Mirabegron Daytime versus Nighttime Dosing for Women with Overactive Bladder Syndrome: A Randomized Controlled Trial

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Hypothesis / aims of study

To clarify the effect of nighttime versus daytime dosing of mirabegron.

Study design, materials and methods

Between August 2017 to August 2023, all women with overactive bladder syndrome were randomly assigned to receive mirabegron 25 mg once with nighttime or daytime dosing for 12 weeks.

STATA software was used for statistical analysis. Paired t test were used for statistical analysis, as appropriate. A $p<0.05$ was considered statistically significant.

Table 1. Comparisons of the changes from baseline of clinical and bladder diary parameters and the King's Health questionnaire scores between the daytime and nighttime dosing groups (n=109)

Variables	4 weeks †Daytime (n=52)	4 weeks †Nighttime (n=57)	4 weeks ‡p	12 weeks †Daytime (n=40)	12 weeks †Nighttime (n=46)	12 weeks ‡p
USS	-0.8±1.3**	-0.6±1.2**	0.56	-1.1±1.2**	-0.8±1.2**	0.33
OABSS	-2.2±3.5**	-1.7±3.2**	0.43	-1.9±2.9**	-1.7±2.6**	0.76
Voiding episodes (72 h)						
06:00-12:00	-0.9±4.1	-1.2±4.6	0.74	-0.0±4.3	-2.0±3.7**	0.06
12:00-18:00	-1.7±5.1	-0.1±6.0	0.21	-1.4±4.1	-1.8±3.4**	0.69
18:00-24:00	-0.0±3.9	-0.3±5.4	0.82	-1.1±2.9*	-1.1±3.8	0.98
24:00-06:00	-0.1±4.4	-0.5±4.1	0.70	-0.8±2.9	-1.4±1.9**	0.40
All day	-2.8±12.0	-3.0±11.6	0.95	-4.2±7.3*	-5.4±8.7**	0.57
Urgency episodes (72 h)						
06:00-12:00	0.1±2.4	-2.1±3.7**	0.003	-0.3±3.6	-1.3±3.4	0.32
12:00-18:00	-0.5±3.4	-2.0±4.1**	0.09	-1.2±4.4	-1.4±3.4*	0.88
18:00-24:00	0.4±2.7	-1.4±3.0**	0.01	-0.6±2.4	-0.6±2.7	0.99
24:00-06:00	-0.1±2.2	-0.6±2.5	0.19	-0.8±2.9	-1.1±1.6**	0.58
All day	0.1±8.5	-6.4±10.8**	0.005	-3.1±8.4	-4.2±12.0**	0.70
Incontinence episodes (72 h)						
06:00-12:00	-0.0±1.2	-0.0±1.6	0.82	-0.1±1.0	-0.4±0.8	0.24
12:00-18:00	-0.4±1.4	-0.1±1.1	0.27	-0.2±1.6	-0.1±0.5	0.70
18:00-24:00	-0.4±0.9*	-0.2±1.4	0.50	-0.3±1.0	-0.3±0.7	0.92
24:00-06:00	-0.1±0.9	0.2±0.3	0.35	-0.4±1.2	0.0±0.3	0.06
All day	-1.0±3.2	-0.2±3.8	0.38	-1.0±2.3	-0.9±2.5**	0.83
Fluid intake (mL/72 h)						
06:00-12:00	-75±645	34±965	0.58	118±919	-95±902	0.39
12:00-18:00	-75±898	-14±965	0.78	46±839	-85±926	0.59
18:00-24:00	158±731	-227±907	0.053	-7±529	-245±751	0.18
24:00-06:00	-106±733	59±559	0.27	-136±618	-28±329	0.42
All day	-117±2107	-76±2280	0.94	-112±1717	-349±1505	0.59
Total voided volume (mL/72 h)						
06:00-12:00	18±1087	2±862	0.94	234±976	37±914	0.43
12:00-18:00	-183±1099	102±1138	0.28	45±833	-46±615	0.64
18:00-24:00	30±812	-67±1568	0.75	-40±837	-1±751	0.85
24:00-06:00	272±959	95±904	0.42	83±804	-236±627	0.10
All day	136±2473	213±3179	0.91	421±2186	-325±1928	0.17
Voided volume per micturition (mL)						
06:00-12:00	29±95	43±87**	0.51	39±90	68±70**	0.18
12:00-18:00	-3±109	16±103	0.44	25±132	26±62*	0.98
18:00-24:00	-23±141	18±156	0.25	8±127	23±58*	0.57
24:00-06:00	56±163	87±193*	0.48	87±151	24±81	0.09
Frequency	-0.8±1.6**	-0.8±1.4**	0.87	-1.2±1.3**	-1.3±1.6**	0.92
Nocturia	-0.7±1.1**	-0.7±1.3**	0.90	-1.1±1.4**	-1.0±1.3**	0.93
Urgency	-0.6±1.5**	-0.9±1.7**	0.36	-1.0±1.7**	-0.7±1.8*	0.49
Urge incontinence	-0.9±1.5**	-0.9±1.5**	0.86	-0.8±1.7**	-1.1±1.7**	0.53
Stress Incontinence	-1.0±1.6**	-0.7±1.3**	0.25	-0.8±1.3**	-0.7±1.5**	0.85
Nocturnal enuresis	-0.4±1.0**	-0.1±1.1	0.13	-0.2±0.9	-0.3±1.1	0.79
Intercourse incontinence	-0.1±0.5	-0.1±0.5	0.97	0.1±0.6	-0.0±0.5	0.54
Waterworks infections	-0.8±1.5**	-0.8±1.5**	0.92	-0.7±1.7*	-0.7±1.2**	0.83
Bladder pain	-0.5±1.4**	-0.2±1.2	0.24	-0.8±1.4**	-0.4±1.2	0.14
General health perceptions	-12±25**	-5±24	0.15	-13±27**	-14±26**	0.86
Incontinence impact	-18±38**	-20±35**	0.80	-19±38**	-24±37**	0.62
Role limitations	-14±29**	-21±30**	0.23	-19±24**	-26±38**	0.34
Physical limitations	-26±40**	-20±32**	0.35	-37±37**	-25±40**	0.20
Social limitations	-10±34*	-9±26*	0.86	-17±28**	-18±34**	0.81
Personal relationships	-5±23	-2±12	0.52	-10±26	-3±19	0.31
Emotions	-17±25**	-6±19	0.006	-17±28**	-13±26**	0.48
Sleep/energy	-18±31**	-18±28**	0.96	-19±32**	-31±28**	0.09
Severity measures	-10±21**	-12±22**	0.70	-14±23**	-13±21**	0.84

OABSS=Overactive Bladder Symptoms Score. USS=Urgency Severity Scale.

†By paired t test. *:$p<0.05$; **:$p<0.01$. ‡By paired t test. Changes are calculated as the subtraction of pre-treatment values from post-treatment values, and expressed as the mean ± standard deviation.

Results and interpretation

A total of 109 patients were enrolled in the study. Fifty-two patients were in the daytime dosing group, and the other fifty-seven patients were in the nighttime dosing group after 4 weeks of mirabegron treatment. Forty patients in the daytime dosing group and forty six patients in the nighttime dosing group underwent 12 week of mirabegron treatment.

Owing to the presence of statistical differences in the baseline urgency episodes and emotions, we used linear regression analyses adjusted by the above variables to investigate the effect of dosing.

After 4 weeks of treatment, the nighttime dosing group had a more benefit in the decrease of the urgency episodes at 06:00-12:00 (change from baseline: -2.1±3.7 versus 0.1±2.4, p=0.003), 18:00-24:00 (change from baseline: -1.4±3.0 versus 0.4±2.7, p=0.01) and all day (change from baseline: -6.4±10.8 versus 0.1±8.5, p=0.005), compared with the daytime dosing group (Table 1). After adjustment by the corresponding baseline variables (i.e.,
urgency episodes in each time interval or total urgency episodes), the coefficients remained statistical significant (i.e., the coefficients for the nighttime dosing for the urgency episodes were -1.6 (95% CI = -2.6 to -0.5) , p=0.003 at 06:00-12:00; and -4.1 (95% CI = -7.4 to -0.7), p=0.02 at all day, respectively.

After 12 weeks' treatment, the nighttime dosing group had a trend to be significant that about the improvement of voiding episodes at 00:00-06:00 (change from baseline: -2.0±3.7 versus -0.0±4.3, p=0.06), compared with daytime dosing (Table 1).

Nonetheless, the daytime dosing group had a significant improvement of emotions (change from baseline: -17±25 versus -6±19, p=0.006), compared with the nighttime dosing (Table 1).

After adjustment by the baseline emotions score, the daytime dosing had a trend to be significant in the improvement of emotions (i.e., the coefficient of nighttime dosing was 7.68, 95% CI =-0.02, to 15.37, p=0.050).

After 12 weeks of treatment, both groups had significant improvements in Urgency Severity Scales (USS), Overactive Bladder Symptoms Score (OABSS), and many domains of the Kings Health Questionnaire (KHQ), despite of no between-group differences (Table 1).

The improvement of depression (i.e., KHQ Question 6A) was not associated with the improvement of OABSS (4 weeks, -1.97±3.32 vs. -0.46±0.95, Spearman's rho=0.04, p=0.26; 12 weeks, -1.82±2.72 vs. -0.61±1.01, Spearman's rho=0.13, p=0.35).

The improvement of anxiety (i.e., KHQ Question 6B) was not associated with the improvement of OABSS (4 weeks, -1.97±3.32 vs. -0.43±0.96, Spearman's rho=0.04, p=0.67; 12 weeks, -1.82±2.72 vs. -0.60±1.01, Spearman's rho=-0.12, p=0.37).

Interpretation of results

After 4 weeks of treatment, nighttime dosing seems to benefit more women suffering from urgency, especially in the morning, and daytime dosing seems to benefit patients with emotion dysfunction. However, the above effects did not differ between the groups after 12 weeks of treatment.

Conclusions

Mirabegron nighttime dosing of mirabegron appears to benefit more for women suffering from urgency, especially in the morning, and daytime dosing seems to benefit patients with emotion dysfunction in the short term.