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Shimizu N[1], Sugimoto K[1], Yamamoto Y[1], Minami T[1], Nozawa M[1], Yoshimura K[1], Uemura H[1], Hirayama A[2]
1. *Department of Urology, Kinki University Faculty of Medicine,* ***2.*** *Department of Urology, Nara Hospital Kinki University Faculty of Medicine*

EFFECTS OF ANTICHOLINERGIC AGENT ON AUTONOMIC NERVOUS SYSTEM (ANS) FUNCTION OF OVERACTIVE BLADDER SYNDROME PATIENTS

Hypothesis / aims of study

We have reported (2013 ICS abstract No. 172) that “overactive bladder (0AB) patients have an abnormality of autonomic nervous system (ANS) function. It was shown that, at rest, sympathetic nervous system (SNS) function is enhanced, while sympathetic nerve function tends to decrease under an orthostatic load.” Further research is needed to determine whether pharmacological intervention for OAB change ANS function. Therefore, we assessed the effects of anticholinergic agent on ANS activity in OAB patients.

Study design, materials and methods

After exclusion of initial-examination OAB patients with complications having affects on neurogenic and ANS functions, subjects were 10 patients having, within their respective overactive bladder symptom scores (OABSS)[1)], urgency of 2 points or more and a total score of 3 points or more In this study, with OAB patients as subjects, with the imposition of an active standing load, investigation was made of changes in ANS activity using the autonomic reflex orthostatic tolerance test (CROSSWELL Co., Inc.) which enables quantitative analysis of dynamic ANS functioning (Fig.1) For measurements of ANS functions, a heart rate variability analysis method was used. An electrocardiogram (ECG) was equipped, and ECG measurements were made in a resting state (sitting position) for 3 minutes, and, for a standing load, in a standing position for 3 minutes. For measurement data, real-time analysis was performed using heart-rate variability analysis software of CROSSWELL Co., Inc. Computed were heart rate, low-frequency (LF) component and high-frequency (HF) component of heart-rate variability, and the heart-rate variability coefficient (coefficient of variation of R-R intervals, or CVRR); LF/HF was used as the ANS balance (SNS index), CCVHF as the parasympathetic nervous system (PSNS) index, and CVRR as the variability of overall ANS activity.

Anticholinergic agent (0.1 mg of imidafenacin twice daily) was administered for approximately 3 months.

Results

Ten patients were enrolled in this study (males:2, females:8, mean age74±7.2: years). There was significant improvement (p=0.023) of OABSS, from 7.9±3.5 before administration to 4.6±2.9. According to the evaluation score calculation formula used, ANS function improvement was confirmed for 8 of 10 patients (pre-mean 3.75±2.3 points to post-mean 5.4±2.2 points; refer to Table 1). Heart rate significantly decreased (p=0.04), from 79.26±10.6 beats per minute (BPM) to 73.98±11.17 BPM. Sympathetic nervous system (SNS) activity when at rest (sitting position) showed an improving tendency, from 4.86±2 ms^2 to 3.7±4 ms^2. Parasympathetic nervous system (PSNS) activity had a rising tendency, from 1.06±1 ms^2 to 1.54±1.5 ms^2. When standing, SNS function showed an improving tendency, from 0.66±6 ms^2 to 1.52±4.8 ms^2. The result of a more detailed look at individual cases showed that the 3 patients who had pre-administration low blood pressure (standing period-maximum blood pressure immediately before standing; 21 mmHg) did not have post-administration low blood pressure. Also, 3 patients with SNS hyper-reaction when at rest showed an improvement from 5.24 ±1.7 ms^2 to 3.17±.0.5 ms^2. A patient with SNS hyper-reaction when standing showed the suppression from 8.24±3.8 ms^2 to 2.3±5.7 ms^2.

Interpretation of results

It was surmised that anticholinergic agents suppress the PSNS, however, current results showed a slightly rising increase in PSNS. It was a different from that expected. In addition, the present results showed that imidafenacin, which inhibit M3 and M1 muscarinic receptor, suppressed heart rate. This results was also different from that expected: It has been reported that anticholinergic angents, which inhibit M2 muscarinic receptor such as propiverine and tolterodine, increase the heart rate. It is debatable points whether there are differences depending on the type of drug. Since, it was reported that the prevalence of CV comorbidities was significantly higher in patients with than without OAB; previous exposure to medications with antimuscarinic effects was also higher in patients with OAB[2)], the fact that imidafenacin did not increase heart rate was desirable. The orthostatic tolerance test showed that intervention with imidafenacin attenuate orthostatic hypotension and overall improvement in SNS function. Imidafenacin decrease SNS while increase PSNS. This, then, means that pharmacological intervention for OAB change ANS balance. These results support that previous finding: Changing ANS activity could indicate the presenced of urge urinary incontinence[3)]. The present study has the following limitations. It was open label, not placebo-controled, and the number of patients was limited. There is still leeway for future study to determine whether these results were due to the drug (agent) having high bladder selectivity, or if the improvement in OAB symptoms itself had positive effects on ANS function. To draw a definitive conclusion, therefore, extensive additional studies will be required.

Concluding message

Anticholinergic agent not only contributed to improvement of lower urinary tract symptoms, but also brought about improvement effects in ANS function.

Fig1

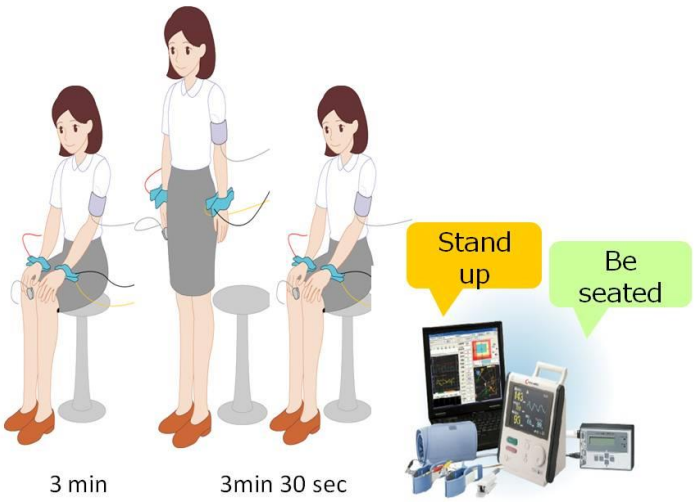

Table1

Evaluation scores are maximum 10 points

Item	Condition	Points
Resting CVRR (The lower value of resting-state CVRR and standing-up CVRR was used.)	Less than the patient age standard low	-1.0
	Standard low ≤ CVRR < Standard high	2.0
	Equal to or more than the patient age standard high	1.0
Resting L/H	< 0.2	0.0
	0.2 ≦ L/H < 0.5	1.0
	0.5 ≦ L/H < 2.0	2.0
	2.0 ≦ L/H < 5.0	1.5
	5.0 ≦ L/H < 10.0	1.0
	10.0 ≦	0.0
Standing up CVRR (Responsiveness)	< 0.1	-1.0
	0.1 ≦ CVRR < 5.0	2.0
	5.0 ≦	1.0
Standing up L/H (Convertibility) Not evaluated when standing up CVRR (Responsiveness) less than 0.1	< 0.5	0.0
	0.5 ≦ L/H < 5.0	2.0
	5.0 ≦ L/H < 10.0	1.0
	10.0 ≦	0.0
Standing position CVRR	< Age standard Lo	0.0
Standing position Δn•CCV (HF) (Resilience) Not evaluated when standing-position CVRR is less than the patient age standard low	< 0	0.0
	0 ≦ Resilience < 20.0	1.5
	≦ 20.0	1.0
Standing position ΔCCV (HF)	< 0	0.0
	0 ≦	0.5
L/H when resting, standing up, and in the standing position	All less than 1.5	-1.0
L/H is “overstressed” when standing up and in standing position	L/H when standing up and in standing position > 10.0	-0.5
Results that were – (minus) were set to “0”		

References
1. Urology 68: 318-323, 2006.
2. BJU Int 106:268-274, 2009.
3. Int Neurourol J 14:232-237, 2010

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