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Original Article

Therapeutic effect of propiverine hydrochloride on mixed-type urinary incontinence in women: The Female Urgency and Stress Urinary Incontinence Study of Propiverine Hydrochloride trial

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Abbreviations & Acronyms
BMI = body mass index
FAS = full analysis set
FUL = functional urethral length
ICIQ-SF = International Consultation on Incontinence Questionnaire-Short Form
MUCP = maximum urethral closing pressure
MUI = mixed-type urinary incontinence
OABSS = Overactive Bladder Symptoms Score
PH = propiverine hydrochloride
QOL = quality of life
SAS = safety analysis set
SUI = stress urinary incontinence
UPP = urethral pressure profile
UUI = urgency urinary incontinence

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Objectives: To show the efficacy of propiverine hydrochloride in the management of symptoms of stress urinary incontinence in female patients with mixed-type urinary incontinence.

Methods: The study was carried out as a multicenter single-arm clinical trial at 64 institutions in Japan. The participants were female patients aged ≥20 years with mixed-type urinary incontinence. The frequency of stress urinary incontinence and urgency urinary incontinence was evaluated at baseline and 4, 8 and 12 weeks after treatment with propiverine hydrochloride. Subjective symptoms were evaluated using the Overactive Bladder Symptom Score and the International Consultation on Incontinence Questionnaire-Short Form. Functional urethral length and maximum urethral closing pressure were also measured at baseline and 12 weeks after treatment at the institutions where the urethral pressure profile was taken.

Results: In total, 49 mixed-type urinary incontinence patients were enrolled in the present study. The number of cases of urgency urinary incontinence was reduced time-dependently, which showed statistically significant differences between baseline and 4, 8 and 12 weeks after treatment. A similar statistically different reduction was also observed for stress urinary incontinence. The mean reduction rates of urgency urinary incontinence and stress urinary incontinence at 12 weeks after treatment were 63.9% and 44.3%, respectively. The total scores of International Consultation on Incontinence Questionnaire-Short Form and Overactive Bladder Symptom Score were gradually reduced, and the differences were statistically significant. Functional urethral length and maximum urethral closing pressure at 12 weeks after treatment did not show any statistical differences compared with those at baseline.

Conclusions: Propiverine hydrochloride can be an effective therapeutic option for stress urinary incontinence in patients with mixed-type urinary incontinence.

Key words: propiverine hydrochloride, stress urinary incontinence, urgency urinary incontinence.

Introduction

Recent epidemiological studies suggest that urinary incontinence is a common health concern, and has a serious negative impact on QOL.[1,2] Especially among elderly women aged >60 years, SUI is a relatively more common type of urinary incontinence than UUI.[3] Based on recent treatment strategies, surgical treatments are effective for SUI and can offer a choice for the patient.[4] However, considering the efficacy of mid-urethral sling for SUI patients, some serious adverse events that occur after surgery, including bladder perforation, vaginal perforation, urethral perforation and hematoma formation, can still be problematic.[5–7] Therefore, it is desirable to have effective medications for management of SUI patients.

PH is an anticholinergic drug used to treat UUI.[8–11] Sugaya *et al.* reported on the efficacy of PH on SUI in adult female patients whose chief complaint was stress incontinence, including MUI, by carrying out an interview and assessing the patient's UPP.[12] Although the efficacy of anticholinergic drugs for MUI has been reported, SUI has not been separately evaluated in most previous reports.[13–16] Other than Sugaya's report,[12] only Khullar *et al.* separately evaluated the effects of tolterodine on the number of SUI and UUI episodes among MUI patients.[15] However, tolterodine did not affect SUI in patients with MUI. PH might have some unique characteristics that are unlike any other anticholinergic drug, such as increasing closing pressure and extending the functional urethral length for the treatment of SUI.[12,17–19] Therefore, this clinical trial intended to show the effect of PH on UUI and SUI frequency in patients with MUI, based on a particular interest in the therapeutic efficacy of PH for SUI. Thus, our research hypothesis in the present study was that PH can reduce the frequency of SUI in patients with MUI.

Methods

Study design

The present study was a multicenter, single-arm, prospective clinical trial carried out at 64 institutions in Japan from September 2013 to March 2015. All procedures were in accordance with the ethical standards of the Ethics Committee of Shinshu University School of Medicine (Permission No. 2339, 2013), the Helsinki Declaration of 1975, as revised in 2008, and the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labor and Welfare of Japan, revised in 2008 and enforced in April 2009. Written informed consent was obtained from each patient. This clinical trial has been registered at University Hospital Medical Information Network (UMIN) Center (identifier: UMIN000011491). The information on protocol amendment was also registered.

Patients

The study enrolled female patients aged ≥20 years who had suffered from MUI for >3 months, and who gave their written informed consent to participate in this study. With regard to the number of episodes of urinary incontinence, patients who had both UUI (≥1 episodes per week) and SUI (≥3 per week) were enrolled (hereinafter, the number of episodes of urinary incontinence per week is referred to as "urinary incontinence frequency"). The presence of urinary incontinence was confirmed using a bladder diary prespecified by each patient, as well as the ICIQ-SF. As for the ICIQ-SF questionnaire, eligible patients had to meet all of the following requirements: (i) they had an Item 1 score of ≥2 points – frequency of leakage: How often do you leak urine?; (ii) they had an Item 2 score of ≥2 points – perceived amount of leakage: We would like to know how much you think leaks. How much urine do you usually leak (whether you wear protection or not)?; and (iii) they selected "leaks when you cough or sneeze" and/or "leaks when you are physically active/exercising" as the perceived cause of leakage in Item 3 and 5 of the last question in ICIQ-SF. Bladder condition including descent of the bladder, dilatation of the bladder neck, hypermobility of the urethra and intrinsic sphincter deficiency were evaluated in each institution. Decrease in urethral reflex was also evaluated during UPP for the patients who received UPP.

Patients had to have a post-void residual urine volume of <100 mL at baseline. All the enrolled participants were asked to keep a bladder diary for 7 days before baseline and each visit during this study to make an assessment of urinary incontinence.

Patients with urethral stricture, bladder stone, bladder tumor, urinary tract infection, pregnancy and pelvic organ prolapse were excluded. Patients who had severe bladder dysfunction, such as urinary retention or lack of urine sensation, were also excluded from the present study. Patients who took medicines for urinary tract dysfunction within 2 weeks before enrollment of this trial were also excluded.

ICIQ-SF is a patient-rated, disease-specific questionnaire that measures the symptoms and QOL of patients with urinary incontinence (leakage). It consists of the following four items: (i) the frequency of leakage (scored as an integer from 0 to 5); (ii) the amount of leakage (from 0 to 6); (iii) QOL (from 0 to 10); and (iv) the cause (type) of leakage (without score). The OABSS is also a patient-rated, disease-specific questionnaire that measures the symptoms of patients with overactive bladder.

All patients who received at least one protocol therapy after registration, unless they withdrew their informed consent, were included in the SAS. The FAS included patients who received at least one protocol therapy after registration. Patients were excluded if: (i) they withdrew their informed consent at any time during the trial; (ii) they were judged to be ineligible after registration; (iii) they did not have baseline data; and (iv) they were not evaluated for efficacy due to failure to undergo the examinations and so on.

Interventions and end-points

MUI patients were given PH at 20 mg orally once daily after a meal for 12 weeks. When the response was inadequate and the patient wished it, the dose of PH was allowed to increase to 30 or 40 mg daily given in two divided doses.

The efficacies of PH were evaluated by the self-reported frequencies of urinary incontinence in the patient's diary. The primary end-point was the frequency of urinary incontinence (the number of episodes of urinary incontinence per week) including SUI; UUI; unclassified urinary incontinence at baseline and 4, 8 and 12 weeks after commencement of treatment with PH; and the decreasing rate of each type of urinary incontinence. The number of MUI episodes was defined as the sum of the number of SUI and UUI episodes. The secondary end-points included the number of urinations per week, the number of urinary urgency episodes per week, the number of pads used per week, percentage change from baseline frequency of urinary incontinence, questionnaires on voiding symptoms including OABSS and ICIQ-SF, residual urine volume, and adverse events. We counted only the number of incontinence pads used and did not confirm the use of diapers in the study. Adverse events were collected until 12 weeks after commencement of treatment with PH.

As exploratory end-points, the FUL and MUCP at week 12 were compared with those at baseline. They were measured at six institutions where UPP was available. Patient demographics were examined for whether they contributed to the decrease in SUI frequency. The results obtained from UPP were analyzed by the study expert committee (the chair is KS).

Additionally, all of the adverse events that occurred after commencement of PH treatment were also reviewed to evaluate the safety of PH. The occurrence and severity of adverse events were evaluated for each patient. A causal relationship between PH administration and an adverse event was judged by investigator.

Statistical analysis

The sample size was 200 participants, which was based on the feasibility of recruiting patients and the availability of drug information relating to mixed-type urinary incontinence.

Efficacies were evaluated using paired participant data between baseline and at 4, 8 or 12 weeks for all end-points except UPP, and those between baseline and at 12 weeks for UPP by the Wilcoxon signed rank test. Patient demographic factors for the decrease in SUI frequency were examined by regression analysis. All analyses were predefined in the statistical analysis plan before the database lock in February 2016, and were carried out using SAS version 9.3 (SAS Institute, Cary, NC, USA). Data were expressed as the mean ± standard deviation for continuous variables, and as frequencies and percentages for discrete variables, unless specifically mentioned. The level of significance was set at $P < 0.05$ (two-tailed).

Results

Patients

The disposition of patients through the study is shown in Figure 1. Two patients were excluded from the enrolled participants, so the number of participants in the SAS was thus 60. A total of 11 participants were excluded from the SAS and 49 participants provided data for the FAS. The number of participants who submitted their bladder diaries at 4, 8 and 12 weeks after commencement of treatment with PH was 49, 44 and 41, respectively. However, one patient who submitted her diary at 12 weeks discontinued PH treatment after 8 weeks, but we decided that the patient's bladder diary should be evaluated, as PH had been administered for >8 weeks and the effects of PH at 12 weeks cannot be completely neglected. The clinical characteristics of the enrolled patients for both safety and efficacy analyses are shown in Table 1.

Efficacy

Almost all FAS patients (93.9%) reported that they had taken >75% of the PH prescribed during the study. As expected, the frequency of UUI episodes per week was reduced in a time-dependent manner, which showed statistically significant differences in the paired comparison between baseline and at 4, 8 and 12 weeks after treatment. A similar statistically different decrease was also observed in SUI frequency.

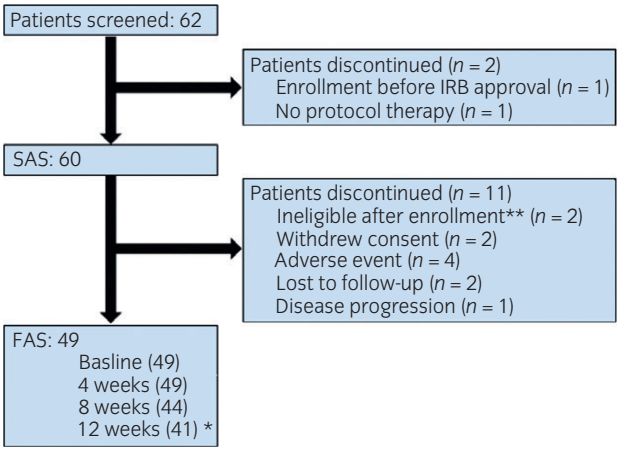

Fig. 1 Disposition of patients through the study. *A total of 40 patients completed all of the protocols of the study. See text for further explanation. **UUI frequency <1/week at baseline. One patient who submitted her diary at week 12 dropped out after week 8, but we decided that the patient's diary should be evaluated, as PH had been administered over a period of 8 weeks, and some effects at week 12 cannot be completely neglected.

However, although the number of unclassified urinary incontinence episodes at 8 weeks after PH did not decrease significantly, there was a significant improvement in the number at 4 and 12 weeks. The mean rates of decrease in UUI and SUI frequency at 12 weeks after PH were 63.9% and 44.3%, respectively, and the efficacy of PH on SUI frequency seemed to be less than on UUI frequency.

Following the protocol, >90% of the patients filled out their bladder diary. The results of the bladder diaries and subjective symptoms are shown in Table 2. The total scores of ICIQ-SF and OABSS were gradually reduced, and these differences were statistically significant. The volume of residual urine at week 12 did not significantly change after treatment with PH. When compared with baseline, neither FUL nor MUCP measured at 12 week's showed a statistically significant difference.

Safety

A total of 23 adverse events were reported in 20 (33.3%) out of 60 patients, with the frequent symptoms being oral thirst ($n = 6$, 10%), and constipation ($n = 4$, 6.7%), as shown in Table 3. There were no serious adverse events, and the incidence of mild, moderate and severe adverse events was 11 (18.3%), five (8.3%) and four patients (6.7%), respectively. Although 55% of the adverse events were considered to be related to the use of PH, a causal relationship with PH cannot be denied in 25% of the events (data not shown).

Factors associated with SUI change

The influence of patient demographic factors on the decreased rate of SUI frequency at week 12 was investigated by regression analysis and the results are shown in Table 4. Just two factors, the increase in diastolic blood pressure ($P = 0.011$)

Table 1 Patient characteristics for evaluation of safety and efficacy

			FAS			
	SAS		All patients		Patients with UPP	
	n	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD
Age (years)	60	67.7 ± 9.9	49	68.0 ± 10.5	17	72.1 ± 8.5
Bodyweight (kg)	54	55.1 ± 8.3	46	54.3 ± 7.5	16	58.3 ± 9.8
Height (m)	54	1.5 ± 0.6	46	1.5 ± 0.1	16	1.5 ± 0.1
BMI (kg/m^2)	54	23.7 ± 3.4	46	23.5 ± 3.3	16	25.4 ± 3.3
Parity (cases)	59	2.2 ± 0.9	45	2.2 ± 0.7		
Menopause (cases)	Yes	51		41		
	No	6		6		
	Missing	3		2		
Time since menopause (months)	40	212.9 ± 112.2	31	218.3 ± 120.4		
Complication (cases/%)						
Hypertension	59	28/46.7	31	21/42.9		10/58.8
Diabetes mellitus	59	7/11.9	31	5/10.2		1/5.9
Other	60	27/45.8	31	21/42.9		8/47.1

Table 2 Clinical and urodynamic effects of PH in patients with MUI

		Baseline	4 weeks	*P*-value	8 weeks	*P*-value	12 weeks	*P*-value
Bladder diary	*n*	49	49		44		41	
MUI (UUI + SUI)	(/week)	29.4 ± 17.7	20.0 ± 18.6	<0.0001	17.9 ± 18.9	<0.0001	15.0 ± 15.9	<0.0001
	(-%baseline†)	0.0	30.6 ± 66.9		41.5 ± 48.8		51.7 ± 39.5	
UUI	(/week)	12.2 ± 11.1	7.1 ± 11.2	0.0001	4.6 ± 7.2	<0.0001	4.5 ± 7.9	<0.0001
	(-%baseline†)	0.0	34.1 ± 104.2		64.5 ± 47.1		63.9 ± 76.9	
SUI	(/week)	17.2 ± 11.7	12.8 ± 14.9	0.0002	13.3 ± 16.7	0.0166	10.5 ± 12.6	<0.0001
	(-%baseline†)	0.0	27.7 ± 75.0		32.2 ± 60.7		44.3 ± 55.6	
Unclassified urinary incontinence	(/week)	5.1 ± 9.5	3.2 ± 8.2	0.0042	2.7 ± 5.8	0.1045	1.5 ± 3.9	<0.0001
Urinary frequency	(/week)	70.5 ± 16.8	62.8 ± 17.0	<0.0001	59.2 ± 14.6	<0.0001	56.9 ± 12.2	<0.0001
Frequency of urinary urgency	(/week)	24.3 ± 20.0	16.4 ± 18.3	0.0003	11.4 ± 14.5	<0.0001	9.8 ± 15.5	<0.0001
No. used incontinence pads	(/week)	29.0 ± 22.6	21.6 ± 20.4	<0.0001	19.5 ± 21.2	0.0005	16.8 ± 17.3	<0.0001
Subjective symptoms								
OABSS		8.8 ± 3.1	6.4 ± 4.4	<0.0001	5.0 ± 3.9	<0.0001	4.9 ± 3.6	<0.0001
ICIQ-SF		14.1 ± 3.8	10.0 ± 4.9	<0.0001	9.2 ± 4.8	<0.0001	8.8 ± 5.4	<0.0001
	n	49					36	
Residual urine	(mL)	11.5 ± 15.9					8.5 ± 21.0	0.0732
UPP								
FUL	*n*	11					8	
	(cm)	6.6 ± 11.5					9.0 ± 11.0	0.2188
MUCP	*n*	13					9	
	(cmH_2O)	34.3 ± 18.9					36.9 ± 13.6	0.9141

Mean ± SD. *P*-value by paired comparison. †(value at baseline − value at follow up) × 100 / value at baseline.

and severe dilatation of the bladder neck ($P = 0.014$), negatively influenced the decrease in SUI frequency rate.

Discussion

The present study was carried out as a multicenter single-arm clinical trial to show the efficacy of PH in female patients with MUI, especially those with SUI symptoms. A bladder diary was the main tool used to evaluate the effect of PH. In the study, PH reduced the frequency of SUI and UUI each week in a time-dependent manner, which was statistically significant. In addition, urinary frequency, frequency of urgency and the number of pads used similarly decreased after PH treatment. These results suggest that PH improved both UUI and SUI frequency in MUI patients. Furthermore, subjective symptoms evaluated using OABSS and ICIQ-SF also improved. An increase in residual urine volume had been expected after PH treatment, but the volume of residual urine did not show an increase after PH administration, which was similar to a previous report.[8]

Measurements of FUL and MUCP did not significantly change after treatment with PH, so there was no objective evidence regarding improvement in SUI, and the precise mechanism of PH action on SUI is still unknown. However, the number of patients who underwent UPP examination was just eight (13.3%) at six institutions. The study's expert

Table 3 Adverse events

	n	%
Total no. patients for safety evaluation	60	100.0
Total no. patients with any adverse events	20	33.3
Total no. adverse events	23	
No. serious adverse events	0	
No. patients with adverse events leading to study withdrawal	10	16.7
Severity of adverse events	20	
Mild	11	18.3
Moderate	5	8.3
Severe	4	6.7
Adverse events	20	33.3
Oral thirst	6	10.0
Constipation	4	6.7
Abdominal pain	1	1.7
Cough	1	1.7
Acute cystitis	1	1.7
General fatigue	1	1.7
Oral discomfort	1	1.7
Dyspepsia	1	1.7
Tongue pain	1	1.7
Dizziness	1	1.7
Increase in urinary incontinence	1	1.7
Urinary tract infection	1	1.7
Difficulty in micturition	1	1.7
Blurry vision	1	1.7

Table 4 Patient demographic factors influencing decreased rate of SUI at week 12

	Regression coefficient	*P*-value
Age	−0.18	0.835
BMI	−1.05	0.707
Systolic blood pressure	−0.02	0.976
Diastolic blood pressure	−2.16	0.011
Heart rate	−0.60	0.502
Parity	2.36	0.834
Menopause (yes/no)	3.56	0.898
Years after menopause	−0.08	0.433
Diabetes mellitus (yes/no)	41.80	0.221
Hypertension (yes/no)	12.84	0.483
Descent of bladder		
Type I	88.22	0.062
Type IIA	33.91	0.527
Type IIB	−16.28	0.760
Dilatation of bladder neck		
Severe	−105.47	0.014
Moderate	−37.67	0.254
Hypermobility of urethra (yes/no)	−14.96	0.709
Intrinsic sphincter deficiency (yes/no)	−50.16	0.165
Decrease in urethral reflex during UPP (yes/no)	53.17	0.121
Total OABSS score at baseline	0.05	0.987

Results of univariate regression analysis. Data regarding the condition of the bladder and urethra (type of bladder descent, extent of bladder neck dilation, and presence or absence of urethral hypermobility and intrinsic sphincter deficiency), which were examined routinely using transabdominal ultrasonography, cystography or vaginal examination within 6 months before registration were collected as baseline characteristics.

committee investigated the cause of this failure, and reported that the length and pressure were not measured properly at several institutions, and concluded that the results could not be evaluated. We were therefore unable to clarify the mechanisms of PH, as shown in the previous report.[12] Further investigation should be carried out to clarify the mechanisms of PH on SUI patients.

Our regression analysis showed that the increase in diastolic blood pressure and the high dilatation of the bladder neck might have a negative influence on the decrease in SUI frequency. Further investigation is required to show the exact relationship among PH, SUI frequency and diastolic blood pressure. In addition, high dilatation of the bladder neck attenuated the effect of PH on SUI frequency more than mild dilatation.

As in previous studies, oral thirst and constipation were the main symptoms of the adverse events observed after PH administration in the present study.[9–12] No serious adverse events were observed, and most of the adverse events were either mild or moderate in severity. These results suggest that PH can be a prospective treatment option for SUI without severe adverse events.

Many conservative treatments for SUI have been reported previously. Pelvic muscle exercise is an effective treatment for SUI.[20] Medications, such as antihypertensives, duloxetine and hormone preparations, and neuromodulation, have also been shown to have some effect on SUI.[21–25] However, these conservative options have certain limitations, such as lacking a high degree of evidence and leading to adverse events. Considering such limitations, the above conservative treatment options for SUI are insufficient to manage SUI with satisfactory QOL. Effective medications are warranted for refractory SUI patients, and PH can be considered an alternative candidate for SUI treatment.

To the best of our knowledge, the present study is the first investigation showing the effect of PH on SUI frequency in MUI patients. However, this study had certain limitations that must be considered when interpreting the results. In addition, PH is allowed to be used only for UUI patients in Japan. In these aspects, this trial is suitable as the first step to show the clinical effect of PH for SUI patients. As the next step, a randomized, double-blind, placebo-controlled study with a large number of isolated SUI patients would be required to verify the present findings. Second, the effects of the investigational drug were evaluated mainly using subjective tools filled out by the participants. Third, this trial was carried out for MUI patients. As SUI and UUI cannot be clearly separated, the reduction of SUI might be affected by the effects of PH on UUI. Despite these limitations, our findings show that PH might have the effect of improving function of the urethra or bladder neck through the non-anticholinergic pathway, and can be considered a prospective treatment option for SUI patients without leading to severe adverse events. Further investigation considering the aforementioned limitations should be carried out as the next step.

In conclusion, PH can be a candidate for a therapeutic option for SUI frequency in patients with MUI.

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Conflict of interest

TM reports personal fees as a speaker at educational seminars for Taiho Pharmaceutical, outside the submitted work.

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