Transdermal Scopolamine Alters Phasic REM Activity in Normal Young Adults

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Summary: Transdermal scopolamine has been widely used for the prevention of motion-sickness by travelers due to its potent anticholinergic effects and the ease of administration. Nevertheless, its effects on sleep physiology are not known, despite the well-known fact that the administration of scopolamine as an injection or an oral form could influence the sleep architecture, especially prolonging rapid eye movement (REM) sleep latency and shortening duration of REM sleep. This study aimed to measure the influence of transdermal scopolamine on REM sleep in order to examine whether it affects REM sleep as in the previous studies. We studied eight young healthy male adults polysomnographically for three nights including one adaptation night in a double blind crossover design and compared REM sleep-related variables between sleeps with and without scopolamine patch of 1.5 mg. We found no differences in tonic REM sleep measures such as REM duration and REM latency, but phasic REM sleep measures such as total REM activity (p<0.05) and total REM density (p<0.05) were significantly suppressed by the transdermal scopolamine; REM densities of the first (p<0.05) and the second (p<0.05) REM sleep periods as well as REM activity of the fourth REM sleep period (p<0.05) were decreased significantly on the scopolamine patch nights compared with placebo patch nights. These results suggest that phasic REM components reflect cholinergic mechanism in the central nervous system (CNS) even at the lowest commercial dose, and could be useful markers of CNS cholinergic activities in the future research.

Key Words: transdermal delivery system; polysomnography; REM sleep; REM density; REM activity; muscarinic antagonists

INTRODUCTION

CENTRAL CHOLINERGIC NERVOUS SYSTEM facilitates REM sleep. Animal studies indicate that central cholinergic agonists induce REM sleep,1-5 while microinjection of anticholinergic agents, such as atropine and scopolamine, blocks the induced cholinergic REM sleep.5-7

In humans, infusion of physostigmine6,9 and arecoline10,11 rapidly induce REM sleep. Oral administration of RS8612 and pilocarpine13 also induces REM sleep. On the contrary, injection of scopolamine, a nonspecific muscarinic cholinergic receptor antagonist,14,15 blocks the effects of arecoline,11 increases the REM sleep latency, decreases REM sleep amount,10,16-18 decreases REM activity and REM density,19 and increases body movements during sleep.16 These cholinergics and anticholinergics including scopolamine seem to affect REM sleep in a dose-dependent manner.12,17,20

Although transdermal delivery systems (TDS) of scopolamine have been widely used for the prevention of motion-sickness,21 it is not known whether it affects human REM sleep. Since the administration of scopolamine through TDS has different pharmacokinetics22 compared with parenteral administration, we were interested in seeing whether it also affects human REM sleep. We hypothesized that the scopolamine patch would inhibit REM sleep measures.

METHODS

Subjects

Eight normal young healthy male adult volunteers were studied with polysomnography. The study was approved by the Institutional Review Board of the Seoul National University Hospital and each subject signed an informed consent prior to participation in the study. All study procedures conformed to the Declaration of Helsinki. Mean age of the subjects was 23.3 ± 1.0 (22-25) years, with mean height and mean body weight 172.2 ± 5.8 (165-180) cm.

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and 65.7 ± 3.9 (62-73) kg, respectively. Inclusion criteria were as follows: 1) males; 2) with no history of mental and physical disorders at present and in the past that might influence sleep architecture. Subjects with depression were ruled out by using the Hamilton Rating Scale for Depression and Beck Depression Inventory (cut-off score of 10); 3) without sleep disturbance factors such as heavy snoring and overweight (greater than 120% of ideal body weight); 4) without sleep disorders such as sleep apnea syndrome, narcolepsy, and periodic limb movement disorder, confirmed with overnight polysomnography; 5) without history of drug abuse; and 6) without current medications that may affect sleep. Also, drugs and alcohol were not allowed during the study period. There were two very mild smokers out of eight subjects. We permitted smoking as an usual life pattern.

Methods

Polysomnographic recordings were done with Grass model 78 polysomnograph, which included electroencephalography (EEG), left and right electro-oculography (EOG), submentalis electromyography (EMG), left and right anterior tibialis EMG, electrocardiography (ECG), snoring microphone, oro-nasal airflow, chest and abdominal respiratory movements, and arterial oxygen saturation.

Two channels of EEG were recorded at C3/A2 and O2/A1 according to the international 10-20 system. EOG electrodes placement was done following the standard method. ECG electrode was attached at modified lead II position. The snoring microphone was attached at the surface area nearest to the vocal cord. Oro-nasal airflow was monitored with the thermocouple positioned at the mouth and the nostrils. Chest and abdominal breathing movements were monitored with impedance pneumograph applied to the chest and abdomen at the maximum excursion of breathing. Oxymeter probe was attached at the tip of the non-dominant second finger. All recordings were done at the paper speed of 10 mm/second. Behavioral monitoring was also done with infrared closed circuit camera system.

Polysomnography was conducted for three nights. The first night was for adaptation and to rule out sleep disorders. On the second night, one scopolamine or placebo patch was administered in a double blind randomized crossover design. One scopolamine patch (Kimite®) contains 1.5mg of scopolamine. Both placebo and scopolamine patches were generously provided by Myung Moon Pharmaceutical Company as the identical shape and color. Every patch was applied between 20:30 and 21:05 on the intact skin in the posterior auricular area about three hours before retiring to bed. Recording started between 22:45 and 24:20. The patch was removed the next morning. After wash-out period of minimum 84 hours, the third night polysomnography was carried out and the other patch was administered in a counter-balanced order. Subjects main-

### Table 1. Comparison of sleep variables between placebo and scopolamine patch nights

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Scopolamine</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in bed (min)</td>
<td>469.8</td>
<td>480.4</td>
<td>-0.98</td>
<td>N.S.</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>454.6</td>
<td>464.7</td>
<td>-0.28</td>
<td>N.S.</td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>7.8</td>
<td>8.0</td>
<td>-0.70</td>
<td>N.S.</td>
</tr>
<tr>
<td>Stage 2 (%)</td>
<td>59.1</td>
<td>61.3</td>
<td>-0.70</td>
<td>N.S.</td>
</tr>
<tr>
<td>Stage 3 (%)</td>
<td>7.4</td>
<td>6.3</td>
<td>-0.70</td>
<td>N.S.</td>
</tr>
<tr>
<td>Stage 4 (%)</td>
<td>0.4</td>
<td>1.0</td>
<td>-1.75</td>
<td>N.S.</td>
</tr>
<tr>
<td>REM sleep (%)</td>
<td>25.4</td>
<td>23.5</td>
<td>-1.12</td>
<td>N.S.</td>
</tr>
<tr>
<td>Total waking time (%)</td>
<td>3.3</td>
<td>3.4</td>
<td>-0.14</td>
<td>N.S.</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>3.3</td>
<td>3.0</td>
<td>-0.51</td>
<td>N.S.</td>
</tr>
<tr>
<td>No. of waking</td>
<td>17.3</td>
<td>18.0</td>
<td>0.00</td>
<td>N.S.</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>96.8</td>
<td>97.0</td>
<td>-0.67</td>
<td>N.S.</td>
</tr>
<tr>
<td>REM sleep latency (min)</td>
<td>107.6</td>
<td>93.3</td>
<td>-0.98</td>
<td>N.S.</td>
</tr>
<tr>
<td>TTREMP&lt;sup&gt;a&lt;/sup&gt; (min)</td>
<td>131.4</td>
<td>121.3</td>
<td>-0.98</td>
<td>N.S.</td>
</tr>
<tr>
<td>TREM&lt;sup&gt;b&lt;/sup&gt; (min)</td>
<td>116.4</td>
<td>109.3</td>
<td>-0.56</td>
<td>N.S.</td>
</tr>
<tr>
<td>No. of REM sleep periods</td>
<td>4.3</td>
<td>4.1</td>
<td>-0.40</td>
<td>N.S.</td>
</tr>
<tr>
<td>No. of REM fragments</td>
<td>13.8</td>
<td>12.3</td>
<td>-1.01</td>
<td>N.S.</td>
</tr>
<tr>
<td>Mean REM duration&lt;sup&gt;c&lt;/sup&gt; (min)</td>
<td>32.3</td>
<td>29.5</td>
<td>-0.28</td>
<td>N.S.</td>
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<tr>
<td>REM fragmentation index</td>
<td>3.4</td>
<td>3.0</td>
<td>-0.93</td>
<td>N.S.</td>
</tr>
<tr>
<td>REM sleep efficiency (%)</td>
<td>89.1</td>
<td>90.1</td>
<td>-0.42</td>
<td>N.S.</td>
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</tbody>
</table>

<sup>a</sup>TTREMP: total time of REM sleep periods
<sup>b</sup>TREM: total REM sleep time
<sup>c</sup>Mean REM duration: mean of REM sleep period durations

N.S.: non-significant
tained their usual lifestyle except during experimental night times.

Sleep records were scored manually in 30-second epochs, using Rechtschaffen and Kales criteria.26 Rapid eye movement activity during REM sleep was scored in 60-second epochs using semi-quantitative scale of 0 to 8.27 Sleep parameters were summarized using PSDENT program (Stanford Univ. Sleep Clinic, version 1.2).

**Measured variables**

**Sleep continuity and sleep architecture measures** - Time in bed (TIB), total sleep time (TST), percentage of each sleep stage 1, 2, 3, 4, and REM, sleep latency, percentage of total waking time (TWT), number of waking (NOW), and sleep efficiency (TST/ TIB) were obtained.

**Tonic components of REM sleep measures** - REM sleep latency, total time of REM sleep periods, total REM sleep time (calculated by excluding intervening NREM sleep or wake time from total time of REM sleep periods), number of REM sleep periods, number of REM fragments (defined as one REM fragment if followed by less than 25 minutes of NREM sleep or wake time), mean of REM sleep period durations, REM fragmentation index (number of REM fragments/ number of REM sleep periods), and REM efficiency (total REM sleep time/ total time of REM sleep periods) were calculated.

Additionally, in each REM sleep period, REM sleep period duration, actual REM sleep time, REM efficiency, and number of REM fragments were also obtained.

**Phasic components of REM sleep measures** - REM activity (calculated on 0-8 scale per minute of REM sleep), REM density (REM activity/ total REM sleep time), and REM intensity (REM activity/ TST) were measured.

**Periodic relationship between REM sleep and NREM (non-REM) sleep** - REM sleep period cycle length (time from the midpoint of a REM sleep period to the midpoint of the following REM sleep period) and Vogel’s $\gamma$ were calculated. Vogel’s $\gamma$ is defined as Pearson correlation of each REM sleep period length with the duration of all preceding NREM sleep periods.

We compared variables between scopolamine and placebo patch nights by using the Wilcoxon signed-rank test. Statistical software package was PC SAS for Windows version 6.12.29

**RESULTS**

The first night polysomnography for adaptation did not show any pathologic findings. The second and third night results are listed below:

**Sleep continuity and sleep architecture measures**

There were no significant differences between transdermal scopolamine and placebo nights in TIB, TST, percentage of each sleep stage 1, 2, 3, 4, and REM, percentage of TWT, sleep latency, NOW, and sleep efficiency (Table 1). Thus, a single patch of transdermal scopolamine did not influence the subjects’ sleep continuity and architecture.
Tonic components of REM sleep measures

REM sleep latency was not significantly different between transdermal scopolamine and placebo nights. Total time of REM sleep periods was shorter on transdermal scopolamine than on placebo, but the difference was insignificant. Total REM sleep time and mean of REM sleep period durations also did not differ significantly between transdermal scopolamine and placebo nights (Table 1).

Number of REM sleep periods, number of REM fragments, REM fragmentation index, and REM efficiency did not differ significantly between the transdermal scopolamine and placebo patch nights (Table 1). When compared in each REM sleep period, there were no significant differences in the duration of REM sleep period, actual REM sleep time, REM efficiency, and number of REM fragments between transdermal scopolamine and placebo patch nights. However, the duration of the second REM sleep period tended to be shorter on transdermal scopolamine patch nights than placebo nights (p<0.09).

Phasic components of REM sleep measures

Figures 1 & 2 show that total REM activity was significantly reduced (p<0.05) on transdermal scopolamine compared with placebo nights (228.0 ± 76.8 vs. 309.1 ± 38.1 units). Also, total REM density (p<0.05) and REM intensity (p<0.01) were significantly suppressed by transdermal scopolamine (2.15 ± 0.84 vs. 2.74 ± 0.56 units/min and 0.49 ± 0.17 vs. 0.68 ± 0.09 units/min, respectively).

REM activity of the fourth REM sleep period was significantly lower on transdermal scopolamine (p<0.05) than on placebo nights and that of the second REM sleep period tended to be lower on scopolamine (p<0.08), but other REM activities of each REM sleep period did not show any significant differences.

REM densities of the first and second REM sleep periods were significantly lower on transdermal scopolamine (p<0.05) than on placebo night, and that of the fourth REM sleep period tended to be lower on scopolamine night (p<0.07).

Periodic relationship between REM sleep and NREM sleep

REM sleep period cycle length and Vogel's γ were not significantly different between transdermal scopolamine and placebo patch nights.

DISCUSSION

In this study, a patch of transdermal scopolamine had no effects on sleep continuity, sleep architecture, or tonic REM sleep components in contrast to the previous studies using parenteral administration of scopolamine. Sagales et al. injected scopolamine (6 mg/kg) intramuscularly (IM) and observed delayed REM latency, shortened REM duration, increased body movement, and increments of stages 1 and 2. Poland et al. found that REM latency increased in a dose-dependent manner after IM injection of 3 mg/kg and 6 mg/kg of scopolamine.

Discrepancies between the above studies and ours may be attributable to the fact that the dose of one scopolamine TDS patch is probably too small to affect sleep architecture.
and tonic components of REM sleep. One patch contains 1.5 mg of scopolamine, but the initial priming dose of scopolamine in the adhesive layer is 0.14 mg, which is gradually released during the first six hours.\textsuperscript{22,30} Utilizing the data from the study of Poland et al.,\textsuperscript{17} the smallest effective dose of patched scopolamine would be calculated in the following way. When the body weight of a subject was 66.0 kg (i.e., the average weight of the study subjects) and he was injected with 3 mg/kg scopolamine, the smallest effective parenteral dose,\textsuperscript{17} the total amount of scopolamine administered would be approximately 0.20 mg. Thus, the initial priming 0.14 mg of scopolamine in one TDS patch, which is gradually released over six hours, might not cause any changes in sleep continuity, sleep architecture, or tonic REM components. After the initial six hours, a patch of scopolamine is designed to release the rest of scopolamine constantly (5 \(\mu\)g/hour) through the rate-controlling microporous membrane for the next 66 hours.\textsuperscript{22} Therefore, the amount of scopolamine being released constantly is almost negligible, because it contributes at most 0.025 mg to the total amount of scopolamine administered until the end of polysomnography of presumably eight hours.

The timing of TDS patch application onto the skin should also be considered. Transdermal scopolamine should be applied eight hours prior to the sea travel or at least four to six hours before the onset of motion for antiemetic effect.\textsuperscript{30,31} As of now, there are no data as to when the transdermal scopolamine starts to affect sleep. In our study, the scopolamine patch was applied about three hours before bedtime and significant changes were evenly found either at later part of night in REM activity or at earlier part of night in REM density (Figure 2).

Based on Sitaram et al.'s report,\textsuperscript{10} we expected that the scopolamine TDS would lengthen the intervals between REM sleep periods, and thus influence the sleep cycle oscillation. However, no significant differences in REM sleep period cycle length were found between scopolamine and placebo patch nights. Both of scopolamine and placebo nights showed positively correlated Vogel's \(\gamma\) with no difference between them. Sleep cycle oscillations in normal young adults do not seem to be altered by one scopolamine TDS patch application.

The effects of scopolamine upon phasic REM components are robust. This is consistent with our initial expectation and with the previous report of Sagales et al.\textsuperscript{32} in which total number of eye movements decreased after scopolamine injection.

REM density was once considered as a sensitive index of the intellectual level\textsuperscript{33} or the sleep satiety.\textsuperscript{34} Antonioli et al.\textsuperscript{35} asserted that REM density was constant through the REM deprivation and independent of other tonic REM sleep variables. REM activity and density were also presented as differentiating markers between the depressive and the normal\textsuperscript{19,36-38} and as markers of depression subtypes.\textsuperscript{37,39} Foster et al.\textsuperscript{39} and King et al.\textsuperscript{40} mentioned REM density as a neurophysiological indicator of structural or metabolic disturbances of CNS. Poland et al.\textsuperscript{19} insisted that the decreases of REM density and REM activity by scopolamine reflected cholinergic hyperactivity in depression. Many consider REM density as a relatively constant, sensitive, and objective index, independent of other sleep variables, and alteration of REM density seems to reflect changes of CNS. Our results suggest that the REM activity and density are sensitive reflectors of central cholinergic nervous activities.

We conclude that anticholinergic activity of transdermal scopolamine at the dose of 1.5 mg over 11 hours suppress phasic REM components such as REM activity, REM density, and REM intensity, interestingly without changes of tonic components of REM sleep and sleep architecture. It seems that phasic events of REM sleep are affected more sensitively than tonic events of REM sleep by the transdermal scopolamine.

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**REFERENCES**