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Abstract *Objective:* To evaluate the effects of exogenous melatonin on the frequency of wet nights, on the sleep-wake cycle, and on the melatonin profile in children with therapy-resistant MNE.

Patients and methods: 24 patients were included. Patients had to maintain a diary including time of sleep and arousal, and whether they had a dry or a wet bed in the morning. We measured baseline melatonin profiles in saliva. Hereafter, patients were randomized to synthetic melatonin or placebo. After 3 and 6 months we evaluated the frequency of enuresis and the melatonin profiles.

Results: 11 patients were randomized to melatonin, 13 to placebo. We evaluated melatonin profiles of 7 patients in the melatonin group and of 8 in the placebo group. We observed a change in profile in the melatonin group, but we did not observe a difference in the sleep-wake cycle or the frequency of wet nights in either group.

Conclusion: This is the first time exogenous melatonin has been evaluated in the treatment of MNE. Although we observed a change in melatonin profile after the use of exogenous melatonin, we did not observe a change in enuresis frequency or in the sleep-wake cycle of this select group of patients.

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Introduction

Monosymptomatic nocturnal enuresis (MNE) is a stressful disorder, both for the individual and on a social level, the latter mainly by causing stress within the families of patients.

Besides this, MNE is common: 20% of children in their first grade experience

MNE [1]. Although the spontaneous cure rate of MNE is around 15% each year, 1—2% of children stay wet up until puberty [2,3]. Current therapies for MNE include alarm treatment, oxybutynin, desamino-D-arginine vasopressin (dDAVP, desmopressin), tricyclic antidepressants (imipramine) and behavioural techniques, or a combination of treatments [4,5]. Despite several treatment options, a group of children remain who do not respond effectively to current therapies. Long-term cure rates vary greatly and relapse rates for combination therapy are approximately 20% after 1 year [4,6—11]. For these reasons, other methods of therapy are worth exploring.

Van Gool et al. postulated a functional relationship between MNE, age and development of the normal nocturnal rise in arginine vasopressin (AVP) release with night-time anti-diuresis, difficulties with arousal from sleep and the 24-h melatonin profile [12]. The endogenous melatonin cycle is, amongst other factors, an important regulator of the sleep-wake cycle in humans [13—15]. This conclusion is acknowledged by several studies about the efficacy of exogenous melatonin in the treatment of different sleep-wake disorders, and circadian rhythm disorders in blind people [14—18]. Children with MNE experience difficulties in their arousal from sleep [19—22], possibly associated with disturbances of the circadian rhythm. A number of children with MNE do not have the normal nocturnal rise of endogenous AVP, which is associated with circadian melatonin excretion [12]. Furthermore circadian melatonin excretion is age-dependent: highest levels are found in the age range of 1—5 years. Just before puberty, melatonin levels decline and stay low with increasing age [23,24]. Several studies show that exogenous melatonin is able to shift the sleep-wake cycle: 1—2 h forwards when taken at dusk, 1 h backwards when taken at dawn [18,25—27]. Considering these observations and previous comments, exogenous melatonin may have a therapeutic function in the treatment of MNE. To our knowledge, exogenous melatonin has not yet been reported as a treatment option in MNE.

The aim of this study was to evaluate the effects of exogenous melatonin on the frequency of wet nights, on the sleep-wake cycle, and on melatonin profiles in children with therapy-resistant MNE.

Patients and methods

The design of the study was a randomized placebo-controlled double trial aiming to include 90 patients between 10 and 16 years of age with therapy-resistant MNE. Patients were enlisted during a period of 2 years in a single-center setting. To be eligible for inclusion, patients had to experience a minimum of 2 wet nights weekly. At the time of inclusion no patient used any drug that could influence the MNE. All patients had a clinical evaluation which included medical history and voiding history, physical examination, ultrasonography of kidneys and bladder, urinalysis, and uroflowmetry with ultrasound residual volume measurement.

Patients who had received a positive long-term effect from any medication were excluded, as well as patients with a history of urinary tract infections. MNE was defined as a normal void occurring at an inappropriate and socially unacceptable time and place, in this case at night in bed [28]. Informed consent was obtained from patients and their parents.

Before randomization, all patients were asked to keep a nocturnal enuresis diary for at least 2 weeks, including time of sleep and time of arousal, and whether they had a dry or wet bed in the morning. Additionally, a melatonin profile was measured in saliva samples [29]: every 2 h, from 6 pm until 8 am, patients had to chew on a cotton plug for 1 min. The samples were collected under dim light while the patients were sleeping in the dark. Hereafter, the samples were kept unexposed to light, wrapped in aluminium foil, and were frozen and sent to the laboratory. Melatonin levels were measured using a radioimmunoassay method (Buhlmann Laboratories AG, Switzerland). Melatonin in saliva was expressed as pg/ml. The detection limit of the assay was 0.5 pg/ml for each sample [29]. The melatonin rhythm in saliva has the same time curve as in serum with no delay [29—31].

After baseline measurements, children were randomly assigned to 3 months of 5 mg synthetic melatonin orally or placebo, to take at 8 pm daily. The dose of melatonin was based on findings described in a review of several studies by Jan et al. [14].

After randomization, children had to keep a nocturnal enuresis diary, with help from their parents, for another 6 months. After 3 and 6 months another melatonin profile was measured with salivary samples using the same procedure as before randomization. The primary outcome variable was the frequency of wet nights as this was considered the most clinically relevant measure of efficacy. Secondary outcomes were sleep-wake rhythm, melatonin profile and quality of life within the family of the patient. We considered children with a reduction of 90% or more in frequency of wet nights as responders, a reduction of 50% as partial responders and less than 50% as non-responders. We planned for 90 patients to be included, 45 in each arm. Assuming a 5% response rate in the placebo group, this number is sufficient to demonstrate an absolute difference in response rate between the randomized groups of 25% or more with 80% power (1-beta) and alpha 0.05. In the event, we included considerable fewer patients than planned. The study was stopped because no positive response with regard to bedwetting was found in either group. Therefore, we restricted our statistical analyses to the continuous variables as these are generally associated with more statistical power. Consequently, we analyzed the difference between the randomized groups in change in the frequency of wet nights and levels of melatonin from baseline to 3 months and 6 months of follow-up using analysis of covariance. We refrained from analysis of the 6-month measurements of melatonin levels as, by that time, the missing rate for melatonin measurements was 40%.

Results

All patients with therapy-resistant MNE were screened and, if possible, included. After inclusion of 24 patients, we had to end the study and broke the randomization code because of excessively slow inclusion and therapeutic failure. By that time, 11 patients were randomized to melatonin, and 13 to placebo. Of the included patients, 3 (12.5%) were girls, 1 in the melatonin and 2 in the placebo group. Patient characteristics are shown in Table 1. The mean weekly number of wet nights before start of the treatment was not substantially different between the melatonin and the placebo group indicating successful randomization (Table 2). For 5 patients in the melatonin group we managed to retrieve a full melatonin profile, consisting of a profile before randomization, one 3 months after start of medication and one 6 months after randomization. For 2 patients we could only obtain a partial profile, but enough to determine the effect of melatonin after 3 months. In the placebo group we managed to retrieve 7 full melatonin profiles and 1 partial profile. In the melatonin group, we observed a shift in profile after 3 months of medication: the mean melatonin level peaked 4 h earlier after the use of melatonin (Fig. 1). In the placebo group we observed no difference between the mean baseline melatonin profile and the curves after 3 months (Fig. 2). The mean level of the curve after 3 months was higher in the melatonin than in the placebo group although this difference was not statistically significant (Table 3). Although we observed a change in melatonin levels in saliva after the use of melatonin, we did not observe a significant change in the frequency of wet nights after the use of melatonin (Table 2). No side-effects of melatonin use were mentioned.

Discussion

MNE is caused by a combination of pathogenic factors, such as small functional bladder capacity, difficulties with arousal from sleep and nocturnal polyuria [19–22,32,33]. Of children with nocturnal enuresis, 41%–90% have good short-term results with an enuresis alarm, different training modalities, desmopressin, oxybutinin, tricyclic anti-depressives or a combination. Unfortunately the relapse rate of these therapies is significant [7–11]. Most of our patients had a smaller functional voided volume than one would expect according to age (Table 1). All patients in this highly selected group had an elevated sleep arousal

Table 1 Baseline characteristics of patients.

Variable	Melatonin (11 pts)	Placebo (13 pts)
Age, mean $\pm$ SD, years	12.03 $\pm$ 1.38	13.32 $\pm$ 1.81
Male gender, n	10	11
Weight, kg (mean)	43.5 $\pm$ 12.14	51.5 $\pm$ 11.23
BMI, kg/m^2	17.86 $\pm$ 2.93	19.48 $\pm$ 3.42
Max. measured bladder volume (mean)	213.54 $\pm$ 101.3	292.76 $\pm$ 3.42
< 75% functional bladder capacity, n	9	8

Table 2 Clinical outcome variables according to randomized treatment.

Variable	Melatonin (11 pts)	Placebo (13 pts)
No. of wet nights at baseline (per week), mean $\pm$ SD	6.41 $\pm$ 1.32	5.11 $\pm$ 1.46
No. of wet nights at 3-month follow-up (per week), mean $\pm$ SD	6.55 $\pm$ 0.96	4.99 $\pm$ 1.83
Baseline adjusted difference at 3-month follow-up, mean (95% CI)[a]	0.60 (−0.46; 1.65)	
No. of wet nights at 6-month follow-up (per week), mean $\pm$ SD	6.55 $\pm$ 0.97	4.86 $\pm$ 1.90
Baseline adjusted difference at 6-month follow-up, mean (95% CI)[a]	0.64 (−0.38; 1.67)	
Responders, n	0	0
Partial responders, n	0	1
Difficulties with arousal, n	11	13

[a] Difference (95% confidence interval) between treatment groups adjusted for baseline value.

threshold and had proven to be resistant to the treatment options mentioned above. In the outpatient clinic, the history of MNE patients often shows a link between difficulties in arousal, enuresis and the sleep-wake cycle: when patients travel across different time zones westward, inducing a cycle change, the MNE can stop for several months. Furthermore, when patients stay over with friends or family the wet night frequency can decrease, possibly due to a more superficial sleep [12].

The pineal gland hormone melatonin, the rhythm of which is controlled by the suprachiasmatic nuclei, is known to give the body information about the time of day and possibly, because secreted at night, it reinforces darkness-related behaviour like sleep initiation [34]. It is also known
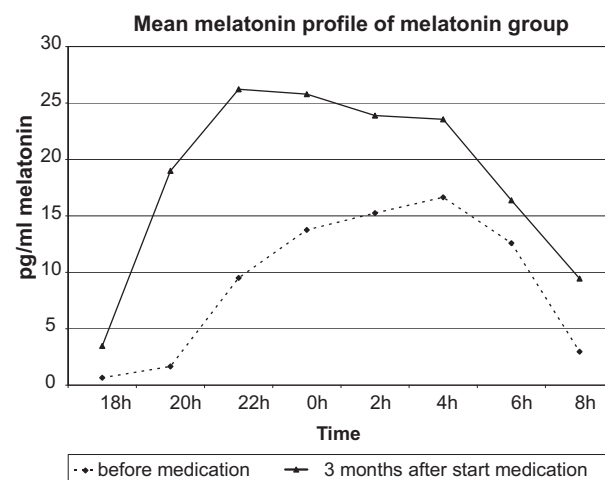

Figure 1 Mean saliva melatonin profile in melatonin group. We observed a shift in melatonin profile as well as a change in height of the curve after 3 months.
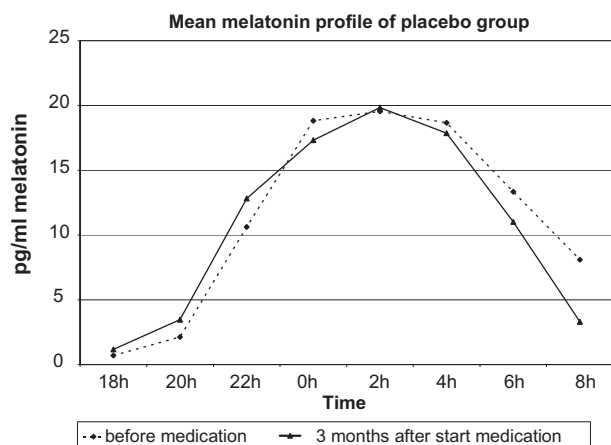
Figure 2 Mean saliva melatonin profile in placebo group. After 3 months, neither a shift in melatonin profile occurred, nor a change in height of the curve.

that melatonin can act as a zeitgeber in blind people [15,35]. Circadian rhythm seems not only important for the sleep-wake cycle, but also it may have its effects on other circadian rhythms, like the release of endogenous AVP. Rittig et al. [36] described abnormal circadian AVP levels in MNE patients compared to non-enuretic controls, which resulted in symptomatic treatment of MNE with desmopressin [9,36].

Melatonin concentrations are low in the daytime, rising at around 10.00 pm to peak at 02.00–03.00 pm, and declining back to baseline in the morning [34]. The increase of melatonin seems to coincide with the moment of urine loss in MNE patients, which could imply a relationship between increase of sleep arousal threshold and bed-wetting [37]. Although our groups were small and levels of melatonin differed between patients, we observed the same baseline melatonin rhythm as described. These findings are confirmed by Ardura-Fernandez et al., who compared melatonin levels in saliva between enuretic patients and controls [37]. Another report showed no differences in endogenous production of melatonin between children with MNE and controls [38]. It is known

that exogenous melatonin can shift the phase of the sleep-wake cycle forward when taken before sleep-time at night [18,25–27]. Van Gool et al. mentioned the possibility of manipulation of the 24-h melatonin profile with exogenous melatonin and the possible effect on enuresis in children with MNE [12]. We tested this theory by randomizing patients to melatonin and placebo before they went to sleep. Although we observed a shift in peak-time and height of the melatonin profile in the group who received melatonin (Fig. 1), we did not observe a change in sleep-wake cycle. Also, the ability of patients to wake up from sleep did not seem to be influenced by exogenous melatonin, as parents still reported difficulties in arousal.

When we looked at frequency of wet nights, we did not observe a difference in either group, although one patient in the control group improved significantly, possibly because of a change from summer to winter time (Table 2). This lack of positive effect on enuresis could explain why a lot of our patients were not motivated to collect their salivary melatonin samples in the correct way after 3 and 6 months.

Conclusions

To our knowledge, this is the first time exogenous melatonin has been evaluated in the treatment of MNE. Although we observed a change in level and peak-time of melatonin in saliva after the use of melatonin, we did not observe a significant change in enuresis frequency, nor did we observe a change in sleep-wake cycle. Therefore, we conclude that the role of melatonin in the treatment of therapy-resistant MNE is limited. However, the studied population was relatively small and consisted of a select group of patients resistant to all other forms of therapy. Further studies are necessary to explore new treatment options for this difficult group of patients.

Funding

Conflict of interest

None.

Ethical approval

Approved by the MEC of the University Medical Center Utrecht.

Table 3 Changes in maximum levels of melatonin (M max) and peak-Time (T) from baseline (T max 0) to 3 months of follow-up (T max 3).

Variable	Melatonin (n = 7)	Placebo (n = 8)
Mean ± SD M max 0 (pg/ml)	20.7 ± 10.3	22.0 ± 10.1
Mean ± SD M max 3 (pg/ml)	32.0 ± 18.1	22.6 ± 8.0
Group difference[a]	12.2 (−3.1; 27.4)	
Mean T max 0 (24 h)	2.00	2.00
Mean T max 3 (24 h)	22.00	2.00
% shift of curve[b]	71.4%	25%

[a] Corrected for baseline values using analysis of covariance (95% confidence interval).
[b] Percentage of patients with time shift of melatonin peak to an earlier hour.

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