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Efficacy and Safety of Propiverine Chloride Flexible Dose in Female Mixed Urinary Incontinence Patients

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Abstract

Purpose: We investigated the efficacy and safety of propiverine chloride (BUP-4) flexible dose in female patient with mixed urinary incontinence.

Methods: The participants were women with mixed incontinence, including urgency (grade 3 or more, one or more episodes per day) or mild stress incontinence (grade I) or both. The subjects were received 4 weeks of treatment with propiverine 20 mg once daily. If the response of the 4 week treatment was insufficient, the dose was increased to 30 mg/day. The patient who satisfied with initial treatment sustained propiverine 20 mg for next 8 weeks. The efficacy of treatment was assessed base on the response of Benefit, Satisfaction and Willingness to Continue questionnaire (BSW questionnaire). Change of Overactive Bladder Symptom Score (OABSS), micturition diary parameters was assessed. Adverse events were evaluated throughout the study.

Results: A total of 86 patients with mixed incontinence were enrolled, 76 patients completed the 3 month study. 29 patients (33.7%) responded as “dissatisfied” with the treatment at week 4 and treated with escalated dose to 30 mg propiverine next 8 weeks. (20 mg group; 48 subjects, 30 mg group; 28 subjects) 90% of patients in 30 mg group satisfied with their treatment at final follow-up on week 12. Three patients still dissatisfied with 30 mg propiverine treatment in spite of escalating the dose. The change in OABSS score were significantly improved after 12 week propiverine treatment at both groups. Most clinical parameters showed much more improvement in 20 mg group than 30 mg group. Most common adverse event was dry mouth and constipation. Two patients complained dry mouth, one patient had constipation and two patients had dyspepsia.

Conclusions: Propiverine 30 mg could be an effective treatment of mixed incontinence without increasing the incidence of side effect compared to propiverine 20 mg. It could be considered to propiverine 30 mg as a starting dose.

Keywords: Propiverine hydrochloride; Female incontinence; Mixed urinary incontinence; Dose; Flexibility

Introduction

Mixed urinary incontinence is frequently encountered by physicians, and is the most common form of urinary incontinence in women from those aged in their 20’s to those who are middle-aged [1-3]. Treatment with an anticholinergic agent has been advocated as a reversible first-line therapy for the patients with mixed urinary incontinence, based on the confirmed efficacy of anticholinergic therapy in patients with OAB alone [4].

Propiverine hydrochloride (referred to in the following as propiverine) has been shown to combine both anticholinergic and calcium channel blocking actions and reported to be effective for the treatment of stress incontinence as well as detrusor overactivity [5]. In daily practice, propiverine, an anticholinergic drug indicated for urge incontinence, is given to patients who have both urge incontinence and stress incontinence [5].

The aim of the present study was to examine the efficacy and safety of propiverine chloride in female patient with mixed urinary incontinence.

Materials and Methods

This is a Phase IV, prospective, non-randomized, open-label, observational, multicenter study. The study was conducted by four investigators from 4 hospitals in accordance with International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was approved by the appropriate Institutional Review Boards and/or Independent Ethics Committees of each participating center. All subjects provided written informed consent.

Participants

Women with mixed urinary incontinence were enrolled in propiverine 20 mg treatment. Women who feel unsatisfactory their symptom after 4 weeks of propiverine 20 mg once daily treatment were increased the dose to 30 mg propiverine daily.

Inclusion criteria:

- Women aged between 20 and 80 years old
- a. Symptoms of OAB as verified by the screening 3 day bladder diary; number of micturition-related urgency episodes more than 1 episode/24 hours (with a urinary sensation scale rating of more than 3 marked for the corresponding micturition in the bladder diary) (or)
- b. Grade I stress urinary incontinence (or)
- c. The patients who had mixed incontinence that is suitable with both symptom
- Symptom duration at least 3 months
- Pretreated patients with anticholinergics had to undergo a 2-week wash-out phase before attending to the trial.

Exclusion criteria:

patients with neurogenic bladder; patients with the history of acute urinary retention needed catheterization; patients with predominant stress urinary incontinence (>grade 2), patients with pelvic organ prolapsed; patients who had undergone surgery on lower urinary tract for past 6 months; significant hepatic or renal disease; patients with any condition that is a contraindication for anticholinergic therapy including uncontrolled narrow-angled glaucoma, myasthenia gravis, urinary retention or gastric retention.

Determination of propiverine 30 mg therapy

If improvement of symptom was inadequate after propiverine as starting dose (20 mg once daily), the dose of propiverine was increased to 30 mg/day for another 8 weeks (30 mg group).

The efficacy of treatment was judged from the response of BSW questionnaire. Satisfactory patient who sustained 20 mg propiverine once daily included the patients who responded "much benefit" or "very satisfied" on BSW questionnaire (20 mg group).

Sample size determination

The sample size for this study was decided with reference to the study of the efficacy and tolerability of anticholinergics conducted by Chapple et al. [6].

At 5% of two-sided significance level, 85% of power and 20% of drop-out rate, 63 subjects per group (total 126 subjects) are needed to demonstrate the no inferiority of propiverine 30 mg to propiverine 20 mg.

Clinical assessment

The primary endpoint was the proportion of the patients who responded as "satisfied" after 12 weeks propiverine treatment at each group. Secondary endpoints were the change of the parameters of micturition diaries (voiding frequency; daytime, nighttime, urgency episodes, incontinence episodes) after 12 weeks propiverine treatment at each group.

The parameters of micturition diaries, Overactive bladder symptom score (OABSS) questionnaire [7] were evaluated at baseline and week 12. BSW questionnaires [8] were assessed at week 4 and 12. We classified adverse events according to severity and relationship to the study treatment.

Safety assessment

All adverse events were monitored throughout the study. Laboratory analyses, physical examination and vital signs measurement were conducted. The severity and the likely relation to the treatment were assessed by the investigators. All adverse events were assorted as dry mouth, constipation, indigestion, headache and others according to severity.

Statistical analysis

The proportion of the patients who responded as "satisfied" after 12 weeks propiverine treatment was estimated with a 95% confidence interval. Baseline characteristics were compared between the propiverine 20 mg group and propiverine 30 mg group by Two-sample t-test. Efficacy analyses for micturition diary variables and symptom questionnaire assessments including BSW questionnaire, OABSS were performed based on changes from baseline according to two sample t-test of Wilcoxon signed rank test.

Results

Subject population

A flow diagram depicting the patient population in our study is shown in Figure 1. A total of 120 patients were screened and 86 patients participated in this study. Patients who had incomplete variables were excluded from analysis.

Ultimately, 76 patients were included in the final analysis set (20 mg group; 48 subjects, 30 mg group; 28 subjects) baseline patient characteristics are listed in Table 1.

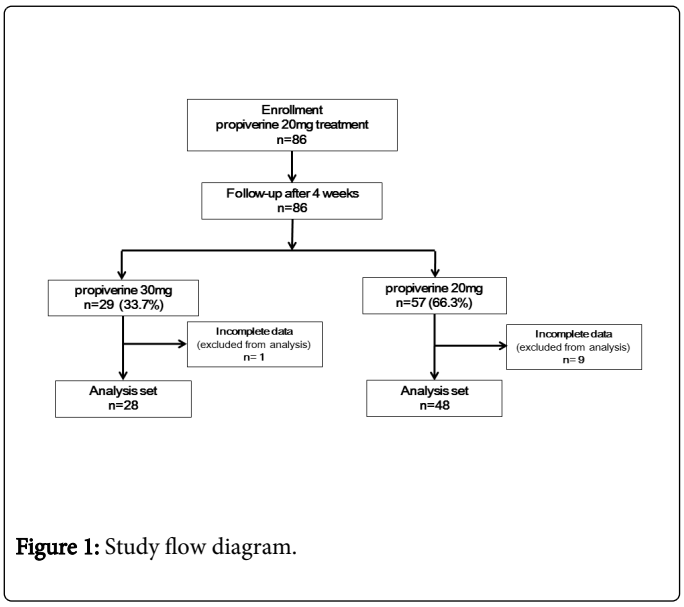

Figure 1: Study flow diagram.

Variables	Total (N=76)	30 mg group (N=28)	20 mg group (N=48)	p-value*
Age (year)	55.1 ± 13.8	56.1 ± 13.8	54.5 ± 13.9	
Body weight (kg)	56.5 ± 6.7	56.8 ± 7.0	56.4 ± 6.6	
Symptom (case, [%])				
OAB	63 (82.9%)	22 (78.6%)	41 (85.4%)	
Mixed urinary incontinence	12 (15.8%)	6 (21.4%)	6 (12.5%)	
Urgency	1 (1.3%)	1 (2.1%)	0 (0%)	
OABSS				
Total score	7.1 ± 2.6	6.9 ± 2.7	7.2 ± 2.6	0.556
Item 1	1.1 ± 0.5	1 ± 0.5	1.2 ± 0.5	0.035§
Item 2	1.9 ± 0.9	1.8 ± 1.0	1.9 ± 0.9	0.598
Item 3	3 ± 1.5	2.9 ± 1.4	3.2 ± 1.6	0.404
Item 4	0.9 ± 1.2	12 ± 1.4	0.9 ± 1.2	0.33
Voiding diary variables				
Nocturnal micturition	1.7 ± 1.1	1.3 ± 0.8	1.9 ± 1.2	0.022§
Daytime micturition	10.8 ± 3.1	10.6 ± 3.0	10.9 ± 3.1	0.721
Urgency episodes per 24 h	4.4 ± 3.3	5 ± 4.1	4.1 ± 2.8	0.274
Incontinence episodes per 24 h	0.49 ± 0.72	0.77 ± 1.02	0.4 ± 0.51	0.194

Table 1: Baseline characteristics of patients (mean ± standard deviation) [*p-values from comparison tests of baseline parameters between propiverine 30 mg group and 20 mg group by Two sample t-test; § $p<0.05$].

Proportion of escalating the dose of propiverine

Of 86 subjects who performed 4 weeks treatment of propiverine 20 mg, 29 patients (33.7%) responded as "dissatisfied" with the treatment at week 4. They treated with escalated dose to 30 mg propiverine next 8 weeks. About (30 mg group) 57 patients (66.3%) responded that they satisfied with the treatment of 20 mg propiverine once daily and they sustained the treatment as same dose for next 8 weeks (20 mg group).

Proportion of the patients who satisfied with 12-week propiverine treatment

Of 28 patients who dissatisfied with initial treatment of propiverine 20 mg and followed up with propiverine 30 mg at week 12. About 90% of patients satisfied with their treatment at final follow-up on week 12. Three patients still dissatisfied with 30 mg propiverine treatment in spite of escalating the dose. All forty-eight patients (100%) who sustained their treatment with propiverine 20 mg due to satisfying the initial treatment responded that they consistently satisfied with their 12 week treatment. At final visit, the responses of benefit, satisfaction and willingness to continue except missing values were listed in Table 2.

Variables	Total (N=69)	30 mg group (N=27)	20 mg group (N=42)
Benefit			
Yes	69 (100)	27 (39.1)	42 (60.9)
Little benefit	17	10	7
Much benefit	52	17	35

No	0	0	6 (12.5%)
Satisfaction			
Yes	66 (95.7)	24 (34.8)	42 (60.9)
A little satisfied	31	12	19
Very satisfied	35	12	23
No	3 (4.3)	3 (4.3)	0
A little dissatisfied	3	3	0
Very dissatisfied	0	0	0
Willingness to continue			
Yes	59 (85.5)	22 (31.9)	37 (53.6)
A little bit willing	19	9	10
Very willing	40	13	27
No	10 (14.5)	5 (7.2)	5 (7.2)
A little unwilling	7	3	3
Very unwilling	3	1	2

Table 2: The response of Benefit, Satisfaction and Willingness to Continue questionnaire at final visit (n,[%]).

Changes in clinical parameters

The change in OABSS score were improved after 12 week propiverine treatment at both groups. The mean change amount of OABSS were -3.6 ± 3.2 in 30 mg group, and -4.4 ± 2.8 in 20 mg group. There was no difference between two groups (p=0.263). Parameters measured in micturition diaries such as number of micturitions per 24 hr, daytime micturitions, and urgency episodes decreased significantly after 12 weeks propiverine treatment. When we compare the changes in micturition diary parameters between 20 mg group and 30 mg group, day time frequency and night time frequency showed much more improvement in 20 mg group than 30 mg group (p<0.05). Changes in clinical parameters and questionnaire responses after propiverine treatment for each study group is listed in Table 3.

	Total		**30 mg group**		**20 mg group**		**P-value§**
Variables	**Baseline**	**Change***	**Baseline**	**Change***	**Baseline**	**Change***	
OABSS total score	7.1 ± 2.6	-4.1 ± 3.0	6.9 ± 2.7	-3.6 ± 3.2	7.2 ± 2.6	-4.4 ± 2.8	0.263
Voiding diary variables							
Nocturnal micturition	2.3 ± 1.4	-0.3 ± 1.2	1.3 ± 0.8	-0.7 ± 0.8	1.9 ± 1.2	-1.4 ± 1.2	0.006
Daytime micturition	10.8 ± 3.0	-4.6 ± 3.9	10.6 ± 3.0	-3.1 ± 2.6	10.9 ± 3.0	-5.7 ± 4.3	0.005
Urgency episodes/24 h	4.5 ± 3.3	-3.6 ± 3.0	5.2 ± 4.1	-3.6 ± 3.3	4.2 ± 2.8	-3.5 ± 2.9	0.973
Incontinence episodes/24 h	0.52 ± 0.75	-0.52 ± 0.84	0.7 ± 1.03	-0.76 ± 1.05	0.42 ± 0.52	-0.34 ± 0.61	0.085

Table 3: Changes in clinical parameters and symptom scores after 12 weeks of propiverine therapy [*changes were the difference of parameters from baseline to week 12; §: P-values from comparison tests of changes in clinical parameters between propiverine 30 mg group and 20 mg group by Two sample t-test].

Safety assessment

All adverse events were monitored throughout the study. Most common adverse event was dry mouth and constipation as well-known adverse events from the treatment of anticholinergics. Two patients complained dry mouth, one patient had constipation and two patients had dyspepsia with severe severity. There was no patient experienced dysuria or retention. There was no serious adverse event during treatment. All of the adverse events resolved after discontinuation of the treatment (Table 4).

	Week 4		Week 8		Week 12	
	30 mg	20 mg	30 mg	20 mg	30 mg	20 mg
Variables	**(n=28)**	**(n=58)**	**(n=28)**	**(n=51)**	**(n=28)**	**(n=48)**
Adverse events	11 (12.8)	5 (5.8)	11 (13.9)	7 (8.9)	10 (13.2)	5 (6.6)
Dry mouth	9 (10.5)	3 (3.5)	9 (11.4)	1 (1.3)	6 (7.9)	2 (2.6)
Mild	6	0	6	1	5	2
Moderate	2	3	2	0	1	0
Severe	1	0	1	0	0	0
Constipation	6 (7.0)	2 (2.3)	7 (8.8)	3 (3.8)	7 (9.2)	2 (2.6)
Mild	4	0	5	1	3	0
Moderate	2	2	1	2	4	2
Severe	0	0	1	0	0	0
Dyspepsia	1 (1.2)	1 (1.2)	1 (1.3)	3 (3.8)	1 (1.3)	2 (2.6)
Mild	0	0	0	2	0	1
Moderate	0	0	1	1	1	1
Severe	1	1	0	0	0	0
Anorexia	0	0	0	0	0	0
Headache	0	0	0	0	0	0
Others	0	1 (1.2)	0	2 (2.5)	0	0

Table 4: Adverse events at each visit throughout the treatment (case, [%]).

Discussion

This study investigated the clinical efficacy of propiverine in mixed urinary incontinence. Significant improvements in all outcome parameter regarding subjective satisfaction proved the efficacy of propiverine under conditions of clinical practice based on the response of BSW questionnaires, OABSS, and micturition diary parameters.

Even though it has generally been found that both types of incontinence, urge incontinence and stress urinary incontinence are improved by few medications such as clenbuterol hydrochloride, tricyclic antidepressant, imipramine hydrochloride, and duloxetine, [9-12] there was no definite medical treatment for female urinary incontinence. Anticholinergic therapy is often used as a reversible first-line treatment option for patients with mixed urinary incontinence, which is one of the common medical treatments for reducing bladder hypersensitivity. Thus anticholinergic drugs had been used for the patient with urge incontinence as a result of involuntary bladder contractions [13,14]. Propiverine is one of the useful medications for both stress incontinence and mixed urinary incontinence [5]. In one study of 37 patients with stress and mixed incontinence, the number of episodes of stress incontinence decreased significantly from 2.6 ± 2.3 times per day to 0.4 ± 0.6 times per day after 8 weeks [5].

In the present study, the starting dose of propiverine was 20 mg/day, but was increased to 30 mg/day after 4 weeks in twenty-nine patients because of inadequate efficacy. 90% of these patients showed improvement and satisfied with their treatment after following 8 weeks. The difference of satisfaction rate between two dose groups at final visit resulted from the criteria of dividing the two groups. Because the patients who belong to 30 mg group were dissatisfied with usual 20 mg propiverine for 4 weeks, the patients may have more severe symptoms unresponsive to the medication. We focused that 90% of 28 patients finally satisfied with their treatment after additional 8 week treatment with 30 mg propiverine who dissatisfied with initial treatment of propiverine 20 mg. Just three patients remained dissatisfied with their treatment.

When the physicians prescribed the anticholinergic drugs to the women with detrusor overactivity, major concern regarding the treatment was adverse events. In one study, only 18% of patients, who were prescribed anticholinergic medication, continued with the treatment for more than 6 months due to adverse events. However, propiverine was proved to be well tolerated and safe even using in children and adolescents [15]. In the current study, all of the adverse events that occurred were events that have already been reported such as dry mouth or constipation. No newly presented events were noted throughout the whole study period. The incidence of adverse events in the patients treated with propiverine 30 mg is not appreciably different from the incidence of side effect compared to propiverine 20 mg. Thus, physicians do not need to be afraid of prescribing propiverine 30 mg to patients with urinary incontinence as starting dose.

One of the major limitations of the current study is lack of urodynamic data such as phasic detrusor overactivity as well as the resolving of incontinence. However, we considered that the change of subjective satisfaction in daily living circumstance is much more important to the patients rather than objective test at well-controlled examination room. Unfortunately we could not perform the analysis about the predictors determining the responsiveness to the medication with propiverine 20 mg or 30 mg for meeting the purpose of the current study. The extended study for investigating that who is suitable for propiverine 30 mg treatment as a starting dose could support the result of the current study.

Conclusion

Propiverine is as effective in improving subjective symptoms of mixed urinary incontinence. If the treatment with propiverine 20 mg/day leads to insufficient effect to patient with mixed urinary incontinence, escalating the treatment dose of propiverine could be one of alternative plans. Propiverine 30 mg could be an effective starting dose for treatment of mixed incontinence without increasing the incidence of side effect compared to propiverine 20 mg.

Conflict of Interest

This is an Investigator Initiated Trial sponsored by Jeil Pharma Inc. The funder had no involvement in study design, data collection, data analysis, manuscript preparation, and/or publication decisions. Each of the authors has had in the past 36 months no relationships with the pharmaceutical company as an investigator, advisor, consultant, or speaker.

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