka Y, Masumori N, Tsukamoto T. Urodynamic effects of solifenacin in untreated female patients with symptomatic overactive bladder. Int J Urol, 2010;17(9):796-800.
[11] Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck P, Victor A, Wein A. The standardization of terminology of lower urinary tract function: report from the Standardization Sub-committee of the International Continence Society. Neurourol Urodyn, 2002;21(2):167-178.
[12] Homma Y, Yoshida M, Seki N, Yokoyama O, Kakizaki H, Gotoh M, Yamanishi T, Yamaguchi O, Takeda M, Nishizawa O. Symptom assessment tool for overactive bladder syndrome–overactive bladder symptom score. Urology, 2006;68(2):318-323.
[13] Matza LS, Thompson CL, Krasnow J, Brewster-Jordan J, Zyczynski T, Coyne KS. Test-retest reliability of four questionnaires for patients with overactive bladder: the Overactive Bladder Questionnaire (OAB-q), Patient Perception of Bladder Condition (PPBC), Urgency Questionnaire (UQ), and the Primary OAB Symptom Questionnaire (POSQ). Neurourol Urodyn, 2005;24(3):215-25.
[14] Coyne KS, Matza LS, Kopp Z, Abrams P. The validation of the patient perception of bladder condition (PPBC): A single-item global measure for patients with overactive bladder. Eur UrN, 2006;49(6):1079-1086.
[15] Coyne KS, Payne C, Bhattacharyya SK, Revicki DA, Thompson C, Corey R, Hunt TL. The impact of urinary urgency and frequency on health-related quality of life in overactive bladder: Results from a national community survey. Value Health, 2004;7(4):455-463.
[16] Hashim H, Abrams P. Is the bladder a reliable witness for predicting detrusor overactivity. J Urol, 2006;175(1):191-195.
[17] Dmochowski RR, Sanders SW, Appell RA, Nitti VW, Davila GW. Bladder–health diaries: an assessment of 3-day vs 7-day entries. BJU Int, 2005;96(7):1049-1054.
[18] Andersson KE. Antimuscarinics for treatment of overactive bladder. Lancet Neurol, 2004;3(1):46-53.
[19] Fox RI, Konttinen Y, Fisher A. Use of muscarinic agonists in the treatment of Sjögren's syndrome. Clin Immunol, 2001;101(3):249-263.
[20] Vardy MD, Mitcheson HD, Samuels TA, Wegenke JD, Forero-Schwanhaeuser S, Marshall TS, He W. Effects of solifenacin on overactive bladder symptoms, symptom bother and other patient outcomes: result from VIBRANT study. Int J Clin Pract, 2009;63(12):1702-1714.
[21] Michel MC, Wetterauer U, Vogel M, de la Rosette JJ. Cardiovascular safety and overall tolerability ofsolifenacin in routine clinical use: a 12 week, open-label, post-marketing surveillance study. Drug Saf, 2008;31(6):505-514.
[22] Pelman RS, Capo JP Jr, Forero-Schwanhaeuser S. Solifenacin at 3 years: a review of efficacy and safety. Postgrad Med, 2008;120(2):85-91.
[23] Flisser AJ, Walmsley K, Blaivas JG. Urodynamic classification of patients with symptoms of overactive bladder. J Urol, 2003;169(2):529-534.
[24] Wein AJ. Pathophysiology and categorization of voiding dysfunction. In: Walsh PC, Retik AB, Vaughan ED, and Wein AJ, eds. Campbell's Urology, 8th ed. Philadelphia: WB Saunders, 2002:887-899.
[25] De Groat WC. The urothelium in overactive bladder: passive bystander or active participant? Urology, 2004;64(6):7-11.
[26] Latini JM, Giannantoni A. Pharmacotherapy of overactive bladder: epidemiology and pathophysiology of overactive bladder. Expert Opin Pharmacother, 2011;12(7):1017-1027.

7/5/2013