

Single uroflow study as a tool in predicting the possibility of abnormal voiding symptoms after the administration of antimuscarinic agents in treating overactive bladder syndrome

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Summary

Purpose of study: The aim of this study was to evaluate the efficacy of uroflowmetry in predicting the possibility of abnormal voiding symptoms following antimuscarinic treatment for overactive bladder syndrome (OAB) in Taiwanese women. **Materials and Methods:** A retrospective study was conducted on women with OAB. Forty-five women with abnormal voiding patterns shown by urodynamic study comprised the main group and 38 women with normal voiding patterns comprised the control group. All patients were prescribed two mg tolterodine once daily for one week. Follow-up on complaints of abnormal voiding symptoms was done one week later. **Results:** One woman in control group and 12 women in main group complained of abnormal voiding symptoms. There was a significant difference in the occurrence of abnormal voiding symptoms after antimuscarinic administration between main study group and control group (26.7 % vs 2.6 %, $p = 0.02$). **Conclusion:** Uroflowmetry is a non-invasive and simple tool to predict the occurrence of abnormal voiding symptoms after antimuscarinic use.

Key words: Overactive bladder; Antimuscarinics; Urodynamics; Voiding pattern; Uroflowmetry.

Introduction

The International Continence Society (ICS) has announced a definition of overactive bladder syndrome (OAB), which was from then on to be regarded as a syndrome whose diagnosis was made purely on the basis of symptoms presented without the need to perform urodynamic examination [1]. Thinking behind, the definition was that the doctor could give their patients medicines directly according to their clinical complaints without any examinations before administration. Antimuscarinics are the first-line and also a safe pharmacotherapy for OAB at present [2-4].

Regarding antimuscarinics, dry mouth is the most common side effect and it has long attracted much attention [5, 6]. On the contrary, few of articles have showed the side effects of abnormal voiding symptoms caused by antimuscarinics. In the present authors' clinical experience, they did often find them to cause abnormal voiding symptoms such as small caliber, slow stream or strained voiding, all of which can cause patients hesitancy to continue with antimuscarinics treatment. Some articles reported the idea that OAB symptoms can be caused by problems during the voiding phase and have led to a wider attention [7-9]. Some articles have showed that symptoms from the voiding phase may display as urinary fre-

quency and urgency, which may in turn lead to wrong diagnosis and inappropriate treatment being offered [10, 11].

Up to now, there has been no better way to predict the possibility of abnormal voiding symptoms before administration of antimuscarinics. Therefore, this paper sets out to examine the possibility of abnormal voiding symptoms occurring because of antimuscarinic agent use in women with OAB. These agents were prescribed according to clinical symptoms without the aid of an urodynamic examination, relying on the value of uroflowmetry in predicting the occurrence of abnormal voiding symptoms.

Materials and Methods

In this retrospective chart-review study, the authors review 173 women with OAB syndrome treated by a week regimen of antimuscarinic agents From January 2004 through July 2009 at Chang Gung Memorial Hospital at Keelung. All patients suffered from one or more typical OAB symptoms for more than one year. The symptoms of OAB are defined as urinary urgency with or without urge incontinence, usually with urinary frequency (voiding eight times or more in a 24-hour period), and nocturia (awakening two times or more at night to void) [1].

Patients with complaints of abnormal voiding symptoms, previous abnormal urinary routine examinations, histories of urinary tract

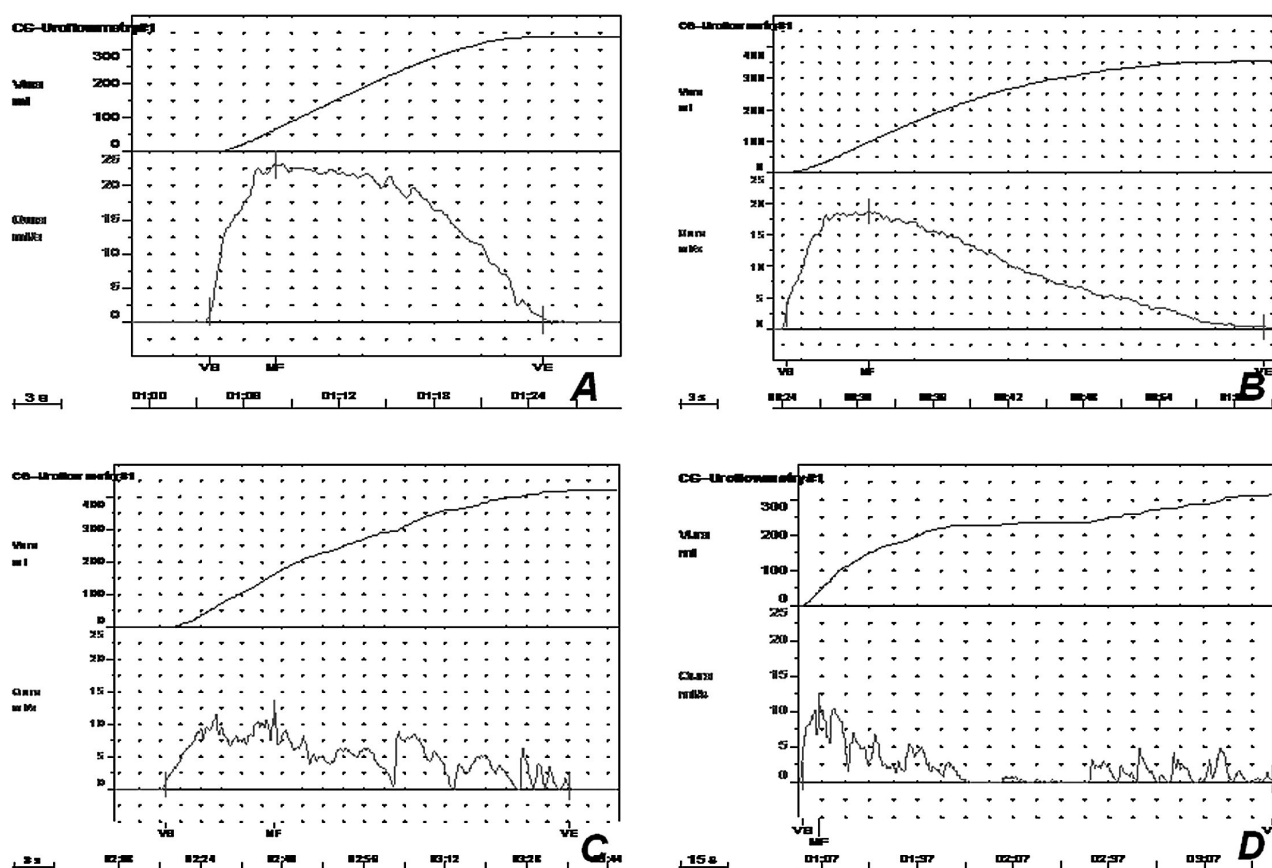


Figure 1. — (A) Example of normal voiding patterns as shown in uroflowmetry. The chart has a smooth single curve with a maximum flow rate exceeding 15 ml/sec and a voided volume above 200 ml. (B, C, D) Examples of abnormal voiding patterns as shown in uroflowmetry. All charts show curves that are not smooth, multiple, interrupted peaks or show an abnormal low flow rate below 15 ml/sec. (Line in upper section: voided volume, line in lower section: uroflow rate).

abnormalities or lithiasis, surgeries of the pelvic floor or bladder, chronic pelvic pain, painful bladder symptoms, and other medical or neurogenic diseases were excluded. Patients on medication that would affect bladder function were not included. Combined symptoms of any type of urinary incontinence and abnormal voiding symptoms also constituted exclusion criteria. Pelvic examination revealed no obvious cystocele, uterine prolapse, and urogenital anomalies. Sonographic examination revealed no significant increase in the sizes of either the uterus or the pelvic mass.

All patients underwent a urodynamic examination consisting in the measurement of post-micturition residuals, urethral pressure uroflowmetry, electromyography (EMG), and cystometry according to the criteria of the ICS [12]. Uroflowmetry was performed under natural conditions. In general, typical uroflowmetry results showed a smooth single curve with a maximum flow rate exceeding 15 ml/sec and a voided volume above 200 ml (Figure 1A). If the curve was not smooth, had multiple interrupted peaks or showed an abnormal low flow rate, these patients were considered to be suffering from abnormal voiding patterns regardless of whether they had clinical symptoms or not (Figure 1B-1D). All procedures and the interpretation of the results were performed by one of the authors (H.Y. C.).

Follow-ups were done immediately after completion of the regimen in clinics. Observations included the presence of the usual abnormal voiding symptoms associated with regular protocol of tolterodine administration. The complaints of abnormal voiding

symptoms such as small caliber, decreased force of urinary stream, urinary hesitancy, or strained voiding were recorded.

A three-day urinary diary had to be completed to make sure that the subjects included voided more than eight times per day, awoke two times or more at night to void, and had no fluid overload during the whole day. No questionnaires were used to quantify the impact of symptoms, but all subjects had these symptoms as their chief complaints, which significantly affected their quality of life. Of note is that the patients did not report any voiding difficulties or discomfort when having OAB symptoms.

All statistical analysis was conducted using a version of the 12.0 SPSS software program. Demographic characteristics of the patients are presented as the mean \pm SD or percentage according to the variables. Furthermore, cross-tabulation was employed to describe the relationship between voiding patterns in urodynamics and voiding difficulties. Comparison of the relationship between voiding patterns in urodynamics and voiding difficulties after tolterodine treatment was made by the chi-square test (χ^2) with $p < 0.05$ considered significant.

Results

Of the 173 women with overactive bladder syndrome at the present clinic arranged to undergo an urodynamic study

Table 1. — Characteristics of patients with overactive bladder symptoms.

	Normal voiding pattern (n = 38)	Abnormal voiding pattern (n = 45)	p
Age (years)	48.39 ± 12.13 (23-78)	48.39 ± 12.13 (22-76)	0.164
Postmenopausal	11 (28.95%)	13 (28.89%)	0.995
NSD only	32 (84.21%)	32 (71.11%)	0.161
CS only	2 (5.26%)	6 (13.33%)	0.219
NSD and CS	1 (2.63%)	1 (2.22%)	0.905
Nulliparous	3 (7.89%)	6 (13.33%)	0.433

Values are given as mean ± standard deviation (range) or n (%).

NSD: normal spontaneous delivery, CS: cesarean section.

and that were enrolled onto the authors' original database, only 83 women with OAB symptoms were subsequently offered and completed a week regimen of two mg once daily of tolterodine.

The demographic characteristics of these 83 subjects are listed in Table 1. All were Taiwanese. Their mean age was 48 years with no predominant age group found. There was no significant statistically discrepancy in the characteristic data between two groups. Among them, about 28% were postmenopause in two groups, indicating that menopause is not a very significant factor in the occurrence of OAB syndrome. In contrast, the rate of OAB cases for nulliparous women were only 7.89% and 13.33% in two groups, respectively. The majority of OAB patients (84.2% and 71.1%) in two groups had normal spontaneous delivery (NSD) and only implied a close relationship between NSD and OAB syndrome.

Table 2 shows the cross tabulation of voiding symptoms after administration of a week regimen of two mg once daily of tolterodine. Forty-five of 83 women (54.2%) with abnormal voiding patterns and 38 of 83 (45.8%) with normal voiding patterns were shown in an uroflow study. Twelve of 45 women (26.7 %) with abnormal voiding pattern had complaints of abnormal voiding symptoms after taking tolterodine for one week. On the contrary, only one of 38 (2.6%) patients with normal voiding patterns had complaints of abnormal voiding symptoms after tolterodine use. The *p* value was 0.002 which was statistically significant.

Twenty-four of 173 women (13.9 %) did not return for follow-up or treatment after an original urodynamic examination during this study period. The authors conducted a telephone interview exploring the reasons why they refused to follow-up or receive treatment. Although they did not do any statistical analysis of their responses, they discovered two common reasons for their refusal to follow-up. These were the discomfort felt during the invasive examination procedure and a self-diagnostic misunderstanding thinking they had urinary tract infection due to irritative voiding symptoms after examination. Because of this misunderstanding, these patients lost confidence in the present authors' care.

Table 2. — Cross-tabulation of voiding symptoms after administration of tolterodine and voiding pattern. Incidences of voiding symptoms between the normal voiding pattern group and abnormal voiding pattern group.

	Abnormal voiding symptoms (n = 13)	No voiding symptoms (n = 70)	p	OR (95% CI)
Normal uroflow pattern (n = 38)	1	37	0.002*	13.46 (1.66~109.14)
Abnormal uroflow pattern (n = 45)	12	33		

*Chi-square test

Discussion

In this study, 105 of 173 (59.0%) OAB women demonstrated involuntary detrusor contractions on urodynamic examination. This result was similar to findings published earlier [13, 14]. It signified that around 40-50% OAB symptoms might be caused by problems originating from the voiding phase. In the past, women's abnormal voiding symptoms were often ignored or attributed to anti-incontinence surgery or pelvic organ prolapse. With a better study of physiology in pelvic floor, dysfunctions in voiding phase are now known to be the result of a spastic rhabdosphincter in the urethra or spastic levator ani muscle. It is common among women with problematic voiding habits, habitual refraining from voiding, or chronic pelvic pain [15, 16]. Often some of these women have complaints similar to typical OAB symptoms rather than abnormal voiding symptoms [5, 10].

Abnormal voiding symptoms, such as urine retention, are rare incidences caused by antimuscarinics (1.1 to 6%) [2]. Even lower dosage of antimuscarinics (two mg once daily of tolterodine) was used in this study; 13 of the 83 women (15.7%) were found to have abnormal voiding symptoms which caused them to cease taking medicine. The difference in the dosage used in most published reports and the present study may be due to the effect of medicines on differing body frames, i.e. between Western and Eastern bioavailability. This implies caution must be observed in the administration of antimuscarinic agents in treating OAB.

Diagnosis of overactive bladder can be purely based on history, physical examination, and clinical symptoms without urodynamics. In this study, OAB women with abnormal voiding patterns had a higher incidence of suffering from abnormal voiding symptoms after antimuscarinic treatment compared with those with normal voiding patterns (26.7 % vs. 2.6 %, *p* = 0.002). This implied that the importance of performing uroflow study before providing OAB women with prescriptions of antimuscarinic agents. Without the aid of uroflow study to find OAB women with abnormal voiding patterns, the abnormal voiding symptoms may occur subsequently. In fact, women with abnormal voiding pattern in uroflowmetry seem to have more severe voiding symptoms

than those without such abnormalities [9]. However, women with OAB symptoms may have voiding abnormalities that are missed by cystometrography only [9]. Therefore, uroflow study is useful for properly diagnosing such cases.

Urodynamic study is the useful examination to confirm abnormalities in both the storage and voiding phases, however the invasive nature and discomfort of urodynamics make its application limited in daily practice. Twenty-four of the 173 (13.87 %) cases refused to return for follow-up appointments or treatment after undergoing urodynamic examination during this study period. Telephone interviews with these cases revealed that most of the patients complained of discomfort felt during the examination and/or voiding irritative sensations misunderstood by them to be a urinary tract infection due to the examination. To avoid possible infection during examination and the discomfort caused by placing the catheter, the authors suggested that a non-invasive single uroflowmetry examination can be done before antimuscarinic use to predict the possibility of abnormal voiding symptoms after it is used.

In the authors' experience, they found Taiwanese women often could not tolerate a full dose of antimuscarinics over a long period. Side effects included not only dry mouth and abnormal voiding symptoms, but also dizziness, sleepiness, and constipation. They found patients were more concerned about the side effects rather than the effectiveness of the medication in the early treatment stage. This led the present authors to choose a half dosage in this study. Though there is no evidence confirming any difference due to ethnicity in antimuscarinic usage, the conjecture can be presumed from general pharmacology. The efficacy of medicine represents the observed interplay among multiple processes that regulate drug disposition (pharmacokinetics) and response (pharmacodynamics). For orally administered antimuscarinic agents, their pharmacologic action relies on adequate intestinal absorption and distribution to sites of action, before their elimination by metabolic and excretory pathways. The entire process can be described as the LADMER system (i.e. liberation, absorption, distribution, metabolism, elimination and response). Furthermore, some metabolism reactions are primarily mediated by the cytochrome P450 (CYP) family of enzymes, which are highly related with gene and race.

The mechanisms of OAB might be caused by more complicated factors and merit further investigation. Attention that OAB women with abnormal voiding patterns had a higher incidence of abnormal voiding symptoms than in OAB women with normal voiding patterns should be paid before administration of antimuscarinics. Though urodynamic study is not a necessary for diagnosis and treatment of OAB, single non-invasive uroflowmetry may be a good tool for a prediction of abnormal voiding symptoms after antimuscarinic use. Some side effects due to ethnic differences after antimuscarinics should be applied with great caution. For example, prescription of a lower dose is recommended. There were only a small number of patients involved in this study. Larger case number are needed to investigate the feasibility and effectiveness regarding this issue.

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