LETTER TO THE EDITOR

Melatonin Treatment in Smith Magenis Syndrome

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DEAR EDITOR,

SMITH MAGENIS SYNDROME (SMS) IS A RARE GENETIC CONDITION CHARACTERIZED BY A TYPICAL PHYSICAL PHENOTYPE, DEVELOPMENTAL DELAY and behavioral problems, including self-harm and aggression as well as sleep disturbance.1 The primary defect involves an interstitial deletion on the short arm of chromosome 17 (del 17p11.2). The sleep disturbance of SMS occurs in most patients and causes much disruption to the families involved. During the day, this typically involves sleep attacks and daytime napping with consequent disruption of nocturnal sleep.2 It appears that this disruption lies primarily in an inversion of the circadian rhythm of melatonin, a hormone secreted by the pineal gland, causing daytime secretion as opposed to nocturnal secretion.3 There have been reports indicating that giving melatonin in SMS improves these sleep abnormalities.4,5 However, there do not appear to be any reports of randomized double-blind placebo controlled trials aimed at confirming this. In rare conditions such as SMS trials of this nature may not be feasible due to the logistics of recruitment.

We used a double blind, n-of-1 study design with randomization via a pre-prepared block randomization schedule over a total duration of 12 consecutive nights, with dosing of either 6mg of melatonin or placebo prepared in capsules. The patient was a 3-year-old boy suffering from SMS confirmed by cytogenetics. His clinical course had previously been complicated by developmental delay, recurrent asthma and obstructive apnea. Of particular concern to his family was the disrupted pattern of his sleep, which exhibited a similar pattern to many of the literature reports (day night sleep reversal and multiple arousals). Either placebo or treatment was given at the first night time arousal.

The primary outcome measure was time to sleep after dosing. The secondary outcome measures were duration of uninterrupted sleep after dosing, total nocturnal sleep, total day-time sleep and total sleep over 24 hours. Five point ordinal scales were recorded for daytime behavior, paternal sleep quality, maternal sleep quality and global satisfaction with the treatment. The outcome measures were recorded by the parents in a treatment diary. Overnight pulse oximetry was performed on 1 occasion for each treatment and on completion of the study (analyzed blind to treatment status). The data were analyzed using a paired t-test for normally distributed continuous variables and Wilcoxon rank-sum for ordinal outcome variables. Ethical approval for this study was obtained via the Otago Research Ethics Committee.

Treatment with melatonin was associated with a shorter time to sleep, but not with an increase in the diary recordings of duration of sleep, or with improvement in the quality scores (Table 1). There was a lesser percentage of time with oximetry > 95% on the treatment night in comparison with the placebo night and post-study night (53.1%, 90% and 64.6% respectively) but no increase in duration of oximetry < 89% (4.3, 8.5 and 15.8 minutes respectively).

The present study indicates that melatonin induces sleep in SMS, but does not alter the parental perception of the total amount of nocturnal and diurnal sleep. In addition, we were not able to demonstrate an improvement in behavior, in the quality of parental sleep or overall satisfaction as a result of treatment. There was no indication of significant respiratory depression with melatonin. Hence, the present study confirms that melatonin has potential in the treatment of sleep disorder in SMS but may require modifications, such as slow release formulation or suppression of day-time melatonin release, to improve its effectiveness.4 The study also demonstrates the utility of n-of-1 study designs in improving the evidence base for rare conditions.

ACKNOWLEDGEMENTS

We wish to thank the patient and his family for their enthusiastic involvement in this study.

REFERENCES:


Table 1—Outcome Measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to sleep, mean (S.D.), hours</td>
<td>3.36 (2.23)</td>
<td>7.32 (3.71)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Sleep After Medication, mean (S.D.), hours</td>
<td>0.25 (1.50)</td>
<td>0.96 (0.61)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Total Nights Sleep, mean (S.D.), hours</td>
<td>9.20 (1.44)</td>
<td>8.20 (1.48)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Total Sleep, mean (S.D.), hours</td>
<td>10.83 (1.18)</td>
<td>9.41 (1.75)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Sleep During Day, mean (S.D.), hours</td>
<td>1.60 (0.57)</td>
<td>1.20 (0.87)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Daytime Behavior, median (range)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Paternal Sleep Score, median (range)</td>
<td>3 (2 to 3)</td>
<td>3 (2 to 3)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Maternal Sleep Score, median (range)</td>
<td>3.75 (3 to 4)</td>
<td>3.75 (3 to 4)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Global Score, median (range)</td>
<td>2.50 (2 to 3)</td>
<td>2.50 (2 to 3)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

NB: Median (S.D.) tested using Student’s t-test, Median (range), tested using Wilcoxon rank-sum

Disclosure Statement
Drs. Reith, Wheeler, Taylor, and Simonsen have indicated no financial conflicts of interest.

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