Dokkyo Journal of Medical Sciences
44(1) : 9 ～ 15, 2017

Original

Efficacy and Safety of Once-daily Oxybutynin Patch in Patients with Overactive Bladder Who had Experienced Adverse Reactions Caused by Oral Antimuscarinic Drugs

Hiroshi Yagi, M.D., Gaku Arai, M.D., Shigehiro Soh, M.D., Hiroshi Okada, M.D.

Department of Urology, Dokkyo Medical University Koshigaya Hospital, Saitama, Japan

SUMMARY

Objectives : To evaluate the efficacy and safety of once-daily oxybutynin patch for overactive bladder (OAB) patients not tolerating oral antimuscarinic drugs.

Methods : We prospectively investigated 43 OAB patients treated with once-daily oxybutynin patches for dry mouth and constipation due to oral antimuscarinic drugs.

Results : Oxybutynin patch treatment for 8 weeks significantly improved the visual analogue scale scores for dry mouth and constipation ; total score and subscore (mean number of urgency episodes and daily micturitions) for OAB symptoms ; and King's Health Questionnaire scores for social limitations, emotions and sleep/energy (P=0.016 and 0.001 ; 0.008, 0.041 and 0.015 ; and 0.007, 0.003 and 0.026, respectively). The 3-day frequency volume chart showed significant improvement in hours of undisturbed sleep (P=0.011). Eight patients had adverse reactions at the application site and withdrew from the study, while others only developed mild erythema and pruritus.

Conclusions : Oxybutynin patch reduces adverse reactions caused by oral antimuscarinic drugs.

Keywords : overactive bladder, oxybutynin patch, application site erythema, adverse reactions

INTRODUCTION

Overactive bladder (OAB) is a symptom syndrome that features urgency commonly accompanied by urinary frequency, but not necessarily urgency incontinence[1]. A European epidemiological survey found that the prevalence of OAB increases with age and that 16.6% of persons aged 40 years or older have OAB[2,3]. In Japan, OAB has been reported to affect 12.4% of the population over the age of 40 years[4]. A recent study showed that OAB symptoms negatively influence health-related quality of life (QOL) and increase anxiety and depression[5].

Antimuscarinic drugs are the first-line treatment for OAB[6,7]. However, these drugs frequently cause dry mouth, which cannot be relieved by drinking water because the latter aggravates the accompanying urgency and pollakisuria[8,9]. Constipation, another potential side effect, can further aggravate OAB symptoms, thereby compromising patient adherence to therapy[10]. On the other hand, another therapeutic agent for OAB, namely, transdermal oxybutynin formulation, is reported to reduce the generation of N-desethyloxybutynin (DEO), which is the main cause of adverse reactions[11]. Therefore, we hypothesized that the oxybutynin patch may induce fewer adverse reactions than existing oral antimuscarinic drugs.

Received September 23, 2016 ; accepted October 19, 2016
Reprint requests to : Hiroshi Yagi, M.D.
Department of Urology, Dokkyo Medical University Koshigaya Hospital Saitama Japan.

We investigated the efficacy and safety of a once-daily transdermal application of oxybutynin hydrochloride (oxybutynin patch) in Japanese OAB patients who developed adverse reactions, such as dry mouth or constipation, when treated with oral antimuscarinic drugs.

MATERIALS AND METHODS

This study was designed as a prospective investigation. The study protocol was approved by the Ethics Committee of Dokkyo Medical University Koshigaya Hospital, and this study was conducted in compliance with the Helsinki Declaration (1310). We obtained written informed consent from all participants after thoroughly explaining the efficacy and possible adverse reactions of oxybutynin patch.

Patients who met all of the following criteria were enrolled in this study : (1) age 20 or more ; (2) an average of 8 or more micturitions daily, with an average of one or more urgency or urgency incontinence episodes per day ; (3) presence of OAB symptoms for at least 2 months ; and (4) histoly of adverse reactions such as dry mouth or constipation when treated with oral antimuscarinic drugs. On the other hand, patients with a histoly of any of the following were excluded from the study : (1) urodynamic stress incontinence ; (2) other diseases causing symptoms difficult to differentiate from those of OAB ; (3) residual urine volume of 100 ml or more, and (4) a skin condition that could be exacerbated by the application of the drug patches investigated in this study.

The subjects had been receiving oral antimuscaric drugs until the day of enrollment in this study (day 0). On enrollment, they received 8 weeks of treatment with a once-daily oxybutynin patch (73.5 mg per 35 cm^2 patch). The patch was applied on the lower abdomen, hip region, or thigh, and the site of application was changed every day. If possible, the patches were changed at the same time of the day throughout the treatment period. Patients were asked to refrain from using other medications that influence urinary frequency and incontinence, drugs with anticholinergic activity, and cholinergic agents during the study period.

The efficacy of treatment was assessed using the data collected from a questionnaire and 3-day frequency volume chart (FVC), both before and after the 8-week treatment period. The scores of the visual analogue scale (VAS) for dry mouth and constipation, OAB Symptom Score (OABSS), and King's Health Questionnaire (KHQ) were determined by a physician (HY) who was blinded on the clinical background of the patients. The primary end-point was a change in the mean VAS scores of dry mouth and constipation. The secondary end-points were changes in the means of the following parameters : (1) urgency episodes per day, (2) urgency incontinence episodes per day, (3) number of micturations per night, and (4) number of micturitions per day. The patient's QOL was assessed on the basis of the domain scores of the KHQ.

Safety of the treatment was assessed in terms of the number and severity of adverse events, results of laboratory tests, values of vital parameters, and postvoid residual urine. Adverse events were investigated throughout the treatment period. Laboratory tests and measurement of vital signs were conducted before and the end of the 8-week period (or at discontinuation). Further, postvoid residual urine was measured by abdominal ultrasonography before and at the end of 4 and 8 weeks of treatment (or at discontinuation). The complete blood count was obtained, and blood chemistry tests were performed for the following parameters : serum levels of albumin, lactate dehydrogenase, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, total bilirubin, creatinine, urea nitrogen, sodium, potassium and chlorine. Urinalysis was performed at every visit.

Data are reported as means ± SD and were analyzed using SPSS software version 12.0 (IBM, Chicago, IL USA). Wilcoxon signed-rank test was used to evaluate the effects of treatment, and $P<0.05$ was considered significant.

RESULTS

Baseline Patient profile

In total, 43 (17 men and 26 women) patients were recruited in the study. The study was completed by 33 (13 men and 20 women) patients : 2 patients were excluded for not meeting all the inclusion criteria, while 8 were unable to continue the study because of adverse reactions at the site of patch application. The

Table 1 Clinical characteristics

	n=33
Age (years)	
Mean (SD)	74.7±6.2
Range	67-80
Sex, n (%)	
Male	13 (39.4)
Female	20 (60.6)
Weight (kg)	
Mean (SD)	56.3±9.2
Range	39.2-88.3
Oral antimuscaric drugs, n (%)	
Solifenacin succinate	13 (39.4)
Tolterodine tartrate	9 (27.3)
Imidafenacine	8 (24.2)
Propiverine hydrochloride	3 (9.1)
OABSS	
Total score	7.1±3.3
Number of micturitions per day	0.7±0.6
Number of nocturnal micturations per night	2.1±0.9
Urgency episodes per day	2.6±1.7
Urge incontinence episodes per day	1.6±1.6
UFM and FVC	
PVR (ml)	12.3±16.1
Number of micturitions per day	9.6±2.1
Number of micturations per night	2.5±1.1
NPI	36.6±12.2

OABSS=overactive bladder symptom score
UFM=uroflowmetry
FVC=freaquency volume chart
PVR=post-void residual urine
NPI=nocturnal polyuria index

baseline demographics and characteristics of the 33 patients investigated are provided in Table 1.

Efficacy

The mean VAS scores for dry mouth and constipation were significantly improved after the 8-week treatment period (P=0.016 and 0.001, respectively) (Table 2). The total scores and sub-scores of OABSS (the mean number of urgency episodes and micturitions per day) also showed significant improvement (P=0.008, 0.041 and 0.015, respectively), while other OABSS sub-scores (the mean number of urge incontinence episodes per day and micturations per night) did not. The scores for the KHQ domains of social limitations, emotions, and sleep/energy improved significantly (P=0.007, 0.003 and 0.026, respectively), whereas the others (role limitation, physical limitation, and personal relationship) did not show any such improvement. The FVC showed significant improvement in the hours of undisturbed sleep (HUS ; time between falling asleep and first waking to void) (P=0.011), but not in the other parameters (nocturnal polyuria index, mean number of micturition per day, and nocturnal micturations per night).

Safety

The results of blood biochemistry and urinalysis remained unchanged at 8 weeks (data not shown). Application-site dermatitis occurred in 14 (32.5%) of the 33 patients (5 men and 9 women). Further, the

Table 2 Change in parameters

	Pretreatment	After treatment for 8 weeks	P-value
VAS score			
Dry mouth	4.8 ± 2.3	3.6 ± 2.4	0.016
Constipation	3.0 ± 3.1	1.2 ± 2.3	0.001
OABSS			
Total	7.1 ± 3.3	5.7 ± 2.9	0.008
Urgency episodes	2.6 ± 1.7	2.0 ± 1.5	0.041
Urge incontinence	1.6 ± 1.6	1.4 ± 1.5	0.180
Number of nocturnal micturations	2.1 ± 0.9	1.9 ± 0.9	0.100
Number of micturitions	0.7 ± 0.6	0.5 ± 0.4	0.015
KHQ			
Role limitation	33.0 ± 23.4	29.0 ± 21.4	0.190
Physical limitation	18.6 ± 12.6	14.2 ± 12.1	0.093
Social limitation	10.5 ± 9.4	5.2 ± 8.6	0.007
Personal relationship	17.5 ± 13.9	14.2 ± 13.5	0.068
Emotions	29.1 ± 16.7	19.3 ± 12.8	0.003
Sleep and energy	24.1 ± 12.8	17.6 ± 11.7	0.026
FVC			
Number of micturition	9.6 ± 2.1	9.5 ± 2.8	0.183
Number of nocturia	2.5 ± 1.1	2.4 ± 1.2	0.171
NPI	0.36 ± 0.28	0.32 ± 0.15	0.260
HUS (hours)	2.6 ± 1.4	4.0 ± 1.5	0.021

VAS = visual analogue scale
OABSS = overactive bladder symptom score
KHQ = King's Health Questionnaire
FVC = Frequency volume chart
NPI = nocturnal polyuria index ; ratio of nocturnal urine volume to 24 hour urine volume
HUS = hours of undisturbed sleep ; time between falling asleep and first waking to void

residual urine volume changed from 12.3 ± 16.1 ml to 15.9 ± 33.4 ml, but the increase was not significant. The major skin symptoms observed among the patients were mild erythema and pruritus, and no severe symptoms were observed in any patient. We administered topical steroids and provided appropriate care to the patients who discontinued treatment because of adverse events at the site of patch application. The treatment administered led to successful resolution of the symptoms in all these patients.

DISCUSSION

Non-oral antimuscarinic drugs are associated with better patient adherence compared with oral ones[12]. In Europe and North America, antimuscarinic drugs are marketed in a variety of forms, including extended release, rectal suppository, transdermal patch, and gel preparations[13]. In Japan, however, only the oral form had been available for OAB until 2013 ; this limited the treatment options for patients who experienced strong adverse reactions, such as dry mouth or constipation, when treated with oral antimuscarinic drugs. The beta 3-adrenoceptor agonist is reported to be free of these characteristic adverse reactions of antimuscarinic drugs[14], but it has been launched into the market only recently and its safety profile in pharmacotherapy has not been clearly established. The present study was conducted to investigate the efficacy and safety of a new once-daily transdermal oxybutynin patch in Japanese patients. Transdermal formulations avoid a rapid increase in the blood concentration of oxybutynin, so stable levels are established over a long period[11]. This formulation also reduces the generation of DEO, an active metabolite of oxybutynin, because transdermal delivery avoids the first-pass metabolism in the liver ; therefore, it is

expected to induce fewer adverse reactions than existing oral antimuscarinic drugs[11,15]. Assessment of this study using VAS scores for dry mouth and constipation showed that this oxybutynin patch could induce fewer adverse reactions related to its antimuscarinic effects.

An another transdermal oxybutynin formulation (Oxytrol ; Watson Pharmaceuticals, Corona, CA, USA) that contains 36 mg of oxybutynin is available in the USA and Europe. It is administered by a twice-weekly regimen (3- to 4-day dosing interval), and 3.9 mg of oxybutynin is estimated to reach to the skin with 24-h application[16]. On the other hand, the oxybutynin patch is designed to obtain a stable plasma concentration with application to a different skin site every day[15]. In a previous study, a single oxybutynin patch was applied to the lower abdomen, lumber region or thigh for 24-h, and it was found that 5.1-6.8 mg of the active ingredient entered the skin[17]. In a multicenter, randomized, double-blind, placebo controlled study of transdermal oxybutynin administered by a twice-weekly regimen, the mean decrease in the average daily frequency of urination showed no significant difference between the study group and the placebo group due to the high placebo response[18]. In contrast, in the clinical study of oxybutynin patch with the same design as the transdermal oxybutynin administered by a twice-weekly regimen, the mean number of micturitions per day showed a significant decrease in the oxybutynin patch group despite a high placebo response[17]. These results suggest that a stable and high plasma concentration of oxybutynin makes a contribution to the decrease of the number of micturitions per day.

Once-daily treatment with the oxybutynin patch also had a favorable influence on sleep quality. Although the mean number of nocturnal micturations showed no significant difference, significant improvement was noted in the sleep/energy domain of the KHQ and HUS in FVC. HUS is considered an important indicator of sleep quality and as a useful parameter for evaluating sleep disorder caused by nocturia[19]. Sleep has two main phases : rapid eye movement (REM) sleep and non-REM sleep[19]. Non-REM sleep normally makes up approximately three-quarters of the total sleeping time and is deep sleep that is important for growth hormone secretion and functional restoration, whereas REM sleep is shallow and related to mental health[20]. Slow-wave sleep is a deep and restorative non-REM sleep that occurs within approximately 3 to 4 hours of falling asleep, after which REM sleep and other shallow sleep stages become more prominent[20,21]. The interruption of this restorative non-REM sleep can significantly impair sleep quality, causing fatigue and discomfort. Djavan et al. reported that prolonging early undisturbed sleep may be effective for improving sleep quality[22]. The results of the present analysis showed that the HUS was prolonged by an average of 84 min, which means that early sleep was also significantly prolonged. Prolongation of early sleep is thought to have a positive influence on sleep quality and is reflected by the improvement of the sleep/energy domain in the KHQ.

In the present study, the incidence of adverse events at the site of patch application was 32.5%, and due to these adverse events, 18.6% of the participants exited the study, but none of the patients developed any severe adverse events. In general, adverse events at the application site due to transdermal oxybutynin formulation were reported in 26-40%, and discontinuation due to these adverse events were noted in 5-10 %[20,21]. These adverse events are probably caused by skin stimulation by oxybutynin, but typically, they manifested as erythema or pruritus and resolved quickly without intervention or with the administration of topical formulations[21,23]. The reason for a higher incidence of adverse events and subsequent exit of patients from this study is unclear. However, Yamaguchi et al. attributed the adverse effects of the events the oxybutynin patch observed in Japanese patients to racial differences of cutaneous sensitivity to oxybutynin and the hot, humid Japanese climate[20,23].

The limitations of this study were the small sample size, lack of a placebo group, and the omission of urodynamic data. Future research in the form of prospective, randomized, controlled trial of once-daily administration of the oxybutynin patch in OAB patients experiencing adverse reactions to oral antimuscarinic drugs would be required to confirm the finding of this study.

CONCLUSIONS

The results of the present analysis showed that once-daily administration of the oxybutynin patch alleviates the adverse reactions caused by oral antimuscarinic drugs besides prolonging HUS, which is an indicator of sleep quality. Therefore, we recommend the use of the oxybutynin patch in patients with OAB experiencing adverse effects of oral antimuscarinic drugs and sleep disturbances.

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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