828

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A RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, CROSSOVER TRIAL OF MELATONIN FOR TREATMENT OF NOCTURIA IN ADULTS WITH MULTIPLE SCLEROSIS

Hypothesis / aims of study

Nocturia is a common urinary symptom of multiple sclerosis (MS) affecting both men and women. Those affected experience nocturnal sleep disturbance that greatly impacts on quality of life (QoL). Melatonin is a hormone known to regulate circadian rhythm and reduce smooth muscle activity such as in the bladder. There is limited evidence supporting use of melatonin to alleviate urinary frequency at night in the treatment of nocturia. The aim of this study was to evaluate the effect of melatonin on the mean number of nocturia episodes per night in patients with MS.

Study design, materials and methods

Adult patients with MS with at least one episode of nocturia per night were recruited. Patients were excluded if they had (i) an indwelling urinary catheter; (ii) used desmopressin or investigational medical compounds in the month preceding randomization; (iii) taken antimuscarinic or diuretic medication, unless used long-term prior to study (at least 3 months) and continued at same dosing regimen throughout the study; (iv) use of melatonin/ sleeping tablets on prescription, or purchased over-the-counter/ online; (v) diabetes mellitus/diabetes insipidus; and (vi) if they were a female subject of child-bearing potential and unwilling to use an effective method of contraception throughout the study.

This was a randomized, double blind, placebo controlled crossover trial. Following an initial 4 day pre-treatment monitoring phase, patients in group one received 2mg of capsulated sustained-release melatonin at bedtime for six weeks. Patients in group two received one placebo capsule per night for 6 weeks. There was a one month wash-out period in between treatment phases before the patients crossed over to the other regimen for an additional 6 weeks. Assessments undertaken at screening encompassed a dipstick urinalysis to exclude urinary tract infection, the International Consultation on Incontinence Questionnaires-Nocturia (ICIQ-N), and the Cambridge Multiple Sclerosis Basic Score (CaMBS). Female patients of child bearing age also did a pregnancy test at screening. At baseline, end of treatment phase 1 and end of treatment phase 2 patients did a second dipstick urinalysis and completed the International Consultation on Incontinence Questionnaires-Nocturia QoL (ICIQ-Nqol), Consultation on Incontinence Questionnaires - Lower Urinary Tract Symptoms (ICIQ-LUTS-gender specific), Expanded Disability Status Scale (EDSS), Multiple Sclerosis Quality of Life Index (MSQLI), and the Pittsburgh Sleep Quality Index (PSQI). The ICIQ Bladder Diary was completed for 4 days at the same time points.

A Wilcoxon rank-sum test was used to calculate the significance of treatment effect and a Mann-Whitney test was used calculate the significance of the presence of a period effect and of a carry-over effect. Effect size was quantified using Cohen's d.

Results

In total 13 men and 18 females aged between 34 and 69 were recruited. 31 patients were randomised and four were withdrawn from the trial. The baseline mean number of nocturnal episodes per night for both groups was two (min 1 and max 3).

There was no significant change seen with melatonin on the number of nocturnal episodes per night, average nocturnal output in a 24 hour period or nocturnal polyuria index (NPI). There was no period effect or a carry-over effect seen in the two groups. The results of the secondary end points looking at QoL also revealed that melatonin did not significantly impact on mental or physical health within this group of patients. In the ICIQ LUTS and ICIQ NQoL questionnaires, there was no significant change demonstrated with melatonin or placebo with any of the variables.

In the MSQoL questionnaire, the only significant difference seen was for 'physical overall score' (treatment effect $P = 0.17$). However, the effect size was not significant at $P = 0.05$. From the PSQI, there was a significant period effect on 'daytime dysfunction score' ($P = 0.001$). The effect size was however not significant at $P = 0.05$. The EDSS scores showed that there was a period effect on sensory measure ($P = 0.030$) and the cerebellar ($P = 0.035$). Moreover, there was also a treatment effect on the bowel and bladder ($P = 0.025$). The effect size of these findings were however not significant at $P = 0.05$. The only carry-over effect shown to be present in all analysis was for 'Change in health score' in the MSQoL questionnaire, $P = 0.040$. Nonetheless the effect size was not significant at $P = 0.05$.

18 people were affected by adverse events. Urinary tract infection (UTI) was experienced by five patients. Two patients experienced faecal urgency and the following were present in at least one patient: Uhthoff's phenomenon, new symptoms of exhaustion and feeling drained (patient was not on study drug at the time), cold hands for 3 weeks, episodes of nausea and 'heaviness' in the abdomen. One patient presented with profound somnolence and lassitude. One patient was affected by gastrointestinal upset and abdominal pain and one patient on the placebo reported experiencing vertigo and nausea. Another patient experienced heavy cold and UTI. Some patients encountered more than one episode of the same adverse events. This included one patient experiencing three episodes of epigastric pain. This patient was ultimately diagnosed with cholecystitis. One patient experienced two episodes of reduced mobility that were not related to the study drug, and visual extinction, most likely related to MS and one patient had two episodes of shingles.

Interpretation of results

Melatonin CR 2mg daily does not influence nocturia in an unselected population of people with MS. The aim of this study was to evaluate the effect of melatonin on the mean number of nocturia episodes per night in patients with MS, and no significant difference was identified. There was no clear change in nocturia severity, nocturnal polyuria index, or nocturia bother. Markers of MS were not affected. Adverse events were reported in both the active treatment and the placebo phase, but were generally mild and tolerated. We are unable to identify markers of any subgroup who may be constituted “responders”

Concluding message

Melatonin CR 2mg daily is not an effective therapy for nocturia in an unselected population of people with MS

References

1. Delgado D, Canham L, Cotterill N, Cottrell D, Drake MJ, Inglis K, Owen D, White P: Protocol for a randomized, double blind, placebo controlled, crossover trial of Melatonin for treatment of Nocturia in adults with Multiple Sclerosis (MeNiMS). BMC Neurol 2017, 17(1):63.

Disclosures

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