Efficacy and Safety of Propiverine and Solifenacin for the Treatment of Female Patients with Overactive Bladder: A Crossover Study

Naoki WADA, Masaki WATANABE, Masafumi KITA, Hiroaki OSANAI, Satoshi YAMAGUCHI, Atsushi NUMATA, and Hidehiro KAKIZAKI on behalf of the OAB Study Group in Northern Hokkaido

Department of Renal and Urologic Surgery, Asahikawa Medical University, Asahikawa, Japan and Department of Urology, Hokkaido Social Welfare Association Furano Hospital, Furano, Japan

Objectives: To evaluate the clinical efficacy and tolerability of propiverine and solifenacin in female patients with overactive bladder (OAB).

Methods: A prospective nonrandomized crossover study of propiverine 20 mg and solifenacin 5 mg was conducted. Female OAB patients were assigned alternately to treatment with propiverine for 8 weeks then solifenacin for 8 weeks (Group P-S) or solifenacin for 8 weeks then propiverine for 8 weeks (Group S-P). At baseline, 8th week and 16th week, symptoms were assessed using overactive bladder symptom score (OABSS).

Results: A total of 121 patients were enrolled. Overall, 38 patients (31.4%) discontinued or dropped out and 83 patients were available for analysis (39 in Group P-S and 44 in Group S-P). In both groups, the total score and each score of OABSS were significantly improved after 8 weeks compared with baseline. In only Group P-S (changing over from propiverine to solifenacin), urgency score in the 16th week was further improved significantly compared with the 8th week. The most bothersome symptom at baseline was urgency incontinence (50.6%), followed by urgency (37.3%). Even after symptom improvement, more than half of the patients were bothered by urgency or urgency incontinence. The incidence of adverse events of moderate and severe grade was higher during propiverine treatment than solifenacin (11.1% vs 2.9%, \( P = 0.039 \)).

Conclusion: Propiverine 20 mg and solifenacin 5 mg were effective for treating female OAB patients. Urgency was further improved after switching from propiverine to solifenacin, but not after switching from solifenacin to propiverine. Solifenacin was better tolerated than propiverine.

Key words overactive bladder, propiverine, solifenacin, urgency

1. INTRODUCTION

Overactive bladder (OAB) is defined by the International Continence Society as urinary urgency with or without urgency incontinence, usually with urinary frequency and nocturia.1 A Japanese epidemiologic survey of lower urinary tract symptoms (LUTS) showed that the overall prevalence of OAB in adults aged ≥40 years was 12.4%,2 which is similar to the overall prevalence of OAB in Western countries (16.6%).3 OAB symptoms have a huge negative impact on the patient’s quality of life (QOL). However, the percentage of patients who seek medical treatment of OAB because of impaired QOL from OAB symptoms is as low as 18%.2 Thus, there are many patients with OAB who are not being treated. To popularize and maximize clinical practice for OAB, a simple tool for assessing OAB symptoms is desirable. The overactive bladder symptom score (OABSS) was developed for this purpose.4 The OABSS consists of four storage symptoms, including daytime frequency, nighttime frequency, urgency and urgency incontinence.4 However, there is little English language literature on the efficacy of OABSS as an assessment tool of OAB symptoms.

Anticholinergic agents are the most common and currently the most effective drugs used to treat patients with OAB. Many previous studies reported a significant effect of anticholinergic agents on urinary frequency or urgency in patients with OAB. Among several anticholinergic agents available for OAB treatment, propiverine and solifenacin are most commonly prescribed in our country.

Propiverine (10–40 mg per day) is an antimuscarinic agent with mixed actions, including calcium antagonistic activity, which are enhanced by its pharmacologically

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active metabolites.\textsuperscript{5,6} Propiverine is the least selective drug for muscarinic receptor subtypes. Solifenacin (5–10 mg once daily) is one of the new anticholinergic agents that became available in 2006 in Japan. Solifenacin has a moderate selectivity for M3 over M2 receptor and apparent functional selectivity for the bladder over salivary gland.\textsuperscript{7,8} In the phase 3 trial in Japan, the efficacy and tolerability of solifenacin (5 or 10 mg once daily) was compared to placebo and propiverine (20 mg once daily) in Japanese patients with OAB.\textsuperscript{9} The authors concluded that solifenacin was no worse than propiverine 20 mg for improving OAB symptoms. It was the first comparative study of propiverine and solifenacin, but did not use OABSS as an assessment tool. We believed a clinical study should be conducted that would compare the efficacy of different anticholinergic agents on OAB symptoms by using OABSS. Therefore, the present study was conducted to compare the clinical efficacy and tolerability of propiverine and solifenacin in female patients with OAB. In the present study, OABSS was used as an assessment tool of OAB symptoms.

2. METHODS

This was a nonrandomized crossover study of propiverine and solifenacin without a washout period in view of the disadvantages of patients. Each patient was informed of the nature and purpose of the study and written informed consent was obtained. Women with OAB were eligible for the study. According to the clinical guideline of OAB,\textsuperscript{10} OAB was diagnosed by using OABSS; urgency score \( \geq 2 \) and total score \( \geq 3 \). Exclusion criteria were urinary tract malignancy, postvoid residual urine \( \geq 100 \) mL, bladder stone, urinary tract infection, severe heart disease, liver dysfunction, renal dysfunction and dementia. Concomitant treatment with other medication that would affect lower urinary tract function was not permitted, including anticholinergic drugs, \( \alpha \)-adrenergic antagonist, medications for Parkinson’s disease and depression, and antihistaminergic drugs.

The study design is shown in Fig. 1. Eligible patients were assigned alternately to two groups (Group P-S and Group S-P). Patients in Group P-S received 20 mg of propiverine per day for the first 8 weeks and then 5 mg of solifenacin per day for the next 8 weeks. In contrast, patients in Group S-P received 5 mg of solifenacin per day for the first 8 weeks and then 20 mg of propiverine per day for the next 8 weeks. OAB symptoms were assessed at baseline, 8 weeks and 16 weeks after treatment using OABSS. At each of the three time points (baseline, 8 weeks and 16 weeks after treatment), patients indicated which was most the bothersome of four symptoms of OABSS. At the end of the study, patients were asked to choose either propiverine or solifenacin as the drug they wanted to continue.

The primary endpoint of the study was change of total score and each score of OABSS from baseline to the 8th week and from the 8th to the 16th week. The secondary endpoint was treatment-associated change of the most bothersome symptom. These analyses were made based on the available patients who completed the full study and did not discontinue or drop out.

Safety assessment was conducted for all patients, including those who discontinued drugs because of adverse events. The severity of adverse events was assessed using the following three-point scale: mild (hardly bothersome); moderate (tolerable); and severe (intolerable). Study was discontinued at each physician’s discretion if adverse events occurred.

For the analysis of primary variables, we compared symptom score from baseline to the 8th week and from the 8th to the 16th week in each group using Wilcoxon signed-rank test with a significance level of 0.05. We used \( \chi^2 \) test for adverse event rate in each drug and final drug selection by patients.

3. RESULTS

A total of 121 patients from 11 institutions were enrolled in the study and assigned into Group P-S (59 patients) and Group S-P (62 patients). Overall, 38 patients (31.4%) discontinued before completing the study, including 20 patients in Group P-S and 18 patients in Group S-P (Fig. 2). In Group P-S, 17 of the 20 patients (85%) discontinued before crossover, while in Group S-P, 13 of the 18 patients (72.2%) discontinued before crossover (Fig. 2). Twenty-two patients discontinued during propiverine treatment, including four patients due to adverse events (digestive trouble, vertigo, increased postvoid residual, dry mouth) and 18 patients for other reasons (worsening of symptom in 2. rejection of crossover in 10, dropout in 6). In contrast, 16 patients discontinued during solifenacin treatment, including 2 patients due to adverse events (constipation, blurred vision) and 14 patients for other reasons (worsening of symptom in 1, rejection of crossover in 11, dropout in 2). Finally, 83 patients who completed the full study were available for analysis. Of these 83 patients, 77 (92.7%) had wet OAB with urgency incontinence and 6 (7.2%) had dry OAB without urgency incontinence. According to the clinical guideline of OAB,\textsuperscript{10} OABSS 5 or less, 6–11, and 12 or greater were defined as mild, moderate, and severe OAB, respectively. In Group P-S, 26 (66.7%) and 13 (33.3%) patients were categorized as having moderate and severe OAB, respectively. In Group S-P, 29 (65.9%) and 14
(31.8%) patients were categorized as having moderate and severe OAB, respectively.

Among the available patients both groups were well balanced for age, and total and each score of OABSS at baseline (Table 1).

Compared with baseline, at the 8th week Group P-S and Group S-P showed significant improvement in total score and each score of OABSS ($P < 0.01$) (Fig. 3). At the 16th week total score of OABSS and nighttime frequency score were further improved compared with the 8th week in both groups. However, in only Group P-S urgency score at the 16th week was further improved significantly compared with the 8th week. In 27 patients with severe OAB (13 in Group P-S and 14 in Group S-P), total score of OABSS was significantly improved at the 8th week and further improved at the 16th week in both groups (Fig. 4). In contrast, total score of OABSS was significantly improved at the 8th week, but not further improved at the 16th week in 55 patients with moderate OAB (26 in Group P-S and 29 in Group S-P). Finally, at the 16th week patients with moderate and severe OAB reached almost equal OABSS (Fig. 4).

At baseline, the most bothersome symptom was urgency incontinence (50.6%), followed by urgency (37.3%) and nighttime frequency (9.6%) (Fig. 5). At the 8th week, the most bothersome symptom was urgency (39.8%), followed by urgency incontinence (25.3%) and nighttime frequency (24.1%). At the 16th week, the most bothersome symptom was urgency (30.1%) and nighttime frequency (30.1%), followed by urgency incontinence (21.7%). Thus, the rate of urgency incontinence as the most bothersome symptom decreased from 50.6% at baseline to 21.7% at the 16th week, and the rate of urgency as the most bothersome symptom decreased slightly from 37.3% at baseline to 30.1% at the 16th week, while the rate of nighttime frequency as the most bothersome symptom increased from 9.6% at baseline to 30.1% at the 16th week. There was no significant difference in the distribution of the most bothersome symptom between Group P-S and Group S-P.

Adverse events were reported in 25.9% of the patients treated with propiverine and 16.3% of the patients treated with solifenacin. The most frequent adverse event was dry mouth, which was reported in 15.7% of the patients treated with propiverine and 10.6% of the patients treated with solifenacin. The overall incidence of adverse events was not significantly different between propiverine and solifenacin ($P = 0.088$). However, the incidence of adverse events of moderate and severe grade was significantly higher in propiverine (11.1%) than in solifenacin (2.9%) ($P = 0.039$). In the first 8 weeks, dry mouth and constipation were reported in 15.3 and 3.4% of the patients treated with propiverine and 14.5 and 6.5% of the patients treated with solifenacin, respectively. In contrast, in the last 8 weeks, dry mouth and constipation were reported in 16.3 and 6.1% of the patients treated with propiverine and 4.8% and none of the patients treated with solifenacin, respectively.

Eighty-three patients completed the study and finally selected which drug they wanted to continue. Fifty-one patients (61.4%) selected solifenacin, 21 patients (25.3%) selected propiverine, and others (13.3%) selected neither. There was a significant difference in the selection rate between solifenacin and propiverine ($P = 0.011$, $\chi^2$ test). Of the 21 patients who selected propiverine, 4 patients and only 1 patient had adverse events while taking solifenacin and propiverine, respectively. Adverse events in these five patients were mild grade. In contrast, of the 51 patients who selected solifenacin, 29 and 12 patients had adverse events while taking propiverine and solifenacin, respectively. Adverse events in 12 patients while taking solifenacin were mild grade; however, 8 of 29 patients with adverse events while taking propiverine had moderate and severe grade.

### 4. DISCUSSION

The present study was a nonrandomized crossover study of propiverine and solifenacin using OABSS for female patients with OAB. The results showed that propiverine 20 mg and solifenacin 5 mg were effective for treating female OAB patients. Urgency was further improved after switching from propiverine to solifenacin, but not after switching from solifenacin to propiverine. Solifenacin was better tolerated than propiverine.

OAB is a symptom syndrome with urgency, frequency, and urgency incontinence. A valid tool for describing the symptoms was needed because OAB syndrome is defined...
Fig. 3 Change of total score and each score of overactive bladder symptom score (OABSS) over 16 weeks. *P < 0.01 versus baseline; †P < 0.05; ‡P < 0.01 versus at 8th week. OABSS, overactive bladder symptom score.
The score is obtained as the simple sum of four symptom scores, which address daytime frequency, nighttime frequency, urgency and urgency incontinence. The relative weight among the four scores was determined on the basis of the maximal influence rate of the symptom in the epidemiologic survey. However, OABSS is not universal and there is little English language literature on clinical study of OAB using OABSS. In the present study we used OABSS to compare solifenacin 5 mg with propiverine 20 mg for the treatment of female patients with OAB.

Anticholinergic agent is now the first-line drug for medical treatment of OAB patients. Selectivity for bladder and muscarinic receptor subtypes is a key component of the therapeutic potential of anticholinergics and affects adverse event profiles. M2 and M3 receptors are the main muscarinic receptors that are involved in bladder control. Anticholinergic agents might block acetylcholine binding at more than one muscarinic receptor subtype. Further, receptor-selective agents might block muscarinic receptors outside the bladder and cause adverse events. Propiverine is one of the least selective anticholinergic agents, while solifenacin has a moderate selectivity for M3 receptor over M2 receptor. Compared with propiverine, solifenacin has greater selectivity for muscarinic receptors of the bladder than the salivary gland.7,8

In the present study, both propiverine and solifenacin significantly improved total score and each score of OABSS by the first 8 weeks of administration compared with baseline. This result confirms the usefulness of both drugs for improving OAB symptoms in a clinical setting. After changing over drugs at the 8th week, total score of OABSS and nighttime frequency score were further improved significantly at the 16th week compared with the 8th week in both groups. The only difference in the two groups was that urgency score was further improved at the 16th week only after changing over from propiverine to solifenacin at the 8th week (Group P-S). The efficacy of anticholinergics is mediated through the blockade of the muscarinic receptor in the detrusor muscle and the urothelium. Chuang reported the interesting results that urine collected from humans who had taken solifenacin suppressed carbachol-induced bladder overactivity in rats but urine collected after intake of tolterodine or darifenacin did not suppress carbachol-induced bladder overactivity.11 Urine excreted after oral ingestion of solifenacin may provide a localized pharmacological advantage for OAB. However, in the present study we did not set a washout period at the time of changing over from propiverine to solifenacin at the 8th week (Group P-S).
dry OAB patients. This may be the reason why the incidence of wet OAB patients was so high in the present study. The most bothersome symptom in the present study was urgency incontinence (50.6%), followed by urgency (37.3%). As OAB symptoms were improved by anticholinergic agents, the percentage of patients who felt urgency incontinence as the most bothersome symptom decreased to 21.7%. At the same time the percentage of patients who felt nighttime frequency as the most bothersome symptom increased from 9.6 to 30.1%, while the rate of urgency as the most bothersome symptom did not change so much (from 37.3% at baseline to 30.1% at the 16th week). These findings suggest several issues. If the most bothersome symptom is improved by the treatment, then other symptom can be the most bothersome symptom. Although symptom of nighttime frequency itself is improved by anticholinergic agents, the bother of nighttime frequency increases after the amelioration of urgency incontinence and urgency. This may be consistent with the results of epidemiologic survey of LUTS.14 In that survey nighttime frequency was most frequently (38%) reported to have the greatest impact on health-related QOL. However, it should be noted that more than half of the patients were still bothered by urgency or urgency incontinence after treatment with anticholinergic agents and only 8.4% of the patients had no bothersome symptom after 16-week treatment of propiverine and solifenacin. Higher dosage of these drugs than were used in the present study or other anticholinergic agents may resolve the persisting bother. In clinical practice, however, we should take into account that many patients with OAB continue to be bothered by urgency or urgency incontinence even after symptom improvement. To obtain much higher patient satisfaction, more powerful agents with different pharmacological actions from anticholinergic drugs may be needed.

Regarding drug selection by the patients, solifenacin was more dominant than propiverine. Because in the present study we did not examine the exact reason why each patient selected propiverine or solifenacin as the drug they wanted to continue, we must be careful about the interpretation of the results. However, we speculate that the reason why more patients selected solifenacin is related to tolerability of drugs. The present study showed that adverse events of moderate and severe grade during solifenacin treatment occurred less frequently than during propiverine treatment. In a previous report solifenacin 5 mg was better tolerated than solifenacin 10 mg or propiverine 20 mg.9 Although the incidence of adverse events was not different between solifenacin 5 mg and propiverine 20 mg, most adverse events during solifenacin treatment were mild grade. This difference may originate from more favorable muscarinic receptor selectivity of solifenacin than propiverine.

In the present study only female patients with OAB were enrolled. The results of the present study should not be extrapolated into male patients with OAB. Male patients have different aspects of pathophysiology of OAB. In male patients, OAB is often, but not always associated with bladder outlet obstruction. Although the efficacy and safety of anticholinergic agents on male OAB patients as monotherapy or in combination with α-adrenergic antagonists have been reported, further study is mandatory to compare clinical efficacy and tolerability of different anticholinergic agents on male OAB patients.

In conclusion, both propiverine 20 mg and solifenacin 5 mg once daily are effective for treating female OAB patients. These drugs effectively reduce total score and each score of OABSS. Solifenacin 5 mg may be more effective for treating urgency and better tolerated than propiverine 20 mg. However, it should be kept in mind that many OAB patients are not completely satisfied even after improvement of OAB symptoms with anticholinergic agents.

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