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Author(s)	OKADA, Hiroshi; SENGOKU, Jun; GOHJI, Kazuo; ARAKAWA, Soichi; KAMIDONO, Sadao
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## CLINICAL EFFECT OF PROPIVERINE IN PATIENTS WITH URGE OR STRESS INCONTINENCE

Hiroshi OKADA, Jun SENGOKU, Kazuo GOHJI, Soichi ARAKAWA, Sadao KAMIDONO and Kobe University Incontinence Study Group

*From the Department of Urology, Kobe University School of Medicine*

The efficacy and tolerability of propiverine hydrochloride (20 mg/day) were evaluated in the treatment of a total of 49 Japanese patients (35 with urge incontinence and 14 with stress incontinence) in an open multicenter trial lasting 28 days. The effects on the frequency of urination, urinary incontinence, urinary urgency, and daily living activities were evaluated through the voiding diaries filled out by the patients.

Moderate or greater degree of improvement was attained in micturition frequency by 52 and 54% of the patients with urge incontinence and with stress incontinence, respectively, in urinary urgency by 91 and 58%, in urinary incontinence by 97 and 71%, and in daily living activities by 94 and 64%. Although minor adverse reactions (5 patients) and abnormal values in blood chemistry (2 patients) were recorded in 7 patients, all of these patients completed the trial.

These results suggest that propiverine hydrochloride is a safe and effective drug of choice for the treatment of not only urge incontinence but also stress incontinence in patients diagnosed in a clinical setting.

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**Key words:** Propiverine, Stress incontinence, Urge incontinence

### INTRODUCTION

Propiverine hydrochloride (a benzylic acid derivative) is a synthetic musculotropic antispasmodic agent which has been used mainly in the East Germany since the early 1980's<sup>1,2)</sup> Several trials have demonstrated the effectiveness of this agent against urinary incontinence<sup>2,3)</sup> However, these trials focused on groups of patients with urge incontinence or urinary urgency, and no study has clarified the effectiveness of this agent on stress incontinence in comparison with its effects on urge incontinence. We examined the effectiveness of propiverine for the treatment of patients with urge and stress incontinence.

### PATIENTS AND METHODS

The study was designed as an open, multicenter parallel-group trial. Outpatients, who had been diagnosed as having urge incontinence or stress incontinence between January, 1995 and March, 1996, were enrolled in the trial. All patients complained of hygiene and/or social problems due to involuntary voiding of urine, and were each fully informed in detail regarding the trial. Informed consent was given by each patient prior to entering the trial, which was approved by the Ethics Committee of the Kobe University School of Medicine. Patients who had bladder outlet obstruction, overflow incontinence or overt urinary tract infection were excluded from the study. Also excluded were incontinent patients after transurethral resection of the prostate, and those with

indwelling Foley catheters. Potential pregnancy was an exclusion criterion in addition to concomitant medication which might affect detrusor function. Patients with renal or liver dysfunction and those with cardiovascular disease were excluded.

A total of 49 patients (18 male and 31 female patients) were enrolled. All patients were selected from the out-patient population. They consisted of 35 (18 male and 17 female) patients with urge incontinence and 14 patients (all female) with stress incontinence.

The initial examination was performed before the patient entered the study but after a one-week run-in period. During this time the patients were asked to fill out voiding diaries inquiring as to urinary urgency, limitations of daily living activities, frequency of micturition, and frequency of urinary incontinence. The degree of urinary urgency was scored into 4 grades: very strong, moderate, slight, and no urgency. The degree of limitation of daily living activities was also scored into 4 grades: very, moderately, and slightly bothersome, and no limitation. The entry into the trial was registered at the central office for the trial by mail or by facsimile. Each patient was administered 20 mg of propiverine in the morning for 4 weeks. Patients were requested to visit the physicians' office every 2 weeks with the voiding diaries. The frequency of micturition and frequency of incontinence were recorded by averaging the values recorded for the 3 days immediately prior to attending the clinic. Improvement in the frequency of micturition and frequency of incontinence,

1. Urge incontinent patients

2. Stress incontinent patients

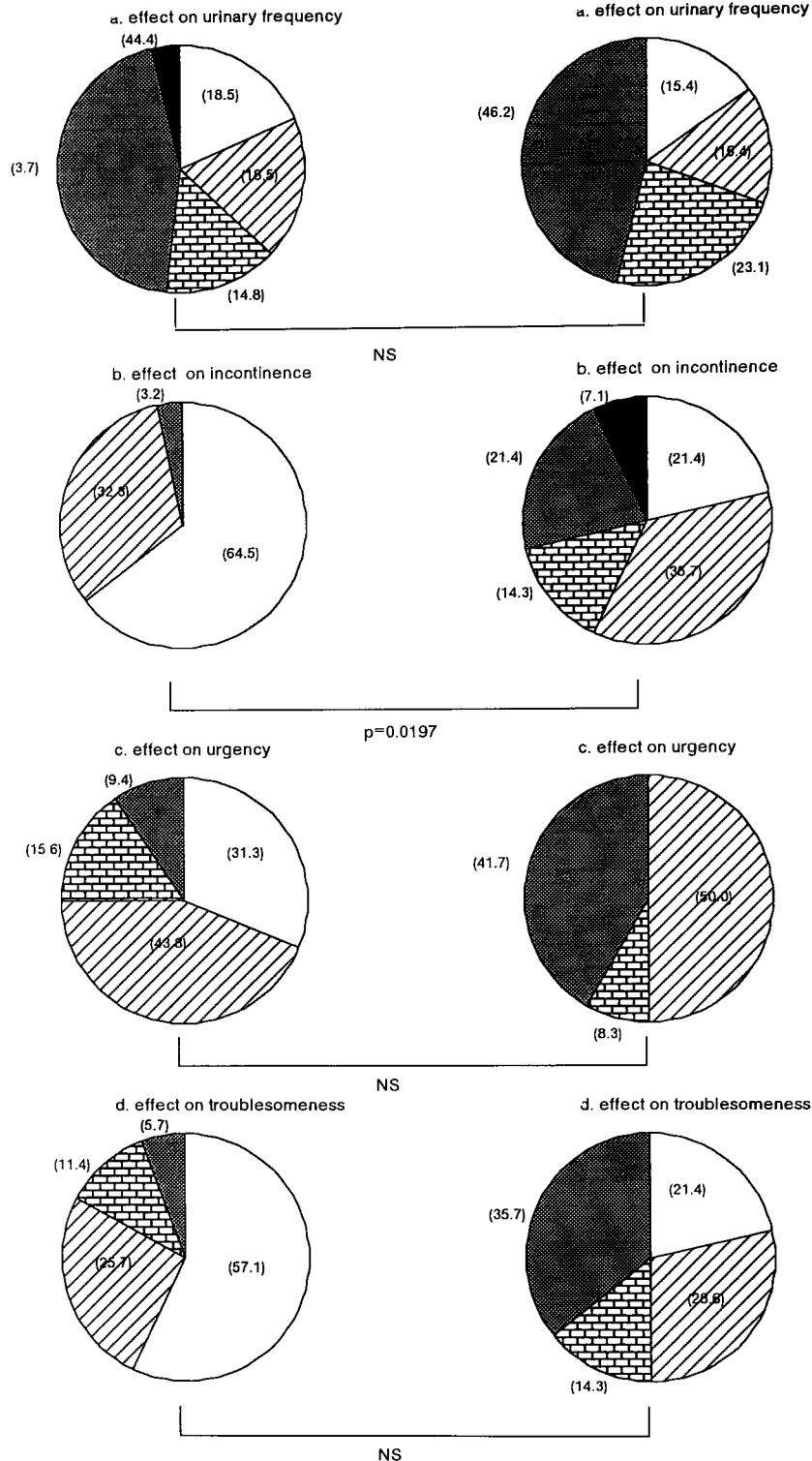


Fig. 1. Pie graphs showing the proportions of patients with each degree of improvement in each symptom. Percentage of each value is shown in the parentheses. Only the improvement of incontinence was significantly greater in the urge incontinent patients than in the stress incontinent patients ( $p=0.0197$ ). , excellent improvement; , moderate improvement; , fair improvement; , poor improvement; , aggravation of condition

and improvement of subjective symptoms were evaluated by the physician who compared the pre- and post-treatment status by consulting the voiding diaries. The degree of improvement was graded as excellent, moderate, or fair improvement, no change,

or aggravated condition. The objective measure of postvoid residual urine volume was recorded before and after the treatment period. A pad test was also applied before and after treatment for stress incontinent patients.

Side effects such as nausea, vomiting, tremor, dryness of mouth, blurred vision, and constipation were also monitored. Complete blood count, routine blood chemistry studies, and urinalysis including urine sediment analyses were performed during the run-in and post-treatment periods.

Mann Whitney's U-test was used for inter-group comparisons of the effectiveness of propiverine treatment. All data processing and calculations were performed by using the statistical standard program package Stat View® (ver. 4.0).

### RESULTS

Improvement of at least moderate degree was seen in 52% and 54% of the urge incontinent and stress incontinent patients, respectively, in frequency of micturition, 91% and 58% in urinary urgency, and 94% and 64% in the daily living activities. The percentage of patients who showed moderately or better improvement in urinary incontinence was 97% and 71%, respectively. This was the only measure for which the improvement in the urge incontinent patients was significantly greater than that in the stress incontinent patients ( $p=0.0197$ ) (Fig. 1). The pad test disclosed no significant change in the amount of incontinence ( $26 \pm 49$  g vs.  $5 \pm 9$  g) in the stress incontinent patients. The post-void residual urine volume changed from  $19 \pm 28$  mL to  $25 \pm 32$  mL in the urge incontinent patients and from  $5 \pm 7$  mL to  $8 \pm 6$  mL in the stress incontinent patients. Neither change was statistically significant.

A total of 6 cases of adverse effects suspected to be related to propiverine were recorded during the trial period. Constipation ( $N=1$ ), epigastralgia ( $N=1$ ) and dryness of the mouth ( $N=2$ ) developed in the urge incontinent group. One stress incontinent patient reported an episode of nausea, and one developed slight dysuria. All were transient symptoms that resolved spontaneously without discontinuation of the drug. Although one patient with urge incontinence experienced transient elevation of the serum level of lactate dehydrogenase and proteinuria, these abnormalities returned to the normal range two weeks later.

### DISCUSSION

Propiverine was introduced into the clinical treatment of incontinence in East Germany in the early 1980's<sup>1,2</sup>, and has been used predominantly in the eastern European countries. There is only one paper in English describing its efficacy<sup>3</sup>. Propiverine is reportedly effective in the treatment of patients with urgency and urge incontinence<sup>1,2</sup>. In 70% of the patients a decrease in micturition frequency was attained after treatment at a dosage of 15 mg/day for 21 days, and the subjective symptoms were improved in 54% of the patients at that dosage<sup>3</sup>.

Our results also revealed that propiverine reduced urinary urgency, incontinence and limitations in daily living activities in over 91% of the patients.

Pathophysiologically genuine stress incontinence is treated by bladder neck suspension by the Stamey or Raz procedures<sup>4,5</sup>. Non-hormonal pharmacologic therapy to increase bladder outlet resistance is appropriate in selected cases, and  $\alpha$ -adrenergic drugs such as epinephrine, phenylephrine, midodrine, norfenefrine and phenylpropranolamine have been used<sup>6,7</sup>. In this study, the anticholinergic drug propiverine was used in stress incontinent patients, who showed reduction of symptoms comparable to that recognized in the urge incontinent patients. Only the urinary urgency was improved more markedly in the urge incontinent than in the stress incontinent group. These results seem conflicting, since in the majority of patients with stress incontinence, the cause is excess urethral mobility that impairs urethral closing pressure<sup>8</sup>. In clinical practice, however, patients who complain of stress incontinence also display some degree of urge incontinence. They often have combined detrusor instability and stress incontinence<sup>9</sup>. This would account for the efficacy of propiverine against incontinence in the stress incontinent patients in this study.

In a clinical setting, physicians are required to start treatment before conducting a thorough urodynamic evaluation. In these instances, propiverine is a drug of choice to treat incontinence with minimum adverse reactions and maximum compliance.

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(迅速掲載)

## 和文抄録

## 切迫性ならびに腹圧性尿失禁に対するプロピペリンの臨床効果に関する検討

神戸大学医学部泌尿器科学教室（主任：守殿貞夫教授）

岡田 弘，仙石 淳，郷司 和男，荒川 創一

守殿 貞夫，神戸大学尿失禁研究グループ

プロピペリン（20 mg/日，28日間）の切迫性ならびに腹圧性尿失禁に対する臨床効果を49名の患者を対象に多施設協同研究で調査した。方法は治療前後の排尿回数，尿失禁回数，尿意切迫感，日常生活の制限の程度を排尿日誌を用いてその変化を調査した。

排尿回数の中等度以上の改善を切迫性および腹圧性尿失禁で52%および54%の患者で達成出来た。尿意切迫感はそれぞれ91%および58%の症例で改善した。尿

失禁はそれぞれ97%および71%の症例で改善した。さらに，日常生活の制限はそれぞれ94%および64%の症例で改善が見られた。また，軽度の副作用を5名に，臨床検査値の変動を2名に認めた。

これらの結果より塩酸プロピペリンは臨床診断が切迫性尿失禁の患者のみならず腹圧性尿失禁の患者に対しても安全で有効な薬剤と考えられた。

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