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A MULTICENTER RANDOMIZED CONTROLLED TRIAL OF LIFE STYLE MEASURES ALONE, VERSUS LIFE STYLE MEASURES PLUS RAMELTEON, FOR NOCTURIA: AN INTERIM ANALYSIS

Hypothesis / aims of study

Ramelteon, a MT1/MT2-receptor agonist and mild hypnotic drug, induces sleepiness by control of the circadian rhythm. We attempted to assess the add-on efficacy of ramelteon compared with lifestyle measures in the improvement of nocturia and nocturia-related sleep disturbance.

Study design, materials and methods

At six Japanese hospitals, patients with nocturia were randomly allocated into two groups (groups A and B). At baseline, all patients were educated regarding certain lifestyle measures, which consisted of a reduction in fluid intake and mild exercise, such as walking. Patients in group B were also administered ramelteon (8 milligrams) at night. Adverse events and outcomes were assessed using several questionnaires [I-PSS, I-PSS QOL, Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Score (ESS)] and frequency volume charts (FVC) both before and at 4 weeks after the initiation of the intervention. The primary endpoint was the comparison of subjective sleep status, assessed by the PSQI and ESS questionnaires. The key secondary endpoints were the differences in nocturic score, assessed in the I-PSS questionnaire, and the differences in objective night-time urination frequency, assessed by FVC.

According to the power analysis, the desired number of patients on entry was 50 in each group. In keeping with the study protocol, an interim analysis was performed when half the number of patients completed the intervention time course.

Statistical analysis, comprising the paired two-tailed t-test, was performed using commercially available software. P values <0.05 were considered statistically significant.

Results

Twenty-five patients were enrolled in each group. Two patients in group A and one in group B were lost to follow-up at 4 weeks. Three patients in group B could not continue treatment with ramelteon because of adverse events (eczema, fatigue, and nocturnal enuresis). Therefore, the data available for the efficacy analysis comprised 23 patients in group A and 21 patients in group B. The differences in baseline data between groups A and B were not statistically significant, except for the ESS questionnaire; where group A scores were lower than those of group B (Table 1). At 4 weeks, the total PSQI and ESS scores except for C6 (hypnotic use) did not improve in either group. The I-PSS nocturic score was significantly lower in group A (p=0.006) than in group B (p=0.07). The objective night-time frequency of urination was lower in group A (p=0.09) than in group B (p=0.30). Improvement in the combined I-PSS and I-PSS QOL score was greater in group A than in group B (Table 2).

Interpretation of results

Neither lifestyle measures alone nor lifestyle measures plus ramelteon improved the subjective sleep status. Improvements in the combined I-PSS, and I-PSS QOL nocturic score, and the objective night-time frequency of urination were greater in patients undertaking lifestyle measures alone, as compared with ramelteon plus lifestyle measures. The addition of ramelteon did not show additional benefit in nocturia as compared with lifestyle measures alone.

Concluding message

The effect of ramelteon on nocturia and nocturia-related sleep disturbance is limited.

Table 1. Baseline characteristics

	Group A	Group B	p-value
Age	75.8 (6.6)	75.3 (5.5)	0.81
Sex (m/f)	18/5	18/3	0.52
BMI	23.3 (3.2)	23.1 (2.4)	0.85
PSQI	7.9 (4.1)	8.8 (3.7)	0.46
ESS	6.0 (3.6)	9.2 (4.7)	0.013
IPSS total	13.2 (6.3)	15.2 (7.1)	0.31
IPSS nocturia	3.6 (1.0)	3.4 (0.9)	0.53
IPSS QOL	4.7 (1.2)	4.6 (1.1)	0.85
Nighttime Frequency	3.2 (1.3)	3.6 (0.9)	0.29

Numbers in parentheses indicate SD.

Table 2. Differences from baseline

	Group A	p-value**	Group B	p-value**
PSQI*	−0.4 (2.8)	0.17	−1.3 (3.1)	0.07
ESS	−0.6 (3.4)	0.42	−0.1 (2.9)	0.88
IPSS total	−2.8 (4.9)	0.016	−2.3 (5.1)	0.05
IPSS nocturia	−0.6 (1.0)	0.006	−0.3 (0.8)	0.07
IPSS QOL	−1.3 (1.4)	0.004	−0.6 (1.0)	0.023
Nighttime Frequency	−0.5 (1.4)	0.09	−0.3 (1.1)	0.30

*: The score of C6 (hypnotic use) was excluded.
**: The data at 4 weeks were compared with those at baseline.
Numbers in parentheses indicate SD.

Disclosures
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