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Effectiveness of Tamsulosin Hydrochloride and Its Mechanism in Improving Nocturia Associated With Lower Urinary Tract Symptoms/Benign Prostatic Hyperplasia

Masaki Yoshida,[1]* Akito Inadome,[1] Koichi Masunaga,[1] Takashi Nagata,[1] and Takashi Yoshiyasu[2]
[1]*Department of Urology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan*
[2]*Department of Post Marketing Medical Research, Astellas Pharma, Inc., Tokyo, Japan*

Aims: To evaluate the action mechanism of α_1-receptor blockers in improving nocturia, we have studied effectiveness of tamsulosin hydrochloride (TAM) in the patients with nocturia associated with lower urinary tract symptoms/benign prostatic hyperplasia (LUTS/BPH). **Methods:** LUTS/BPH patients with nocturia (nocturnal frequency $\geq$2 times per day) were administered TAM (0.2 mg/day) for 8 weeks. A frequency volume chart (FVC), the International Prostate Symptom Score (I-PSS), quality of life (QOL) index, post-void residual, and uroflowmetry were recorded before and after TAM administration for the patients. The parameters affected by TAM were examined. **Results:** The FVC and I-PSS of the 160 patients analyzed revealed significant clinical improvements in the nocturnal frequency. On the basis of the FVC, the patients were divided into two groups: the responder group comprising 97 patients with significantly improved nocturnal frequency and the non-responder group comprising 63 patients with less improvement in the nocturnal frequency. Significant differences between groups were observed in the following parameters: the hours of undisturbed sleep (HUS), the interval between the time of sleeping and the first instance of nocturnal voiding, the volume of urine in the first nocturnal voiding episode, nocturnal urine volume, nocturnal polyuria index, daytime urine volume, maximum and average flow rates, and post-void residual. **Conclusions:** TAM improved the QOL of LUTS/BPH patients by significantly reducing the nocturnal frequency and increasing HUS; moreover, it improved nocturia by decreasing the nocturnal urine volume. *Neurourol. Urodynam. 29:1276–1281, 2010.* © 2010 Wiley-Liss, Inc.

Key words: alpha 1 adrenoreceptor blocker; benign prostatic hyperplasia; frequency volume chart (FVC); lower urinary tract symptoms; mechanism; nocturia

INTRODUCTION

The incidence of benign prostatic hyperplasia (BPH) among elderly men is high. BPH involves lower urinary tract symptoms (LUTS), and these symptoms sometimes greatly reduce the patient's quality of life (QOL).[1–2] The LUTS associated with BPH (LUTS/BPH) include storage symptoms as well as voiding symptoms; although the incidence of voiding symptoms is higher than that of storage symptoms. It has been reported that the storage symptoms have a greater influence on the patient's QOL than the voiding symptoms.[3,4] A previous epidemiological investigation revealed that nocturia was the most bothersome of the storage symptoms.[5]

It is still uncertain as to whether nocturia in middle-aged and elderly men is mainly due to bladder outlet obstruction (BOO) caused by BPH. However, it has been generally accepted that nocturia associated with BOO is the most important symptom, and that nocturia shows a strong correlation with BOO.[6–7] BOO might entail chronic obstruction of the lower urinary tract that eventually leads to tissue damage and thickening of the bladder wall. This reduces the functional bladder capacity and causes an overactive bladder. Nocturia is one of the symptoms of an overactive bladder. It has been suggested that nocturia is not caused by a single factor; that is, in addition to the reduced functional bladder capacity, various other factors such as nocturnal polyuria and sleep disorders may also cause nocturia, depending on the patient's characteristics.[8]

The main approaches for improving LUTS/BPH are the treatment of symptoms and improvement of the patient's QOL. Drug therapy, especially α_1-receptor blockers, is widely used as the first-line therapy.[9] Tamsulosin hydrochloride (TAM) is the most frequently used α_1-receptor blocker, and a substantial amount of data concerning its safety and effectiveness is available.[10–11] In our previous report, we performed a prospective study on the effectiveness of TAM to improve the nocturia associated with LUTS/BPH. In that report, TAM showed significant improvement for total score of international Prostate Symptom Score (I-PSS), QOL score, and the score of each symptom, including nocturia.[12]

Using the data of the previous study, we evaluated the I-PSS, frequency volume charts (FVCs) and uroflowmetry by dividing the patients into two groups (responder group: one or more times in improvement of nocturia per day; non-responder group: less than once in improvement of nocturia per day) and discussed the mechanism by which TAM improves nocturia.

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*Correspondence to: Masaki Yoshida, MD, PhD, Department of Urology, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan. E-mail: akko-maki@umin.net

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MATERIALS AND METHODS

We analyzed LUTS/BPH patients with nocturia who visited medical institutes in Japan between May 2006 and November 2006. However, we selected only those patients with a mean nocturnal frequency of two or more times per day, as indicated by the FVC data for 3 days. Patients who had taken an α_1-receptor blocker in the previous 2 weeks and those with prostate cancer, inflammation of the prostate and the bladder, and with a lower urinary tract stone were excluded from the study. TAM was administered at a dosage of 0.2 mg/day for 8 weeks.

The FVC, I-PSS, QOL index, post-void residual, and uroflowmetry were determined before therapy and at 8 weeks after the TAM administration for the patients. On the basis of the FVCs of the patients, we divided them into two groups: a responder group that showed improved nocturnal frequency (one or more times per day) and a non-responder group that showed less improvement (less than once a day). Comparisons between these two groups before TAM administration were made using the Mann–Whitney *U*-test. Comparisons between before and after TAM administration were made using the Wilcoxon signed-rank test.

This study is based on the Good Post-Marketing Study Practice (GPSP) and was performed as a post-marketing survey by Astellas Pharma, Inc. (Tokyo, Japan).

RESULTS

Between May 2006 and November 2006, 380 LUTS/BPH patients who visited 87 medical institutes in Japan were enrolled in this study. However, only 160 patients were finally analyzed: 111 patients were excluded either because they did not satisfy certain inclusion criteria or because they could not be followed up; 109 patients whose FVCs at 8 weeks after the TAM administration could not be obtained were also excluded. The responder group, finally comprised 97 patients, and the non-responder group, comprised 63 patients.

The age, body mass index and prostate volume of responder and non-responder groups are 69.9 ± 7.0 and 72.5 ± 6.2 years old, 23.1 ± 2.9 and $22.9 \pm 2.6\,kg/m^2$, and 34.6 ± 18.0 and 33.1 ± 18.4 ml, respectively. The data before and after TAM administration in the two groups are shown in Table I ((i) I-PSS and (ii) FVC). Before TAM administration, the baseline values of nocturnal frequency, post-void residual, and periods of undisturbed sleep were significantly different between the two groups, as marked in "#" in Table I (ii). There was no significant difference in the baseline values between the two groups with regard to the other parameters.

Table I also show the effects of TAM administration after 8 weeks on I-PSS and FVC. After TAM administration, there were no significant differences between the two groups with regard to the total I-PSS, each total score of the storage and voiding symptoms and QOL score. In the score of each symptom, significant improvements were observed in both groups after TAM administration, except for the score for straining in the non-responder group.

After TAM administration, the FVCs of the patients in the responder group revealed a significant increase in the hours of undisturbed sleep (HUS) (Fig. 1A) and volume of urine in the first nocturnal voiding episode (Fig. 1B). The daytime frequency and the mean daytime urine volume per void for patients in both groups improved significantly after TAM administration. In the responder group, the 24-hr production decreased significantly after TAM administration. Further, the nocturnal urine volume (Fig. 2A) and the nocturnal polyuria index (Fig. 2B) also decreased significantly. Although there was no difference in the mean nocturnal urine volume per void between the groups, we observed that the mean urine volume per void in the responder group increased significantly after TAM administration.

The post-void residual of the responder group decreased significantly, and the maximum (Q_{max}) and mean (Q_{ave}) urinary flow rates showed an improvement after TAM administration (Fig. 3A,B).

DISCUSSION

There have been many reports on the positive effects of TAM on the subjective symptoms and objective findings of LUTS/BPH, Horiuchi et al.[13] assessed nocturia by estimating the American Urological Association (AUA) symptom score; they found that a TAM dosage of 0.2 mg/day was effective in treating nocturia at 4 weeks after administration. We also performed a similar study using I-PSS[14] and confirmed the improvement in nocturia after TAM administration. Yoshimura et al.[15] reported a 17.9% reduction in the nocturnal frequency after TAM administration (0.2 mg/day); however, the improvement rate of score for nocturia was lowest among I-PSS items. Momose et al.[16] performed a crossover study by using TAM (0.2 mg/day) and naftopidil (50 mg/day) and reported that TAM administration improved nocturia to a greater extent than naftopidil administration did.

There are only a few reports in which the effect of TAM on nocturia has been evaluated by using both I-PSS and FVC. A report has suggested that there is no correlation between the frequency of nocturia determined by using I-PSS and that determined by using FVC.[17] However, in our previous report including the data of both responder and non-responder groups, we obtained similar results by using both the I-PSS and FVC.[12] In that report, the I-PSS nocturia scores before and after TAM treatment were 3.1 ± 1.0 and 2.1 ± 0.9, respectively, and the corresponding scores on the FVC were 2.9 ± 1.0 and 2.1 ± 1.1. The results demonstrated that the effectiveness of TAM for nocturia was confirmed by both I-PSS and FVC.

The mechanism by which TAM improves nocturia has not been elucidated yet. However, from a comparison of the data for both groups, the following mechanism was hypothesized (Fig. 4). TAM improves functional obstruction and decreases urethral resistance by blocking the urethral/prostatic α_1 receptor, as indicated by the significant improvement in the urinary flow rates in the responder group. Further, it has recently been reported that in rats, TAM inhibits the excitation of the urethral sensory nerve by decreasing urethral resistance. Inhibition of the urethra-vesical reflex pathway may affect an increase in bladder compliance and contribute to the improvement of storage symptoms.[18] Hence, TAM might improve nocturnal frequency and other storage symptoms by this mechanism, as indicated by the scores of the responder group. An increase in functional voiding capacity combined with an improvement in the urinary flow rates could increase the mean urine volume per void, resulting in a decrease in the nocturnal and daytime frequencies.

In the responder group, we observed an increase in the volume of urine in the first nocturnal voiding episode; this may be attributed to the increase in the interval between the time of sleeping and the first instance at night when the patient would wake up to void. This increased interval was thought to be very important since non-rapid eye movement

TABLE I. The Data of the Patients in the Responder and Non-Responder Groups Before and After TAM Administration (i) I-PSS and (ii) FVC

	n	Before TAM administration	8 Weeks after TAM administration	Signed-rank test, *P*-value[a]
(i) I-PSS				
Incomplete voiding				
Responder	62	1.9 ± 1.6	1.1 ± 1.1	<0.0001
Non-responder	36	1.8 ± 1.6	0.9 ± 1.2	<0.0001
Frequency				
Responder	62	2.9 ± 1.4	1.8 ± 1.3	<0.0001
Non-responder	36	2.7 ± 1.5	2.1 ± 1.4	<0.05
Intermittency				
Responder	62	1.7 ± 1.7	0.8 ± 1.1	<0.0001
Non-responder	36	2.1 ± 1.7	1.2 ± 1.3	<0.0001
Urgency				
Responder	62	1.9 ± 1.6	1.1 ± 1.2	<0.0001
Non-responder	36	2.0 ± 1.7	1.2 ± 1.1	<0.01
Weak stream				
Responder	62	2.9 ± 1.6	1.6 ± 1.4	<0.0001
Non-responder	35	3.2 ± 1.8	1.8 ± 1.4	<0.0001
Straining				
Responder	62	1.6 ± 1.6	0.7 ± 0.9	<0.0001
Non-responder	36	1.1 ± 1.5	0.7 ± 1.0	NS
Nocturia				
Responder	62	3.1 ± 1.1	1.8 ± 0.8	<0.0001
Non-responder	36	3.1 ± 0.9	2.5 ± 1.0	<0.001
Voiding symptom				
Responder	62	6.1 ± 3.9	3.2 ± 2.6	<0.0001
Non-responder	35	6.3 ± 4.3	3.7 ± 3.1	<0.0001
Storage symptoms				
Responder	62	7.9 ± 3.1	4.7 ± 2.4	<0.0001
Non-responder	36	7.7 ± 2.9	5.8 ± 2.6	<0.0001
Total I-PSS				
Responder	62	15.9 ± 7.2	9.0 ± 5.1	<0.0001
Non-responder	35	15.9 ± 6.7	10.4 ± 5.7	<0.0001
OOL score				
Responder	64	4.7 ± 1.0	2.6 ± 1.2	<0.0001
	36	4.6 ± 0.9	3.3 ± 1.1	<0.0001
(ii) FVC				
Nocturnal voiding frequency				
Responder	97	3.1 ± 1.0[#]	1.7 ± 1.0	<0.0001
Non-responder	63	2.5 ± 0.8	2.8 ± 0.3	<0.0001
Daytime voiding frequency				
Responder	97	8.6 ± 2.4	7.9 ± 2.4	<0.0001
Non-responder	63	8.3 ± 2.7	7.4 ± 2.5	<0.001
Nocturnal urine volume (ml)				
Responder	97	712.5 ± 234.5	533.3 ± 195.1	<0.0001
Non-responder	63	653.5 ± 242.7	701.0 ± 257.1	NS
Daytime urine volume (ml)				
Responder	97	1028.4 ± 419.5	1073.2 ± 403.6	NS
Non-responder	63	991.6 ± 365.2	903.2 ± 372.0	<0.05
Nocturnal polyuria index (%)				
Responder	97	41.9 ± 11.0	33.8 ± 10.9	<0.0001
Non-responder	63	40.3 ± 11.3	44.0 ± 13.0	<0.01
Urine volume per void				
Responder	97	141.0 ± 42.7	156.3 ± 38.5	<0.0001
Non-responder	63	143.7 ± 45.9	150.8 ± 47.2	<0.05
24-hr urine volume (ml)				
Responder	97	1740.9 ± 527.7	1608.2 ± 479.7	<0.0001
Non-responder	63	1645.1 ± 517.9	1604.3 ± 465.3	NS
Nocturnal urine volume per void (ml)				
Responder	95	186.7 ± 74.7	191.8 ± 81.2	NS
Non-responder	63	194.7 ± 80.5	204.2 ± 79.4	NS
Daytime urine volume per void (ml)				
Responder	97	139.5 ± 45.4	160.6 ± 43.7	<0.0001
Non-responder	63	142.6 ± 48.4	148.8 ± 52.9	NS
Urine volume of first nocturnal voiding (ml)				
Responder	97	184.1 ± 84.4	213.3 ± 82.4	<0.0001
Non-responder	63	192.8 ± 89.8	197.5 ± 93.1	NS
Hours of undisturbed sleep (h)				
Responder	97	2.1 ± 1.0[#]	3.5 ± 1.5	<0.0001
Non-responder	62	2.4 ± 0.8	2.3 ± 1.0	NS

(*Continued*)

TABLE I. (*Continued*)

	n	Before TAM administration	8 Weeks after TAM administration	Signed-rank test, *P*-value[a]
Sleep duration (h)				
Responder	97	8.1 ± 1.1	8.0 ± 1.0	NS
Non-responder	57	8.2 ± 1.0	8.6 ± 1.0	<0.01
Post-void residual (ml)				
Responder	56	50.4 ± 55.3[#]	32.8 ± 36.4	<0.05
Non-responder	31	36.6 ± 50.2	39.2 ± 50.7	NS

I-PSS, International Prostate Symptom Score; FVC, frequency volume chart.
[a]For comparisons between before and after TAM administration, *P* values were calculated by Wilcoxon signed-rank test.
[#]$P < 0.05$ by Mann–Whitney *U*-test, for comparisons between responder and non-responder groups before TAM administration.

sleep (non-REM sleep), that is, deep sleep, lasts only for approximately 3 hr after falling asleep.[19] The HUS has recently been defined as the interval between the time of sleeping and the first instance at night when an individual wakes up to void, and HUS should ideally be 3–4 hr after falling asleep.[19,20] In addition, it is one of the good parameters of sleep quality. It has been reported that the TAM-oral controlled absorption system (TAM-OCAS) tablet increases HUS.[21]

A notable observation in our study was that the nocturnal urine volume and the nocturnal polyuria index decreased significantly in the responder group, which probably contributed to the improvement of nocturia. It has been reported that nocturnal polyuria is a key cause of nocturia.[22] Some studies suggest that a relationship exists between nocturnal polyuria and high blood pressure, disturbance of the circadian rhythm of arginine vasopressin (AVP),[23] and atrial natriuretic peptide (ANP).[24] In the case of the responder group in this study, it is speculated that the improvement of sleep quality might improve the circadian rhythm of hormone secretion. Such improvement in the endocrine milieu is thought to increase water reabsorption from the renal collecting ducts during sleep and lead to a decrease in the nocturnal urine volume. Sleep disorders following glucocorticoid treatment were thought to be caused by the decreased expression of AVP mRNA in the suprachiasmatic nucleus, which is thought to be the biological clock in the human brain. This report suggested a relationship between the secretion of AVP and the sleep–awakening cycle.[25] Further studies are required to explore the possibility of improving the endocrine milieu by TAM administration.

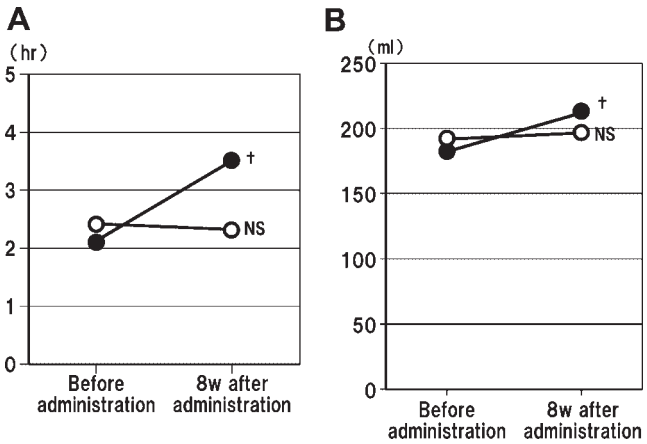

Fig. 1. Effects of TAM administration on the hours of undisturbed sleep (HUS) (**A**) and urine volume of first nocturnal voiding (**B**). Closed circle: responder group, open circle: non-responder group. For comparisons between before and after TAM administration, *P* values were calculated by Wilcoxon signed-rank test. †$P < 0.0001$, NS: not significant.

CONCLUSION

TAM improves nocturia by decreasing nocturnal urine volume, and thereby improves the QOL by reducing frequency

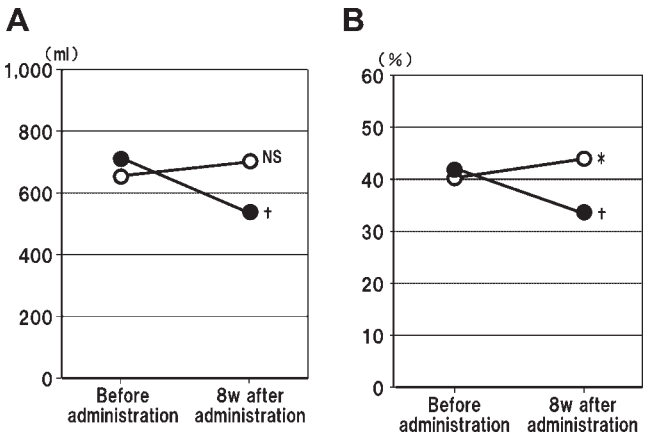

Fig. 2. Effects of TAM administration on nocturnal urine volume (**A**) and nocturnal polyuria index (**B**). Closed circle: responder group, open circle: non-responder group. For comparisons between before and after TAM administration, *P* values were calculated by Wilcoxon signed-rank test. *$P < 0.01$, †$P < 0.0001$, NS: not significant.

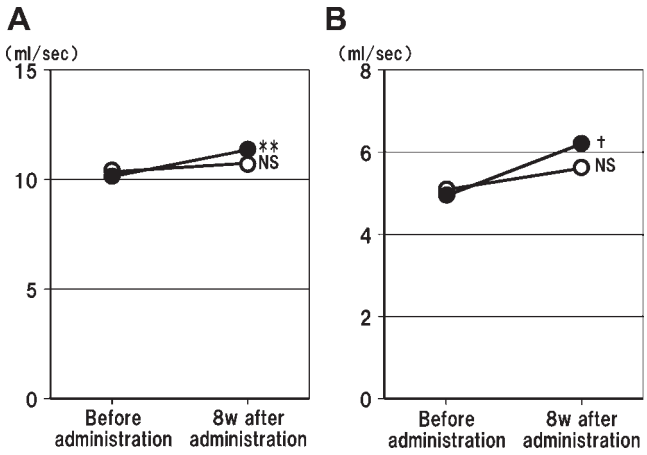

Fig. 3. Effects of TAM administration on maximum flow rate (Q_{max}) (**A**) and average flow volume (Q_{ave}) (**B**). Closed circle: responder group, open circle: non-responder group. For comparisons between before and after TAM administration, *P* values were calculated by Wilcoxon signed-rank test. **$P < 0.001$, †$P < 0.0001$, NS: not significant.

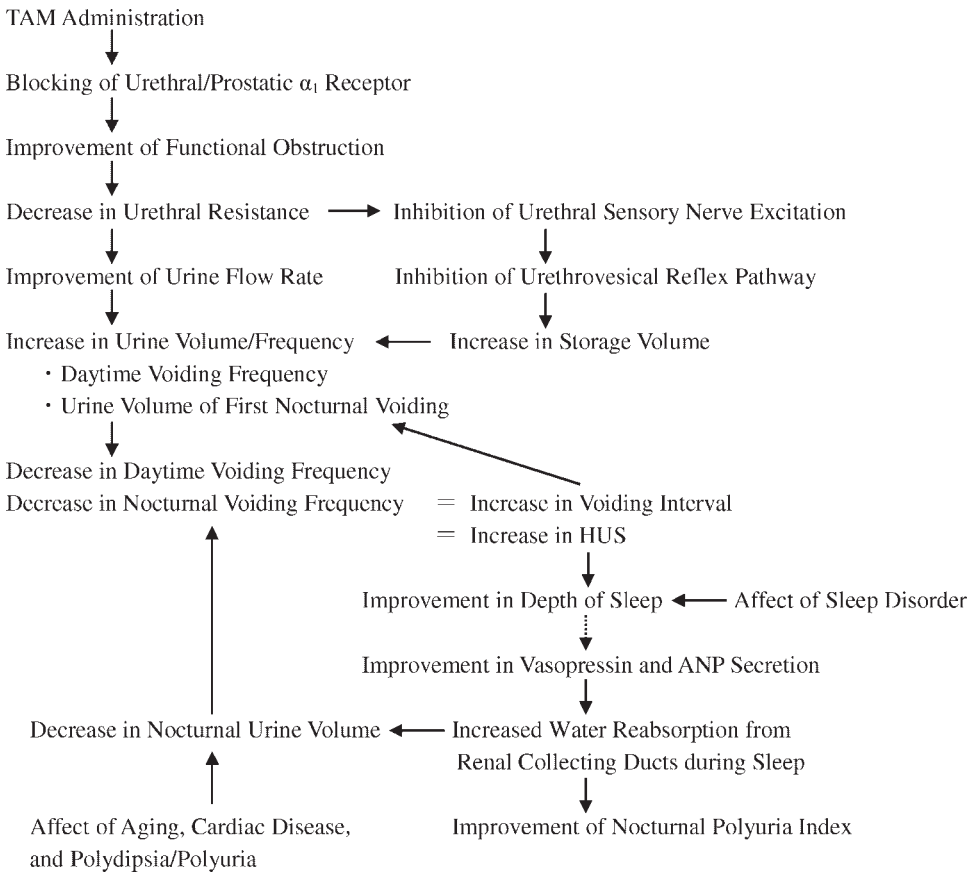

Fig. 4. The speculated mechanism by which TAM improves nocturia. TAM, tamsulosin hydrochloride; HUS, hours of undisturbed sleep; ANP, atrial natriuretic peptide.

and increasing HUS for patients suffering from nocturia-associated LUTS/BPH.

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