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Evaluation of Usefulness of Propiverine Hydrochloride in Poor Responders to Previous Anticholinergics

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Objectives: In recent years, some patients have been unresponsive to anticholinergics used in the treatment of pollakisuria/urinary incontinence. It has been suggested that propiverine hydrochloride, which has not only anticholinergic activity, but also calcium antagonistic activity, may be useful in poor responders to other anticholinergics. In this study, a specific drug use–results survey was conducted in poor responders to other anticholinergics to evaluate the usefulness of propiverine hydrochloride.

Methods: In this survey, propiverine hydrochloride was administered for 12 weeks to poor responders to previous anticholinergics, and its usefulness was evaluated by the overactive bladder symptom score (OABSS).

Results: A total of 3851 subjects at 680 institutions were enrolled in the survey. Of the 3624 subjects included in the safety evaluation (male 1899, female 1725, mean age 73.4 years), 2932 were included in the efficacy evaluation (male 1610, female 1322, mean age 73.8 years). Propiverine hydrochloride significantly improved the OABSS without any safety concerns in poor responders to previous anticholinergics (OABSS, 8.22 at baseline, 6.50 at Week 4, 5.87 at Week 8, and 5.57 at Week 12, $P < 0.001$).

Conclusions: The present findings indicate that propiverine hydrochloride may be a useful therapeutic option for poor responders to previous anticholinergics.

Key words overactive bladder, propiverine hydrochloride, urinary frequency, urinary incontinence

1. INTRODUCTION

Pollakisuria/urinary incontinence is treated with behavioral therapy, drug therapy, electrical/magnetic stimulation, and surgical therapy.[1] Of these, drug therapy, especially anticholinergic therapy, plays a central role in the treatment of pollakisuria/urinary incontinence.

In recent years, various drugs with anticholinergic activity have been developed, and various anticholinergics are used in clinical practice. Nonetheless, some patients are not responsive to these drugs.

Propiverine hydrochloride was compared with placebo and other anticholinergics in some randomized controlled trials for patients with overactive bladder.[2–6] The results reported that propiverine hydrochloride demonstrated its usefulness and safety to the patients with overactive bladder. Furthermore, a randomized controlled trial to treat benign prostatic hyperplasia with overactive bladder using an alpha-blocker combined with propiverine hydrochloride showed usefulness of combined treatment with alpha-blocker and propiverine hydrochloride,[7] and efficacy of propiverine hydrochloride for patients with stress and mixed urinary incontinence.[8]

Propiverine hydrochloride, which has not only anticholinergic activity, but also calcium antagonistic activity,[9,10] is highly expected to be effective in poor responders to other anticholinergics. Thus, we previously conducted a clinical study at 19 institutions to evaluate the usefulness of propiverine hydrochloride in poor responders to other anticholinergics, and demonstrated that the overactive bladder symptom score (OABSS) was significantly improved.[11] Although that study demonstrated the usefulness of propiverine hydrochloride, it was a small study involving only 73 subjects.

Therefore we conducted a specific drug use–results survey with a larger sample size to confirm the usefulness of propiverine hydrochloride in poor responders to other anticholinergics.

2. METHODS

2.1. Eligibility criteria

Eligible patients had pollakisuria and urinary incontinence associated with neurogenic bladder, nervous pollakisuria, unstable bladder, and irritable bladder (chronic cystitis and chronic prostatitis), or with urgency,

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TABLE 1. Baseline characteristics of patients

Factor	Safety evaluation (*n*)	(%)	Efficacy evaluation (*n*)	(%)
Sex				
Male	1899	52.4	1610	54.9
Female	1725	47.6	1322	45.1
Age				
<75 years	1617	44.6	1277	43.6
≥75 years	2007	55.4	1655	56.4
Mean	73.4		73.8	
Diagnosis (single or multiple)				
Overactive bladder	3505	96.7	2842	96.9
Neurogenic bladder	238	6.6	192	6.5
Nervous pollakiuria	56	1.5	45	1.5
Unstable bladder	30	0.8	23	0.8
Irritable bladder (chronic cystitis)	36	1.0	26	0.9
Irritable bladder (chronic prostatitis)	27	0.7	25	0.9
Concurrent disease (except for benign prostatic hyperplasia)				
No	1919	53.0	1513	51.6
Yes	1705	47.0	1419	48.4
Concurrent benign prostatic hyperplasia (only males)				
No	570	30.0	462	28.7
Yes	1329	70.0	1148	71.3
Type of urinary incontinence (only subjects with urinary incontinence)				
Urge	1948	82.2	1610	82.7
Stress	87	3.7	70	3.6
Mixed	287	12.1	229	11.8
Previous anticholinergic				
Solifenacin succinate	1674	46.2	1366	46.6
Imidafenacin	1400	38.6	1126	38.4
Tolterodine tartrate	494	13.6	407	13.9
Previous anticholinergic therapy				
Number of subjects	3566†		2932	
Median duration (days)	139		178	
Reason for switching from previous anticholinergic (single or multiple)				
Lack of efficacy	3624	100.0	2932	100.0
Adverse event	34	0.9	0	0.0
Patient request	3	0.1	3	0.1
Initial daily dose (mg)				
10	612	16.9	479	16.3
20	2864	79.0	2330	79.5
30	17	0.5	14	0.5
40	131	3.6	109	3.7
Maximum daily dose (mg)				
10	510	14.1	394	13.4
20	2813	77.6	2291	78.1
30	48	1.3	39	1.3
40	253	7.0	208	7.1

†Excluding 58 subjects with no data on duration of previous anticholinergic therapy.

pollakisuria, and urgency incontinence associated with overactive bladder who started propiverine hydrochloride in place of previous anticholinergics (at least 4 weeks of treatment) that were discontinued for lack of efficacy at the discretion of a physician. Patients were excluded from this survey if they were still administered propiverine hydrochloride or had over 100 mL residual urine volume, overflow incontinence, obvious urinary tract infection, obstruction of pylorus or duodenums or intestinal, gastric atony or intestinal atony, urinary retention, angle – closure glaucoma, myasthenia gravis, serious heart disease, were pregnant or probably pregnant, or lactating.

2.2. Administration method and follow-up

Propiverine hydrochloride was administered as specified in the package insert. Specifically, the usual adult dosage was 20 mg of propiverine hydrochloride once daily after meals. The dosage was adjusted according to patient age and symptoms, and could be increased to 20 mg twice daily if the drug was not sufficiently effective. The duration of follow-up was 12 weeks, and a case report form (CRF) was completed.

2.3. Registration method

Patients were enrolled by faxing a registration form to the registration center within 2 weeks after the start of treatment with propiverine hydrochloride.

2.4. Evaluation of efficacy

Therapeutic efficacy was evaluated by the OABSS before treatment and at Weeks 4, 8, and 12 of treatment.

2.5. Statistical analysis

Statistical analyses were performed using SAS (ver. 9.2; SAS Institute, Cary, NC, USA). Therapeutic efficacy was

TABLE 2. Common adverse drug reactions and numbers of subjects discontinued from treatment

Event (PT)†	Number of subjects with adverse drug reactions	Incidence of adverse drug reactions (%)	Number of subjects discontinued from treatment	Treatment discontinuation rate (%)
Total number of subjects	480	13.25	232	6.40
Thirst	184	5.08	70	1.93
Constipation	151	4.17	56	1.55
Urinary retention	44	1.21	26	0.72
Voiding difficulty	38	1.05	30	0.83
Residual urine volume increased	31	0.86	13	0.36
Dry mouth	17	0.47	8	0.22
Dizziness	12	0.33	9	0.25

†MedDRA/J ver17.1. PT, preferred term. Analysis set: subjects included in the safety evaluation ($n = 3624$).

TABLE 3. Analysis set: subjects included in safety evaluation ($n = 3624$)

Initial onset of adverse drug reactions	Within 2 weeks	Weeks 3–4	Weeks 5–8	Weeks 9–12	Weeks 13 or later
Number of treated subjects†	3624	3516	3260	2848	2529
Number (%) of subjects with adverse drug reactions‡	136 (3.75)	81 (2.30)	125 (3.83)	76 (2.67)	62 (2.45)
Number (%) of adverse drug reactions§	157 (28.5)	91 (16.5)	139 (25.3)	86 (15.6)	77 (14.0) ¶
Common adverse drug reactions: Event (PT)††					
Thirst	63	29	37	32	23 ¶
Constipation	36	26	51	23	15
Urinary retention	8	8	8	9	11
Voiding difficulty	13	8	10	4	3
Residual urine volume increased	1	3	8	7	12 ¶
Dry mouth	6	3	6	—	2
Dizziness	4	2	4	1	1

†Number of subjects being treated during the relevant period. ‡Number of subjects with initial onset of the adverse drug reactions during the relevant period (percentage relative to number of subjects being treated during the relevant period in parentheses). §Incidence of adverse drug reactions in the relevant period (percentage relative to all 550 adverse drug reactions in parentheses). ¶Including one adverse drug reaction with unknown onset. ††MedDRA/J ver17.1. PT, preferred term.

analyzed by a paired *t*-test at a significance level of 5% without adjustment for multiplicity.

3. RESULTS

3.1. Disposition of subjects

A total of 3851 subjects at 680 institutions were enrolled in the survey during an 18-month registration period from April 2012. Of these, 3624 subjects were included in the safety evaluation, after excluding a total of 227 subjects: 24 from whom the CRF was not collected; 87 who did not visit the clinic after the initial visit; 74 who had benign prostatic hyperplasia, but no overactive bladder symptoms; 30 who were switched from previous anticholinergics for reasons other than lack of efficacy, including unknown reasons; and others. Of the 3624 subjects included in the safety evaluation, 2932 were included in the efficacy evaluation, after excluding a total of 692 subjects (a single subject with multiple reasons for exclusion was counted once): 431 who were treated with previous anticholinergics for less than 4 weeks; 244 with no post OABSS data; 46 with no baseline OABSS data; and 34 who were discontinued from previous anticholinergics because of adverse events.

3.2. Baseline characteristics of patients and treatment compliance

The baseline characteristics of the 3624 subjects included in the safety evaluation and 2932 subjects included in the efficacy evaluation are shown in Table 1. Of the 3624 subjects included in the safety evaluation and 2932 included in the efficacy evaluation, 1617 (44.6%) and 1277 (43.6%) were aged below 75 years, and 2007 (55.4%) and 1655 (56.4%) were aged 75 years or older, with a mean age of 73.4 and 73.8 years, respectively. In the safety evaluation, the most common initial daily dose of propiverine hydrochloride was 20 mg in 2864 subjects (79.0%), followed by 10 mg in 612 subjects (16.9%). The most common maximum daily dose was 20 mg in 2813 subjects (77.6%).

Of the 3624 subjects included in the safety evaluation, 1095 (30.2%) were discontinued from treatment after less than 12 weeks of treatment. The most common reasons for discontinuation were failure to visit the clinic in 299 subjects, adverse events in 267, unchanged symptoms in 251, and patient request in 205. Common adverse events included thirst, constipation, urinary retention, and voiding difficulty.

The reason for switching from previous anticholinergics to propiverine hydrochloride was lack of efficacy in all

subjects, but adverse events were also cited as a reason in 34 subjects (0.9%).

3.3. Safety

The common adverse drug reactions and discontinuations from treatment caused by common adverse drug reactions are shown in Table 2. Adverse drug reactions were reported in 480 subjects, with an incidence of 13.25%. Most of the reported adverse drug reactions were characteristic for anticholinergics (e.g., thirst, constipation).

A total of 13 adverse drug reactions in 11 subjects were assessed as serious by a physician: six cases of urinary retention and one case each of constipation, voiding difficulty, dizziness, abdominal discomfort, headache, bradycardia, and ileus.

Urinary retention was reported in 44 subjects. Of these 44, 34 were male, and 32 of the 34 had benign prostatic hyperplasia. Urinary retention was serious in five of the 34 male subjects, and four of these five had benign prostatic hyperplasia. Of the 13 serious adverse drug reactions, 10 were resolved or resolving, excluding one case of urinary retention that did not resolve and one case each of dizziness and constipation with unknown outcome because of patient transfer to another hospital.

The timings for the initial onset of adverse drug reactions are shown in Table 3. Overall, 248 adverse drug reactions occurred within 4 weeks after the start of treatment with propiverine hydrochloride, 139 at Weeks 5–8, 86 at Weeks 9–12, and 77 at Week 13 or later. Among all adverse drug reactions, 45.1% occurred within 4 weeks, and 70.4% occurred within 8 weeks.

Of 34 subjects who were switched from previous anticholinergics because of an adverse event, 12 (35.3%) experienced an adverse drug reaction to propiverine hydrochloride (all non-serious). The adverse drug reactions in nine of these 12 were the same as those responsible for switching (thirst in four, constipation in four, and urinary retention in one [including synonymous adverse drug reactions]).

3.4. Efficacy

The OABSS data before treatment with propiverine hydrochloride and at Weeks 4, 8, and 12 of treatment are shown in Table 4. The mean total score was significantly decreased from 8.22 at baseline to 6.50 at Week 4, 5.87 at Week 8, and 5.57 at Week 12 ($P < 0.001$). The mean score was significantly decreased from baseline in all subgroups stratified by sex (male or female) and age (<75 or ≥75 years) ($P < 0.001$).

The day-time frequency, night-time frequency, urgency, and urgency incontinence scores over time are shown in Table 5. All of these scores were significantly decreased from baseline at Weeks 4, 8, and 12 ($P < 0.001$).

The OABSS data over time according to previous anticholinergics (solifenacin succinate, imidafenacin, and tolterodine tartrate) are shown in Table 6. The OABSS was significantly decreased from baseline at Weeks 4, 8, and 12, irrespective of the previous anticholinergics ($P < 0.001$).

TABLE 4. Analysis set: subjects included in efficacy evaluation ($n = 2932$)

OABSS	Before treatment	Week 4	Week 8	Week 12
Total	2932†	2668	2078	1823
	8.22 ± 0.06‡	6.50 ± 0.06*	5.87 ± 0.07*	5.57 ± 0.08*
Sex				
Male	1610	1458	1165	1001
	8.11 ± 0.08	6.58 ± 0.08*	5.90 ± 0.10*	5.63 ± 0.10*
Female	1322	1210	913	822
	8.35 ± 0.09	6.40 ± 0.10*	5.84 ± 0.11*	5.50 ± 0.12*
Age				
<75 years	1277	1163	891	777
	7.73 ± 0.09	5.94 ± 0.09*	5.33 ± 0.11*	5.10 ± 0.12*
≥75 years	1655	1505	1187	1046
	8.59 ± 0.08	6.93 ± 0.08*	6.29 ± 0.10*	5.92 ± 0.10*

*$P < 0.001$ (versus baseline, paired t-test). †Number of subjects. ‡Mean ± standard error. OABSS, overactive bladder symptom score.

For 632 subjects included in the efficacy evaluation with OABSS data before the start of previous anticholinergic therapy, the OABSS data before previous anticholinergic therapy, before treatment with propiverine hydrochloride (after previous anticholinergic therapy), and at final evaluation (after treatment with propiverine hydrochloride) are shown in Table 7. In the 632 subjects, the median duration of previous anticholinergic therapy was 120 days. The mean OABSS was 8.92 before previous anticholinergic therapy, 7.92 before treatment with propiverine hydrochloride, and 5.48 at final evaluation, showing that propiverine hydrochloride improved the OABSS more markedly than the previous anticholinergics. Similar results were observed for day-time frequency, night-time frequency, urgency, and urgency incontinence scores ($P < 0.001$).

In this survey, the OABSS over time was also evaluated according to the type of urinary incontinence (urge, mixed, and stress) defined by the standard terms for subjective symptoms of impaired urine storage[12] (Table 8). Propiverine hydrochloride significantly improved the OABSS for all types of urinary incontinence (urge and mixed: $P < 0.001$; stress: $P = 0.002$).

4. DISCUSSION

Pollakisuria/urinary incontinence is primarily treated with drug therapy, and many drugs are currently available for such treatment. Among these drugs, anticholinergics are often selected and used as the first-line treatment, but some patients are not responsive. For the latter patients, the drugs may be changed, but are only changed empirically without clear evidence. In an earlier study, the safety and efficacy of propiverine hydrochloride were evaluated in 73 poor responders to previous anticholinergics at 19 institutions.[11] The usefulness of propiverine hydrochloride was suggested, but the sample size was too small for evaluation according to the baseline characteristics of the patients and previous anticholinergics. Therefore, the present survey with a larger sample size was designed.

TABLE 5. Analysis set: subjects included in efficacy evaluation ($n = 2932$)

	Before treatment	Week 4	Week 8	Week 12
Day-time frequency score	2932†	2663	2073	1819
	0.96 ± 0.01‡	0.80 ± 0.01*	0.75 ± 0.01*	0.70 ± 0.01*
Night-time frequency score	2932	2667	2077	1822
	2.31 ± 0.02	2.05 ± 0.02*	1.90 ± 0.02*	1.83 ± 0.02*
Urgency score	2932	2662	2073	1817
	2.95 ± 0.03	2.23 ± 0.03*	1.96 ± 0.03*	1.86 ± 0.04*
Urgency incontinence score	2932	2665	2072	1818
	1.99 ± 0.03	1.43 ± 0.03*	1.28 ± 0.03*	1.20 ± 0.03*

*$P < 0.001$ (versus baseline, paired *t*-test). †Number of subjects. ‡Mean ± standard error. OABSS, overactive bladder symptom score.

TABLE 6. Changes in overactive bladder symptoms by previous anticholinergic agents

	Before treatment	Week 4	Week 8	Week 12
Solifenacin succinate	1366†	1224	948	840
	8.18 ± 0.08‡	6.57 ± 0.09*	6.02 ± 0.11*	5.84 ± 0.12*
Imidafenacin	1126	1046	809	712
	8.25 ± 0.09	6.43 ± 0.10*	5.76 ± 0.11*	5.35 ± 0.12*
Tolterodine tartrate	407	368	295	249
	8.25 ± 0.15	6.52 ± 0.17*	5.75 ± 0.19*	5.37 ± 0.21*

*$P < 0.001$ (versus baseline, paired *t*-test). †Number of subjects. ‡Mean ± standard error. OABSS, overactive bladder symptom score.

TABLE 7. Six hundred and thirty-two subjects included in efficacy evaluation with OABSS data before the start of previous anticholinergic therapy

	Before previous anticholinergic therapy	Before treatment with propiverine hydrochloride (after previous anticholinergic therapy)	Final evaluation (after treatment with propiverine hydrochloride)
OABSS	8.92 ± 0.12†	7.92 ± 0.12*	5.48 ± 0.13**
Day-time frequency score	1.09 ± 0.02	0.98 ± 0.02*	0.71 ± 0.02**
Night-time frequency score	2.36 ± 0.03	2.20 ± 0.04*	1.79 ± 0.04**
Urgency score	3.22 ± 0.06	2.84 ± 0.06*	1.80 ± 0.06**
Urgency incontinence score	2.25 ± 0.07	1.90 ± 0.07*	1.19 ± 0.06**

*$P < 0.001$ (versus before previous anticholinergic therapy, paired *t*-test). **$P < 0.001$ (versus before treatment with propiverine hydrochloride, paired *t*-test). †Mean ± standard error. OABSS, overactive bladder symptom score. n = 632.

TABLE 8. Changes in overactive bladder symptoms by type of urinary incontinence

	Before treatment	Week 4	Week 8	Week 12
Urge	1610†	1462	1129	998
	9.64 ± 0.06‡	7.62 ± 0.08*	6.81 ± 0.10*	6.44 ± 0.11*
Stress	70	65	45	45
	7.29 ± 0.39	5.54 ± 0.44*	5.29 ± 0.53**	5.27 ± 0.62*
Mixed	229	196	169	148
	9.96 ± 0.17	7.73 ± 0.22*	7.08 ± 0.26*	6.96 ± 0.29*

*$P < 0.001$, **$P = 0.002$ (versus baseline, paired *t*-test). †Number of subjects. ‡Mean ± standard error. OABSS, overactive bladder symptom score.

In this survey, common adverse drug reactions included thirst (5.08%), constipation (4.17%), urinary retention (1.21%), and voiding difficulty (1.05%). These are characteristic for anticholinergics, and did not differ from those reported in previous surveys[13,14] or another study.[11] In addition, there were no differences in the incidence or seriousness of the adverse drug reactions. However, because patients who switch from previous anticholinergics to propiverine hydrochloride not only for lack of efficacy, but also for adverse events are more likely to experience the same adverse events during treatment with propiverine hydrochloride, caution should be exercised for the findings in these patients.

Overactive bladder symptoms are observed in 50–75% of patients with benign prostatic hyperplasia.[1] According to the section for precautions in the package insert for propiverine hydrochloride, the drug should be administered with caution, because voiding difficulty may be exacerbated or residual urine may be increased in patients with benign prostatic hyperplasia. Accordingly, in the present survey, many of the patients who experienced urinary retention as an adverse drug reaction were males with benign prostatic hyperplasia, and a similar trend was observed in patients with serious urinary retention, indicating that propiverine hydrochloride should be administered with caution in patients with benign prostatic hyperplasia.

Regarding efficacy, propiverine hydrochloride significantly improved all of the OABSS subscores. In particular, this survey showed an improvement in the daytime urinary frequency score, which was not observed in a previous study on 73 subjects,[11] thus supporting the usefulness of propiverine hydrochloride in poor responders to previous anticholinergics. In addition, propiverine

hydrochloride significantly improved the OABSS in all types of urinary incontinence (urge, mixed, and stress). Furthermore, it significantly improved the OABSS at all time points in all subgroups stratified by sex, age, symptoms, and previous anticholinergics.

5. CONCLUSION

Propiverine hydrochloride significantly improved the OABSS without any safety concerns in poor responders to previous anticholinergics, and significantly improved the OABSS in all subgroups stratified by sex, age, symptoms, and previous anticholinergics, indicating that propiverine hydrochloride may be one of useful therapeutic options for poor responders to previous anticholinergics.

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