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Propiverine hydrochloride in Japanese patients with overactive bladder: A randomized, double-blind, placebo-controlled trial

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Objectives: The aim of this study was to investigate the efficacy and safety of propiverine for overactive bladder (OAB) in Japanese patients.

Methods: In this multicentre, randomized, double-blind study, patients ≥20 years old with symptoms of OAB for ≥12 weeks were allocated to either propiverine (20 mg once daily) or placebo for 12 weeks. Efficacy and quality of life were assessed using a 7-day bladder diary, the OAB symptom score, and King's Health Questionnaire. Safety was mainly assessed by adverse events and the QTc interval.

Results: A total of 567 patients were allocated. Change in number of micturitions/24 h was significantly greater in the propiverine group than in the placebo group (-1.86 *vs* -1.36, $P = 0.001$). Compared to placebo, propiverine produced significant improvements in urgency, urgency incontinence, urine volume/micturition, and the OAB symptom score. Significant improvements in urgency, urgency incontinence, and micturition frequency were observed at the first 4 weeks of treatment. All nine domains of King's Health Questionnaire were improved more with propiverine than with placebo. Adverse effects with propiverine were mostly mild, and no patient developed QTc interval prolongation exceeding 500 ms.

Conclusion: Propiverine is effective for Japanese OAB patients by improving their symptoms and quality of life with a predictable side-effect profile.

Key words: Japanese, overactive bladder, placebo, propiverine hydrochloride, randomized controlled trial.

Introduction

Overactive bladder (OAB) is characterized by symptoms of urgency, with or without urgency incontinence, usually with frequency and nocturia.[1] OAB symptoms are suggestive of urodynamically demonstrable detrusor overactivity.[1]

There are two main options for primary treatment of OAB: bladder training and drug therapy using anticholinergic agents.[2] Anticholinergic agents are often used to reduce detrusor overactivity and improve OAB symptoms. Since muscarinic receptors are distributed not only in the bladder but also in other organs, anticholinergic agents may cause a variety of adverse effects. Attention should be paid to adverse effects when anticholinergic agents are used.

Propiverine hydrochloride, a typical anticholinergic agent, also acts as a calcium channel antagonist,[3,4] and it is

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widely used in many countries to treat urinary incontinence, as well as frequency associated with detrusor overactivity, such as neurogenic bladder and bladder irritation. In 2002, the International Continence Society (ICS) comprehensively reviewed the terminology of lower urinary tract functions and dysfunctions; consequently, they introduced a new term, "overactive bladder", for symptom-based diagnosis and recommended the term "detrusor overactivity" for urodynamic findings characterized by involuntary detrusor contractions during the filling phase.[1] Detrusor overactivity can be further qualified as neurogenic detrusor overactivity, when there is a relevant neurological condition, or idiopathic detrusor overactivity, when there is no defined cause.[1] In response, the indication for propiverine was reviewed in some European countries, such as Germany and the UK, and it was revised to "idiopathic detrusor overactivity (OAB) or neurogenic detrusor overactivity from spinal cord injuries". Propiverine has become indicated for OAB in those countries.

The efficacy and safety of propiverine for OAB have been studied in a few randomized, controlled trials (RCT).[5–7] One of the trials showed its efficacy for urgency, a key symptom of OAB, as well as frequency and urgency incontinence.[5]

However, in Japan, the efficacy and safety of propiverine have only been confirmed in patients with detrusor overactivity. OAB is often caused by detrusor overactivity, but OAB is not necessarily consistent with detrusor overactivity; for instance, OAB patients do not always have urodynamic findings. So far, propiverine has been used as the active control drug in two RCT of Japanese OAB patients, and in both trials, its efficacy and safety were demonstrated.[8,9] However, these trials were not designed to investigate the superiority of propiverine to placebo.

The efficacy of propiverine for OAB has not been investigated in a Japanese population. The aim of this study was to confirm its superior efficacy over placebo in Japanese OAB patients. The study results were used as evidence in the application for an additional indication for propiverine.

Methods

Male and female outpatients ≥20 years old with OAB symptoms for at least 12 weeks were enrolled in the study. Patients with ≥8 micturitions/24 h as an essential condition and ≥1 urgency incontinence episodes/24 h or ≥1 urgency episodes/24 h were included in this study. The key exclusion criteria were symptoms such as apparent stress urinary incontinence, polyuria with a daily urine volume ≥3000 mL, or a post-void residual volume ≥100 mL. Patients who had lower urinary tract obstruction diseases, received α1-blocker treatment for benign prostatic hyperplasia (BPH), or underwent prostatectomy were also excluded.

This study was conducted as a randomized, double-blind, multicentre, placebo-controlled, phase III study. Fifty-eight clinics and hospitals nationwide in Japan participated. This study was reviewed and approved by the central institutional review boards (IRB) or by the IRB of the participating medical institutions and was performed in conformity with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All patients gave their written, informed consent as approved by the IRB.

A 2-week screening period was required before enrollment. Patients were given placebo once a day in a single-blinded fashion during the screening period, and those who met the enrollment criteria were randomly allocated to propiverine 20 mg, which is the standard dose in Japan, and placebo groups at 1:1. The test drug was given once a day for 12 weeks. To evaluate efficacy and safety, patients visited clinics and hospitals at the time of enrollment (baseline) and 4, 8, and 12 weeks (or at the end of treatment [EOT]) after enrollment. For randomized allocation, block allocation consisting of four patients per set was used. The random allocation sequence was concealed from the investigators enrolling patients until the treatment assignments were completed. Patients and investigators were blinded to treatment assignment during the study.

Table 1 Overactive bladder symptom score

Question	Response	Score
Q1. How many times do you typically urinate from waking in the morning until sleeping at night?	≤7	0
	8–14	1
	≥15	2
Q2. How many times do you typically wake up to urinate from sleeping at night until waking in the morning?	0	0
	1	1
	2	2
	≥3	3
Q3. How often do you have a sudden desire to urinate, which is difficult to defer?	None	0
	< once/week	1
	≥ once/week	2
	About once/day	3
	2–4 times/day	4
	≥5 times/day	5
Q4. How often do you leak urine because you cannot defer the sudden desire to urinate?	None	0
	< once/week	1
	≥ once/week	2
	About once/day	3
	2–4 times/day	4
	≥5 times/day	5

Patients were instructed to circle the score that best applied to their urinary condition during the past week; the overall score was the sum of the four scores.

Efficacy was evaluated based on a 7-day bladder diary and overactive bladder symptom score (OABSS).[10]

In the 7-day bladder diary, micturition conditions (micturition, urgency, and urgency incontinence) were recorded for 7 days before each visit. The times of micturition and urgency were also recorded, and at each micturition on the last 3 days of the 7-day period, the urine volume (mL) was recorded. The 7-day bladder diary was collected at each evaluation time point (baseline and 4, 8, and 12 weeks [or at EOT]).

The OABSS is a symptom assessment questionnaire designed to comprehensively quantify OAB symptoms based on the total score, and it is psychometrically well validated (Table 1).[10]

The primary end-point was change in the number of micturitions/24 h from baseline at 12 weeks. When the value at 12 weeks could not be obtained, the last observed value was used, following the principle of last-observation-carried-forward (LOCF). The secondary end-points were changes in the: number of urgency and urgency incontinence episodes/24 h; urine volume/micturition; and number of nocturia episodes. Changes from baseline at each evaluation time point in the OABSS score were also included in the secondary end-point.

For evaluation of patients' quality of life (QOL), a well-validated questionnaire to measure QOL in patients with

lower urinary tract symptoms, King's Health Questionnaire (KHQ), was used. Patients answered the Japanese version of KHQ[11] at baseline and at 12 weeks, and changes in each domain were evaluated.

Safety was evaluated by adverse events, general laboratory tests, 12-lead electrocardiograms (ECG), blood pressure, and pulse rate. The severity of adverse events was classified into mild, moderate, and severe. Adverse events judged as causally related to the test drug by the investigators were regarded as adverse effects.

Statistical analyses of efficacy and QOL were performed on the full analysis set (FAS) population. The FAS included patients who took at least one dose of the test drug and whose primary efficacy was evaluated at least once, and excluded patients who withdrew their consent, or violated inclusion or exclusion criteria. Safety analyses were performed on patients who took at least one dose of the test drug. Descriptive analyses of the baseline demographic and clinical characteristics were performed. Superior efficacy of propiverine over placebo was confirmed by comparing the primary end-point between the groups. Regarding the secondary end-points, changes were compared between the groups.

For the KHQ, the score was calculated for each domain and compared between the groups.

The incidence of each adverse event was calculated in each treatment group and compared between the groups. The severity and the presence or absence of a causal relationship were summarized for each adverse event. The incidence of abnormal 12-lead ECG was also calculated and compared between the groups. For wording of adverse events and adverse effects, System Organ Class and Preferred Term of MedDRA/JVer.11.0 (MedDRA Japanese Maintenance Organization, Tokyo, Japan) were used.

To confirm superiority of propiverine to placebo, the number of required cases was calculated as 240 per group using previous study results[9] at a two-sided significance level of 5% and power of 90%. The target number of enrollments was set at 250 per group, 500 in total, considering discontinuations and dropouts. For efficacy and QOL, the changes at 12 weeks from baseline were calculated in each treatment group. The two-sided 95% confidence interval was calculated for efficacy, QOL, and safety parameters. The t-test was used for between-group comparisons of continuous variables, and Fisher's direct probability method was used for comparisons between groups of categorical variables. All statistical tests were two-tailed, and conducted with a significance level of 0.05. SAS software ver. 8.2 was used for statistical calculations.

Results

Of the 665 patients screened between November 2007 and June 2008, 567 patients were enrolled and randomly allo-

cated. A patient with duplicate enrollment was excluded before drug administration, and the remaining 565 patients were included in the safety analysis population. After excluding 11 patients (1.9%) from the safety analysis population, 554 patients were regarded as the FAS, that is, the efficacy analysis population (Fig. 1). There were no important differences between the propiverine and placebo groups in the demographic or clinical characteristics at baseline (Table 2). In this study population, there were more female than male patients, and most patients had urinary incontinence, for which urgency incontinence accounted for about 70%.

The efficacy results are summarized in Table 3. The number of micturitions/24 h was fewer at 12 weeks than at baseline in both groups. However, the change in the number of micturitions/24 h, the primary end-point, was significantly greater in the propiverine group than in the placebo group.

Urgency and urgency incontinence episodes decreased throughout the treatment period in the propiverine group compared to those in the placebo group, while the urine volume/micturition increased throughout the treatment period compared to that in the placebo group (Fig. 2). The differences between the groups in these evaluation items were significant at all evaluation time points (4, 8, and 12 weeks). The change in the OABSS total score was greater in the propiverine group than in the placebo group (Table 3).

Changes in KHQ score by domain at 12 weeks are shown in Figure 3. The domain scores improved in the propiverine group compared to the placebo group in seven domains: incontinence impact, role limitations, physical limitations, social limitations, emotions, sleep/energy, and severity. The differences between the groups in the changes were significant.

The incidence of adverse effects in the safety analysis population was 27.5% (80 patients) in the propiverine group and 9.9% (27 patients) in the placebo group, showing a significantly higher incidence in the propiverine group ($P < 0.001$). The main adverse effects and their incidence are shown in Table 4. The severity of adverse effects was mostly mild in both groups. There was one known serious adverse effect: a liver function abnormality, possibly due to hepatitis C, which was diagnosed after discontinuation of propiverine. Urinary retention was not observed in either group.

There were no clinically important differences between propiverine and placebo in the laboratory test values, blood pressures, or pulse rates. There was no clinically relevant difference in QTc (Bazett) between the groups, and there were no patients with QTc interval exceeding 500 ms at 12 weeks in either group. Abnormal 12-Lead ECG variations were noted in three patients each in the propiverine and placebo groups, showing no significant difference between the groups.
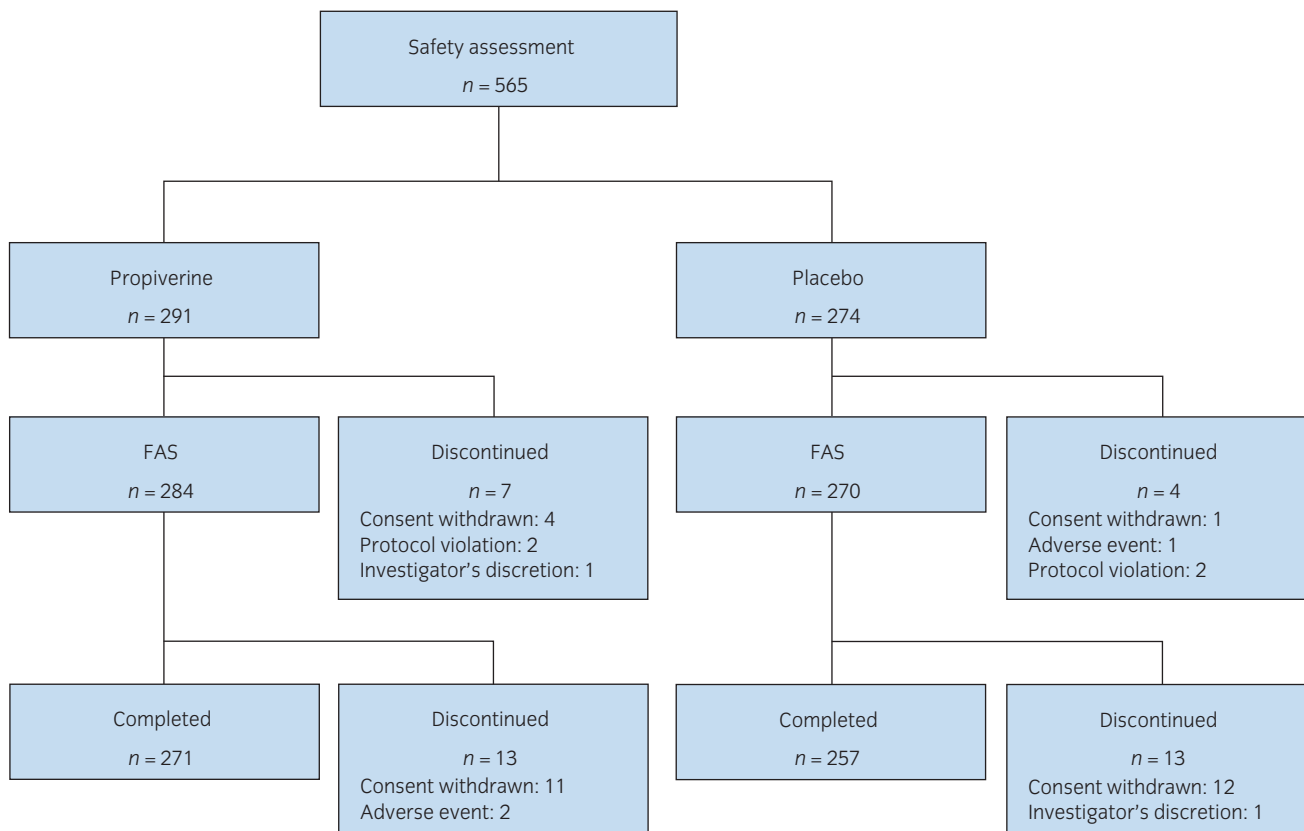
Fig. 1 Patients' disposition. FAS, full analysis set.

Discussion

The objective of this study was to investigate the efficacy and safety of propiverine for OAB in Japanese patients and confirm the superior efficacy of the drug over placebo. The number of micturitions/24 h was reduced at 12 weeks in the propiverine group compared to that in the placebo group; the difference between the groups in the change was significant, confirming the superiority of propiverine to placebo. In addition, the efficacy of propiverine for OAB symptoms (urgency, frequency, and urgency incontinence) was confirmed by comparison with placebo in Japanese OAB patients. Furthermore, QOL, which was reduced by OAB, was improved by propiverine. Adverse effects and their severity were within a range predictable from previous experience with the use of propiverine.

The number of urgency episodes, micturitions, and urgency incontinence episodes, urine volume/micturition, and the total OABSS score over 12 weeks after treatment improved in both the propiverine and placebo groups. Improvements were significantly greater in the propiverine group than in the placebo group throughout the evaluation period. The result that propiverine improved OAB symptoms as early as 4 weeks after treatment started suggests that the efficacy of propiverine for OAB can be seen from the early stages of drug therapy. In this study, the efficacy of propiverine for urgency and urgency incontinence was remarkable. With propiverine treatment, urgency episodes decreased to almost once a day, and urgency incontinence episodes decreased to 2–4 times a week. These changes are important differences for patients and may help patients be aware of the efficacy of their treatment. The number of nocturia episodes was also decreased in both groups, though the change between the groups was not significantly different. The baseline number of nocturia episodes was small in this study population (mean, 1.30 for propiverine and 1.40 for placebo). About one nocturia episode is common in the elderly independent of OAB, and nocturia is affected by many factors other than OAB, such as nocturnal polyuria and sleep disorders. These may have affected the interpretation of the efficacy of propiverine for nocturia. The efficacy of propiverine for OAB in Japanese patients was previously observed.[8,9] However, previous studies were not designed to confirm its superiority to placebo. The efficacy of propiverine for various OAB symptoms was confirmed in this study, which was strictly designed to verify its superiority to placebo.

Propiverine was effective for urgency, frequency, and urgency incontinence, suggesting that it contributes to improving overall OAB symptoms. The main cause of OAB

Table 2 Baseline characteristics of patients included in the full analysis set population

Characteristic	Propiverine	Placebo
	n = 284	n = 270
Age (years)		
Mean (SD)	56.6 (13.6)	58.7 (14.1)
95%CI	55.1–58.2	57.0–60.4
Median (Range)	58.0 (23–85)	61.0 (21–93)
Sex		
Male, n (%)	68 (23.9)	63 (23.3)
Female, n (%)	216 (76.1)	207 (76.7)
Weight (kg)		
Mean (SD)	57.35 (10.48)	56.73 (9.68)
95%CI	56.13–58.58	55.57–57.89
Median (Range)	55.90 (34.3–101.0)	55.00 (34.0–90.0)
Duration from onset of symptoms (years)		
<1 year, n (%)	42 (14.8)	40 (14.8)
1–3 years, n (%)	100 (35.2)	92 (34.1)
≥3 years, n (%)	142 (50.0)	138 (51.1)
Type of incontinence present at beginning of run-in period		
None, n (%)	10 (3.5)	6 (2.2)
Present, n (%)	274 (96.5)	264 (97.8)
Urge urinary incontinence, n (%)	204 (74.5)	183 (69.3)
Mixed urinary incontinence, n (%)	70 (25.5)	81 (30.7)
Post-void residual volume (mL)		
Mean (SD)	7.95 (12.60)	9.89 (16.86)
95%CI	6.48–9.42	7.87–11.91
Median (Range)	0.00 (0.0–79.1)	0.00 (0.0–98.5)

CI, confidence interval; SD, standard deviation.

is detrusor overactivity, i.e. involuntary detrusor contraction. Detrusor contraction activity is controlled by the intracellular calcium ion level.[12] Unlike many other anticholinergic drugs for OAB, propiverine has multiple actions to inhibit bladder smooth muscle contraction: antimuscarinic action and Ca^{2+} channel antagonism, which indirectly suppresses atropine-resistant contraction.[13–15] These mixed actions of propiverine may be one reason for its satisfactory efficacy in OAB patients with diverse backgrounds.

Since OAB negatively influences daily living activities and reduces QOL, improvement of QOL should also be considered, as well as improvement of symptoms, in the evaluation of treatment efficacy. Based on the KHQ evaluation, all nine domains were more markedly improved with propiverine than with placebo, and between-group differences in changes were significant in seven domains. It is suggested that, especially by improving urgency and urgency incontinence episodes, propiverine may have improved the daily living activities impaired by OAB.

No major difference in safety was noted with propiverine compared to placebo. The incidence of adverse effects was higher with propiverine than with placebo, but their severity was mostly mild. In no patient did the QTc interval exceed 500 ms, showing that the risk of QT interval prolongation is low with propiverine. Urinary retention, a concern with anticholinergic agents, did not occur in either group. Propiverine has been used for 15 years, and there is sufficient information about its safety. As the adverse effects observed in this study were within a range predictable from previous reports, the possibility of developing adverse effects that have not previously been reported is considered to be very low, and even if adverse effects occur, they may be treatable.

The ratio of female patients in this study population (76–77%) was greater than that in the general Japanese OAB patient population. This might be due to reduction of the number of enrolled male patients by excluding patients, including those who had lower urinary tract obstruction diseases, received α1-blocker treatment for BPH, or underwent prostatectomy. As the duration of administration was 12 weeks, the efficacy and safety of long-term administration of propiverine for OAB patients were not confirmed. However, based on the safety data of more than 10 000 cases collected during the 6-year re-examination period and adverse effect reports of 1500 cases collected over 15 years'

Table 3 Efficacy end-point results of full analysis set population

Efficacy variables	Treatment groups	Baseline Mean (95%CI)	4 weeks Mean (95%CI)	8 weeks Mean (95%CI)	End of treatment Mean (95%CI)	Change Mean (95%CI)	P-value
Micturition per 24 h	Propiverine	11.03 (10.78, 11.28)	9.61 (9.36, 9.86)	9.29 (9.03, 9.55)	9.17 (8.93, 9.41)	−1.86 (−2.07, −1.64)	0.001
	Placebo	11.10 (10.80, 11.40)	10.37 (10.07, 10.67)	9.97 (9.67, 10.26)	9.74 (9.45, 10.03)	−1.36 (−1.56, −1.16)	
Urgency episodes per 24 h	Propiverine	4.33 (3.99, 4.67)	2.29 (2.02, 2.56)	1.86 (1.59, 2.13)	1.49 (1.25, 1.74)	−2.84 (−3.13, −2.54)	<0.001
	Placebo	4.17 (3.80, 4.53)	3.07 (2.75, 3.40)	2.51 (2.17, 2.84)	2.18 (1.84, 2.51)	−1.99 (−2.30, −1.68)	
Urgency incontinence episodes per 24 h	Propiverine	1.61 (1.37, 1.85)	0.56 (0.42, 0.69)	0.51 (0.36, 0.66)	0.43 (0.26, 0.59)	−1.18 (−1.40, −0.97)	<0.001
	Placebo	1.22 (1.09, 1.36)	0.89 (0.75, 1.03)	0.71 (0.56, 0.86)	0.55 (0.41, 0.69)	−0.68 (−0.81, −0.54)	
Urine volume (mL) per micturition	Propiverine	158.50 (152.62, 164.38)	179.52 (172.73, 186.30)	182.73 (175.87, 189.59)	183.98 (177.60, 190.36)	25.48 (21.32, 29.64)	<0.001
	Placebo	161.62 (155.22, 168.02)	166.33 (159.50, 173.15)	170.09 (163.22, 176.96)	169.79 (162.88, 176.71)	8.18 (3.82, 12.53)	
Nocturia episodes	Propiverine	1.30 (1.18, 1.42)	1.10 (0.98, 1.22)	1.05 (0.94, 1.17)	1.01 (0.89, 1.12)	−0.29 (−0.37, −0.22)	0.471
	Placebo	1.40 (1.27, 1.54)	1.27 (1.15, 1.40)	1.19 (1.06, 1.32)	1.15 (1.02, 1.28)	−0.25 (−0.34, −0.17)	
OABSS score	Propiverine	8.4 (8.1, 8.7)	5.9 (5.6, 6.3)	5.3 (4.9, 5.7)	4.7 (4.4, 5.1)	−3.7 (−4.0, −3.4)	<0.001
	Placebo	8.2 (8.0, 8.5)	7.2 (6.9, 7.5)	6.4 (6.0, 6.7)	5.8 (5.4, 6.2)	−2.4 (−2.8, −2.1)	

Changes shown are calculated by subtracting end of treatment (12 weeks or last-observation-carried-forward) values from baseline. *P*-values of changes between propiverine and placebo were derived with the *t*-test. CI, confidence interval; OABSS, overactive bladder symptom score.
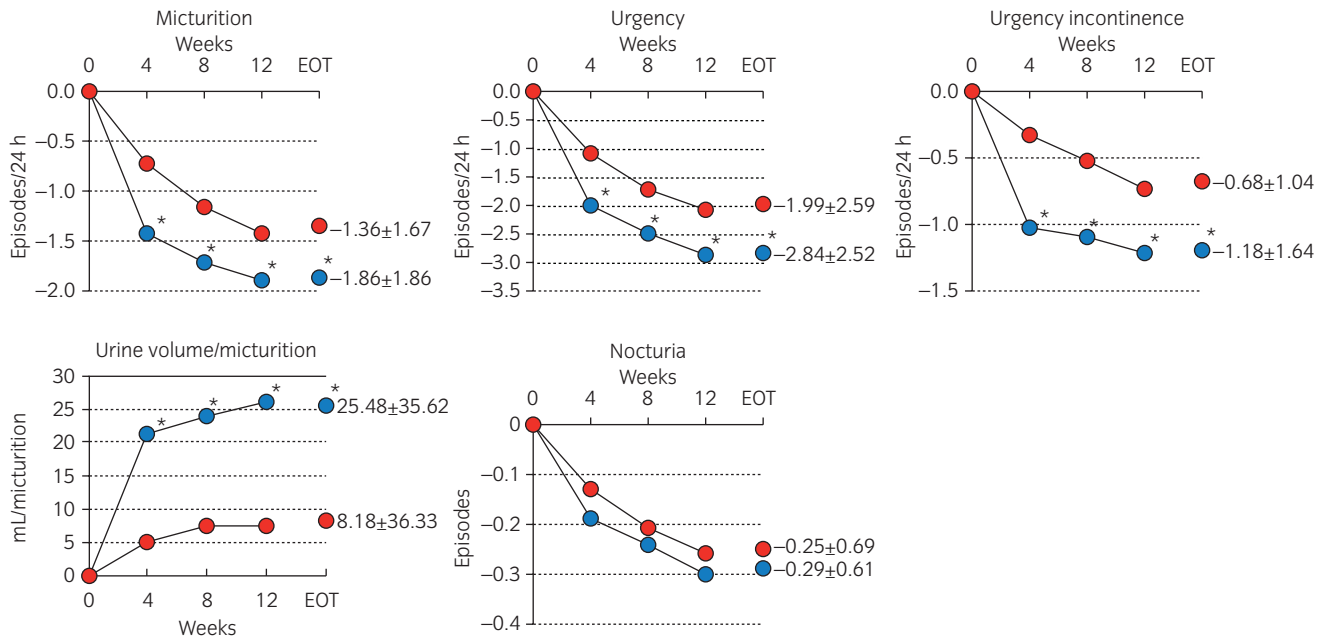
Fig. 2 The mean change over the 12 weeks in urinary episodes and urine volume per micturition. *P < 0.05, propiverine *vs* placebo. End of treatment (EOT) results: mean ± standard deviation. (●) Propiverine; (●) Placebo.
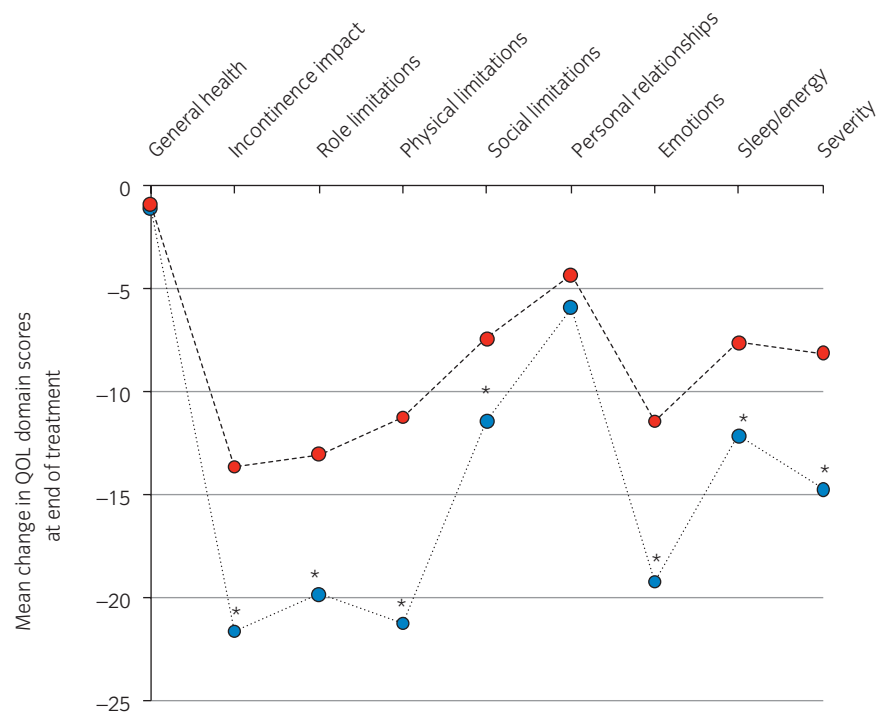
Fig. 3 The mean change from baseline to end of treatment in quality of life (QOL) domain scores of King's Health Questionnaire (n = 280). *P < 0.05, propiverine *vs* placebo. (●) Propiverine; (●) Placebo.

post-marketing experience, adverse effects develop in the early phase of administration before 4 weeks in many cases.[16] Accumulated results of drug use in clinical practice suggest that adverse effects are less likely to develop after 12 weeks of administration.

This study confirmed the efficacy and safety of propiverine for OAB. The present study was the first RCT that

confirmed the efficacy of propiverine for urgency in Japanese OAB patients. It has been reported that propiverine can improve storage dysfunction not only in patients with neurogenic detrusor overactivity from spinal cord injuries,[17] but also in those with idiopathic detrusor overactivity,[18] suggesting wide application of this drug for a variety of storage dysfunctions.

Table 4 Major anticholinergic adverse effects in the safety analysis population

Adverse effects	Propiverine (*n* = 291)		Placebo (*n* = 274)	
	n	%	*n*	%
Dry mouth	57	(19.6)	10	(3.6)
Constipation	18	(6.2)	6	(2.2)
Blurred vision	1	(0.3)	0	(0.0)
Urinary hesitancy	1	(0.3)	0	(0.0)
Decreased urine flow	1	(0.3)	0	(0.0)
Residual urine	1	(0.3)	0	(0.0)

The severity of adverse effects was mostly mild in both groups. The number of patients who had moderate or severe adverse effects was 1 for dry mouth; 1 for urinary hesitancy; and 2 for constipation.

Propiverine, 20 mg once daily for 12 weeks, was effective for Japanese OAB patients and improved patients' symptoms and QOL. Adverse effects and their severity were within a range predictable from previous experience.

Acknowledgments

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Appendix I

Members of the Japanese Propiverine Study Group in the study are as follows (in alphabetical order): Y Aarai, Tokyo; H Aikawa, Chiba; T Arai, Saitama; R Goto, Yokohama; H Hayami, Kanagawa; M Hayashi, Tokyo; T Hisataki, Hokkaido; M Ikegami, Sakai; T Imai, Tokyo; N Ishigooka, Yamagata; Y Ishii, Saitama; J Ishikawa, Hyogo; K Ito, Yamagata; S Iwata, Chiba; S Kageyama, Shizuoka; T Kamijo, Tokyo; K Kato, Nagoya; K Kawahara, Kagoshima; S Kobayashi, Sapporo; M Kojima, Nagoya; I Kondo, Tokyo; O Kuwamitsu, Tokyo; Z Lee, Chiba; Y Mamiya, Tokyo; K Matsumura, Sapporo; Y Mokuo, Kanagawa; R Moriguchi, Tokyo; J Nakada, Tokyo; S Nakagawa, Kyoto; T Nakano, Wakayama; T Namima, Sendai; M Nanri, Saga; H Narita, Nagoya; H Natsume, Nagoya; H Noto, Akita; N Okishio, Shizuoka; T Oonuma, Sendai; N Otani, Obihiro; Y Ozaki, Osaka; N Saito, Tokyo; S Sakamoto, Beppu; T Sato, Tomakomai; Y Sekiguchi, Yokohama; M Senju, Osaka; M Shigeta, Kure; M Takada, Osaka; M Takei, Hakata; H Takeuchi, Kawasaki; S Torii, Yokohama; Y Tsujimoto, Kobe; S Tsujino, Tokyo; M Ueda, Osaka; T Yamaguchi, Yamagata; K Yasuda, Saitama; E Yokoyama, Kanagawa; M Yoshida, Tokyo; T Yoshida, Tokyo; M Yoshida, Kumamoto; F Yuge, Tokyo.

Editorial Comment

Editorial Comment from Dr Sekido to Propiverine hydrochloride in Japanese patients with overactive bladder: A randomized, double-blind, placebo-controlled trial

This study is a high quality, placebo-controlled, randomized clinical trial (RCT) to investigate the efficacy and safety of propiverine, which has been the most widely used anticholinergic in Japan since its approval.[1] Although this trial is designed to investigate the superiority of propiverine to placebo in overactive bladder (OAB) patients for the first time in Japan and is planned to be used as evidence in the application for an additional indication for propiverine, there have already been two large, high quality, randomized, double-blind, placebo- and propiverine-controlled trials in Japan.[2,3] These previous RCT have shown the superior efficacy of propiverine compared with placebo in terms of frequency, urgency, urgency incontinence, voided volume,[2,3] and all domains of the Kings Health Questionnaire (KHQ)[2], although these might be flawed trials in terms of propiverine-specificity. In addition, solifenacin-RCT showed normalization rates of OAB symptoms (56%, 33% and 26% in the propiverine group *vs* 37%, 21% and 21% in the placebo group for incontinence, urgency and frequency, respectively),[2] whereas imidafenacin-RCT showed a statistically significant improvement in severity of urgency (improvement: 85% of patients in the propiverine group *vs* 67% in the placebo group).[3]

The primary end-point of the present new propiverine-specific trial seems to be somewhat classical: a change in the number of micturition/24 h. The secondary end-points were changes in the number of urgency and urgency incontinence episodes/24 h; voided volume; number of night-time voids; Overactive Bladder Symptom Score; and each domain of KHQ. Unfortunately, "validated patient reported outcomes",[4] which evaluate treatment outcome from the patient's perspective, were not included, except for KHQ. Also, "urgency assessment tools"[5] were not used.

In addition, 10 mg, 20 mg, 30 mg or 40 mg/day of propiverine can be used according to the patients' conditions or preferences in real-life practice, although 20 mg/day of propiverine has been a standard dose in Japan. It is noticeable that discontinuation as a result of adverse events was extremely low (only two patients) in the present study, which might suggest a very good tolerability profile of this drug. Recently, dose escalation was allowed in some clinical trials, such as the VIBRANT study.[6] A fesoterodine open label, flexible dose study showed that non-dose escalators had significantly fewer OAB symptoms at baseline and significantly greater improvements than escalators before dose escalation, and that escalators showed increased symptom relief after dose escalation, concluding that patient-optimized doses significantly improved OAB symptoms and patient-reported outcomes in OAB patients.[7] Unfortunately, this kind of important information cannot be derived from the present study.

Because of its mixed action, propiverine might have different profiles compared with pure antimuscarinics. It is hoped that more propiverine trials that include some kinds of patient-reported outcome measures as primary or secondary end-points and that allow dose escalation will be carried out.

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