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Original Article: Clinical Investigation

Effect of propiverine hydrochloride on stress urinary incontinence

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Abbreviations & Acronyms
IPSS = International Prostate Symptom Score
LPP = leak point pressure
OABSS = Overactive Bladder Syndrome Score
propiverine = propiverine hydrochloride
QOL = quality of life
UPP = urethral pressure profile
wks = weeks

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Objectives: To investigate whether the anticholinergic agent, propiverine hydrochloride, is clinically effective for stress urinary incontinence.

Methods: The participants were adult female patients with the chief complaint of stress incontinence. Propiverine (20 mg once daily) was given for 8 weeks. If the response was inadequate after 4 weeks of treatment, the dose was increased to 40 mg/day. Before and after 4 and 8 weeks of treatment, lower urinary tract symptoms were assessed. The urethral pressure and blood catecholamine levels were also measured.

Results: A total of 37 patients (mean age 69 ± 11 years) were enrolled, including 15 patients with stress incontinence and 22 with mixed incontinence. The number of episodes of stress incontinence decreased significantly from 2.6 ± 2.3 times per day to 1.3 ± 2.2 times per day after 4 weeks, and 0.4 ± 0.6 times per day after 8 weeks. The daytime and night-time frequency of urination, and quality of life score showed significant improvement. The maximum urethral closing pressure and the functional urethral length increased significantly after treatment, but blood catecholamine levels, blood pressure and pulse rate at 8 weeks were not significantly different from those at baseline.

Conclusions: Propiverine could be an effective drug for stress urinary incontinence by increasing urethral closing pressure without increasing blood catecholamine levels.

Key words: catecholamine, functional urethral length, propiverine, stress urinary incontinence, urethral closing pressure.

Introduction

Stress incontinence is a urinary symptom that has a marked influence on the QOL of Japanese women from those aged in their 20s to those who are middle-aged.[1] Kegel exercises, bladder training and surgery are used for the treatment of stress incontinence, but few medications are indicated for this condition. In Japan, clenbuterol hydrochloride,[2–4] a β-agonist that is also used to treat asthma, is the only drug indicated for stress incontinence, although the tricyclic antidepressant, imipramine hydrochloride, is also used.[5,6] In Europe, the antidepressant, duloxetine,[6–8] is used for the treatment of stress incontinence. In daily practice, propiverine hydrochloride, an anticholinergic drug indicated for urge incontinence, is given to patients who have both urge incontinence and stress incontinence. It has generally been found that both types of incontinence are improved by such treatment, and it has also been reported that propiverine is effective for pure stress incontinence.[9–13] Anticholinergic drugs reduce bladder hypersensitivity, and thus are indicated for patients with urge incontinence as a result of involuntary bladder contractions. Because stress incontinence occurs due to a low urethral closing pressure, anticholinergic drugs have been considered ineffective, which leads to doctors not prescribing these drugs for patients with stress incontinence. A recent animal study of the anticholinergic agent, propiverine hydrochloride, showed that blood catecholamine levels[14,15] and the urethral closing pressure[16] were elevated by administration of this drug to young rats. Accordingly, the present study was carried out to investigate whether propiverine hydrochloride was clinically effective for stress incontinence through a similar mechanism.

Methods

The participants were female patients aged 20 years or older who presented to any of the participating urology outpatient departments with the chief complaint of stress incontinence

between September 2010 and December 2012 (irrespective of whether they also had urge incontinence), who had episodes of stress incontinence more than twice a month, and who gave written consent to participation in the present study. The following patients were excluded: patients with untreated lower urinary tract disease (urethral stenosis, bladder tumor or bladder calculus), patients with bacterial urinary tract infection (bacterial cystitis) or non-bacterial inflammation (interstitial cystitis), patients receiving drug treatment for dysuria, patients without any urge to urinate, patients with dementia who were unable to complete the interview sheet and other patients whom the attending physician judged to be inappropriate for this study. The Ethics Review Committee of Okinawa Kyodo Hospital reviewed the present clinical study on behalf of all of the participating institutions.

Propiverine (20 mg once daily) was given for 4 weeks to patients with stress incontinence who satisfied the aforementioned criteria. If improvement was obtained, treatment was continued for a further 4 weeks. If the response was inadequate, the dose of propiverine was increased to 40 mg/day (administered once or twice daily) for another 4 weeks. Dose escalation as a result of inadequate efficacy was only carried out in patients with a IPSS-QOL index[17] of 2–6 points who gave consent to treatment at the higher dose. Other drugs that had been used for treatment of other conditions before the start of the present study could be continued if the dosage was not changed throughout the study period. In principle, use of anticholinergic drugs other than the investigational drug for the treatment of dysuria or digestive disorders was prohibited.

Before the start of propiverine treatment, lower urinary tract symptoms (OABSS,[18] IPSS, QOL, daytime urinary frequency, night-time urinary frequency, number of stress incontinence episodes, number of urge incontinence episodes and number of pads used daily) were assessed by carrying out an interview. After 4 weeks and 8 weeks of treatment, a similar interview was carried out along with assessment of the improvement rate (each patient's impression of the effect of treatment: markedly improved, improved, slightly improved, no change, or worsen) and the occurrence of adverse events. Measurement of blood pressure and pulse rate were carried out before and after treatment. Wherever possible, the UPP was carried out before and after treatment. For this, physiological saline (50 mL/min) was infused by a 7-Fr UPP catheter with two side holes, and the drawing speed of the catheter was 1.5 mm/s. The measurement of three blood catecholamines was also carried out before and after treatment.

Results are expressed as the mean ± SD, and the Friedman test or the paired *t*-test (for the UPP) were used for statistical analysis, with $P < 0.05$ showing significance.

Results

A total of 37 patients were registered with a mean age of 69 ± 11 years. They included 15 patients with stress incontinence and 22 patients with mixed incontinence. The duration of stress incontinence was 6.9 ± 7.4 years. A total of 10 patients also had hypertension, two patients had diabetes and 14 patients had other illnesses except neurogenic bladder. Post-void residual urine volume was 10 ± 16 mL before the administration of propiverine. In five patients, the daily dose of propiverine was increased from 20 mg to 40 mg after 4 weeks of treatment. In one patient, the daily dose was decreased to 10 mg after 4 weeks as a result of dry mouth.

The daytime and night-time frequency of urination decreased significantly after 4 and 8 weeks of treatment (Table 1). The number of episodes of stress incontinence decreased significantly from 2.6 ± 2.3 times per day before propiverine administration to 1.3 ± 2.2 times per day after 4 weeks of treatment with propiverine, and 0.4 ± 0.6 times per day after 8 weeks. The number of episodes of urge incontinence also decreased significantly after 4 and 8 weeks of treatment, and the number of pads used daily decreased significantly from 3.0 ± 2.4 sheets per day before propiverine administration to 1.9 ± 2.7 sheets per day after 4 weeks of treatment with propiverine, and 1.1 ± 1.7 times per day after 8 weeks. OABSS and IPSS were also decreased significantly, and the QOL index showed significant improvement. There was no difference in the number of stress incontinence episodes between 15 patients with pure stress incontinence and 22 patients with mixed incontinence at baseline or after 4 weeks and 8 weeks of administration.

The UPP was carried out in eight patients (3 patients after 4 weeks of treatment and the other 5 patients after 8 weeks). There were no overlapped patients between 4 and 8 weeks. The maximum urethral closing pressure increased significantly from 28 ± 10 cmH_2O at baseline to 35 ± 11 cmH_2O after treatment, and the functional urethral length also increased significantly from 26 ± 8 mm at baseline to 33 ± 8 mm after treatment. Blood catecholamine levels were measured in 26 patients. Although only noradrenaline showed a transient increase after 4 weeks, the level at 8 weeks was not significantly different from that at baseline. Propiverine treatment had no effect on the blood pressure or pulse rate.

Regarding each patient's impression of improvement, 18 patients (67%) rated themselves as "improved or better" after 4 weeks of propiverine treatment and 21 patients (72%) did so after 8 weeks. Among five patients in whom the daily dose was increased from 20 mg to 40 mg as a result of inadequate efficacy, three rated themselves as "improved or better" ("improved" in two and "markedly improved" in one) after 8 weeks. The remaining two patients rated themselves as "slightly improved" after both 4 and 8 weeks.

There were 12 episodes of adverse events (32%), but none of these events were serious (Table 2). In one patient, dose reduction to 10 mg daily was carried out at 4 weeks as a result of dry mouth, but this patient did not complain of dry mouth thereafter and continued the study to 8 weeks. This patient's improvement rating was "improved" after both 4 and 8 weeks. One of the five patients with dose escalation from 20 mg to 40 mg daily at 4 weeks as a result of inadequate efficacy experienced mild blurred vision and terminated the study at 8 weeks with the improvement rating of "slightly improved". These adverse events resolved promptly after discontinuation of propiverine treatment.

Discussion

Propiverine has previously been reported to be effective for stress incontinence,[9–13] but these earlier reports did not receive sufficient attention. As the reason, many urologists might not believe in the effect of propiverine, a muscarinic receptor antagonist, on stress urinary incontinence. The present study

Table 1 Changes of symptoms and data from before propiverine administration to after 4 and 8 weeks of treatment

	Before	4 Weeks	8 Weeks
Daytime urinary frequency (times)	10.1 ± 4.3	8.2 ± 3.0**	7.3 ± 2.8**
Night-time urinary frequency (times)	1.6 ± 1.9	1.1 ± 1.3**	1.0 ± 1.0**
Stress urinary incontinence (times/day)	2.6 ± 2.3	1.3 ± 2.2**	0.4 ± 0.6**
Urge urinary incontinence (times/day)	1.6 ± 1.9	1.0 ± 1.8**	0.8 ± 1.8**
Pads used (sheets/day)	3.0 ± 2.4	1.9 ± 2.7**	1.1 ± 1.7**
IPSS			
Incomplete emptying	1.2 ± 1.8	1.0 ± 1.7	0.6 ± 1.1*
Frequency	3.3 ± 1.7	2.4 ± 1.7**	1.8 ± 1.6**
Intermittent stream	0.7 ± 1.5	0.4 ± 1.1	0.6 ± 1.3
Urgency	2.1 ± 1.9	1.3 ± 1.8**	0.8 ± 1.2**
Slow stream	1.1 ± 1.7	0.5 ± 1.1*	0.7 ± 1.4**
Straining	0.6 ± 1.4	0.3 ± 1.0	0.5 ± 1.2
Nocturia	1.6 ± 1.3	1.2 ± 1.3**	0.9 ± 1.0**
Total	10.6 ± 7.5	7.1 ± 6.9**	6.0 ± 5.1**
QOL index	5.3 ± 0.9	3.3 ± 1.9**	2.7 ± 1.6**
OABSS			
Frequency	0.9 ± 0.6	0.7 ± 0.6	0.4 ± 0.6**
Nocturia	1.4 ± 1.0	1.0 ± 1.0**	0.9 ± 1.0**
Urgency	2.5 ± 2.0	1.7 ± 1.8**	1.3 ± 1.5**
Urge incontinence	2.5 ± 1.9	1.7 ± 1.9**	1.1 ± 1.5**
Total	7.3 ± 4.4	5.1 ± 4.2**	3.8 ± 3.5**
Patient's impression of improvement, cases (%)			
Markedly improved		7 (26)	9 (31)
Improved		11 (41)	12 (41)
Slightly improved		5 (19)	5 (17)
No change		4 (15)	3 (10)
Worsen		0 (0)	0 (0)
Systolic blood pressure (mmHg)	127 ± 18	129 ± 18	127 ± 16
Diastolic blood pressure (mmHg)	72 ± 12	72 ± 18	71 ± 12
Pulse rate (/min)	76 ± 11	79 ± 11	78 ± 12
Plasma catecholamine levels (pg/mL)			
Adrenaline	30 ± 15	30 ± 22	26 ± 15
Noradrenaline	532 ± 191	603 ± 309*	610 ± 252
Dopamine	17 ± 9	20 ± 12	19 ± 10
UPP (n = 8)			
Maximum urethral closing pressure (cmH_2O)	28 ± 10		35 ± 11**
Functional urethral length (mm)	26 ± 8		33 ± 8*

*$P < 0.05$, **$P < 0.01$ *vs* before propiverine administration. Urethral pressure profile was carried out before propiverine administration and after treatment in eight patients (3 patients after 4 weeks and other 5 patients after 8 weeks of treatment). Values are mean ± SD. The paired t-test (for the urethral pressure profile) and Friedman test (for others) were used for statistical analysis.

Table 2 Adverse events

Adverse events	Total 12 cases
Constipation	4
Dry mouth	3
Constipation + dry mouth	2
Blurred vision	1
Constipation + blurred vision	1
Constipation + blurred vision + difficulty of urination	1

confirmed the efficacy of propiverine for stress incontinence. Blood catecholamine levels were not increased, and there were no changes of the blood pressure or pulse rate, but it was shown (for the first time) that propiverine treatment increases the maximum urethral closing pressure and functional urethral length. Based on the present findings, propiverine might be an effective drug for stress incontinence.

In rats, it has been reported that blood catecholamine levels become higher with age, and administration of propiverine increased catecholamine levels in young rats, but did not further increase the elevated catecholamine levels in elderly rats.[15] Propiverine increased the baseline urethral pressure and LPP in rats,[16] and these effects were speculated to be due to inhibition of noradrenaline reuptake.[19] The results of the present study suggest the possibility that inhibition of noradrenaline reuptake by propiverine increased urethral smooth muscle contraction and also increased activation of the pudendal nerve controlling the external urethral sphincter from the spinal cord. However, the action of propiverine was not strong enough to elevate blood catecholamine levels, so this drug did not cause changes of the blood pressure or pulse rate. Other than propiverine, no anticholinergic drug has been reported to have an influence on blood catecholamines,[14] and imidafenacin (another anticholinergic drug) did not increase the LPP.[20] Considering that imipramine (a tricyclic antidepressant) and duloxetine (an antidepressant) increased the LPP,[20] these drugs that have an inhibitory effect on noradrenaline and serotonin reuptake are presumed to be effective for stress incontinence through their effect on the LPP.

Propiverine was reported to increase the blood catecholamine levels in young rats, but not in aged rats, and it had no effect on the blood pressure or pulse rate.[14,15] Similarly, in the present study, propiverine did not elevate blood catecholamine levels in either young or elderly patients, and had no effect on the blood pressure or pulse rate. However, both the maximum urethral closing pressure and the functional urethral length were increased by propiverine treatment. The increase of functional urethral length appeared to be secondary to contraction of the bladder neck as a result of an increment of urethral smooth muscle tone. Elevation of the maximum urethral closing pressure was presumably due an increase in the tone of either the urethral smooth muscle or the external urethral rhabdosphincter. Propiverine might enter the central nervous system and inhibit noradrenaline reuptake at the spinal level so that the nucleus of the pudendal nerve is stimulated, which could increase the urethral closing pressure by elevating the tone of the external urethral sphincter through the pudendal nerve.[21,22] Consequently, stress incontinence was improved in the patients of the present study by a similar mechanism to that previously reported in rats.

In the present study, the starting dose of propiverine was 20 mg/day, but was increased to 40 mg/day after 4 weeks in five patients because of inadequate efficacy. Two of these patients showed improvement after 8 weeks, and one achieved marked improvement. One of the patients requiring dose escalation was "slightly improved" after both 4 weeks and 8 weeks, but developed blurred vision and withdrew from the study. All of the adverse events that occurred were events that have already been reported, and no new events were noted. All of the adverse events were rated as mild, and resolved after discontinuation of treatment. Accordingly, if a satisfactory result is not obtained with propiverine treatment at 20 mg/day, the dose should be increased to 40 mg/day, while paying attention to adverse reactions.

Standard management of patients with stress incontinence includes guidance about pelvic floor exercises and keeping a voiding diary, but most patients find it difficult to persist with such measures. We previously carried out a study on the effect of an alarm device.[23] We found that the device group was better motivated to carry out pelvic floor exercises because the alarm reminded them to do so, and the response to exercise was significantly greater in the device group than in the control group. Motivation is important to continue pelvic floor exercises. If propiverine treatment improves stress incontinence to some extent, this could contribute to increasing the motivation of patients to continue pelvic floor exercises.

In conclusion, the findings of the present study suggested that propiverine treatment is useful for both stress incontinence and mixed incontinence.

Conflict of interest

None declared.

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