The Efficacy and Safety of the Melatonin Agonist β-Methyl-6-Chloromelatonin in Primary Insomnia: A Randomized, Placebo-Controlled, Crossover Clinical Trial

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Background: While melatonin agonists are known to regulate circadian sleep rhythms, it is not clear whether melatonin agonists have a direct soporific effect. It has been suggested that melatonin's soporific effect is secondary to its ability to induce hypothermia. β-Methyl-6-chloromelatonin is a high-affinity melatonin receptor agonist that is not associated with hypothermia. The purpose of the present study was to determine if the melatonin agonist β-methyl-6-chloromelatonin has a direct soporific effect in subjects with primary insomnia.

Method: A double-blind, placebo-controlled, crossover safety and efficacy study of 20 mg, 50 mg, and 100 mg of β-methyl-6-chloromelatonin and placebo was conducted in subjects with DSM-IV-TR primary insomnia. Of 84 subjects screened, 40 progressed to randomly receive each of 3 β-methyl-6-chloromelatonin doses or placebo on each of 2 consecutive nights with 5-day washout periods between treatments. The effect of treatment on both polysomnographic and subjectively measured sleep parameters, next-morning psychomotor performance, and safety measures was determined. The primary outcome measure was latency to persistent sleep measured by polysomnography.

Results: A significant effect of β-methyl-6-chloromelatonin on the primary efficacy variable, latency to persistent sleep, was observed ($p = .0003$). The 20-mg dose resulted in a significant 31% improvement in sleep latency compared with placebo, while significant 32% and 41% improvements were observed at the 50-mg and 100-mg doses, respectively (20 mg, $p = .0082$; 50 mg, $p = .0062$; 100 mg, $p < .0001$). Similarly, a significant effect of β-methyl-6-chloromelatonin on subjective measures of time to fall asleep occurred ($p = .0050$), with significant improvement observed at both the 50-mg and 100-mg doses ($p = .0350$ and .0198, respectively) and a trend toward improvement observed at the 20-mg dose ($p = .0582$). Adverse events were mild to moderate in severity and did not differ in frequency between β-methyl-6-chloromelatonin and placebo treatments.

Conclusion: β-Methyl-6-chloromelatonin significantly decreases both objective and subjective measures of sleep latency in subjects with primary insomnia. Thus, these data suggest that melatonin agonists may exert a direct soporific effect, as previous research indicates that β-methyl-6-chloromelatonin is not associated with changes in body temperature, heart rate, or blood pressure.

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Melatonin is a naturally occurring indole associated with circadian rhythms including circadian sleep rhythms. Melatonin (N-acetyl-5-methoxytryptamine) is synthesized in the pineal gland by acetylation and then methylation of serotonin.[1] Production of melatonin is suppressed by light, making melatonin a hormonal signal of darkness.[2] Melatonin modulates circadian rhythmicity in mammals, including humans. While the relationship between melatonin and circadian sleep rhythms is well established, a direct soporific effect of melatonin is controversial.

There are 2 primary issues in assessing whether melatonin agonists have a direct soporific effect in subjects with primary insomnia. First, acute agonist administration must be employed in order to separate the agonist's direct effect on sleep from long-term entrainment of circadian sleep rhythms. Few sleep studies have been performed

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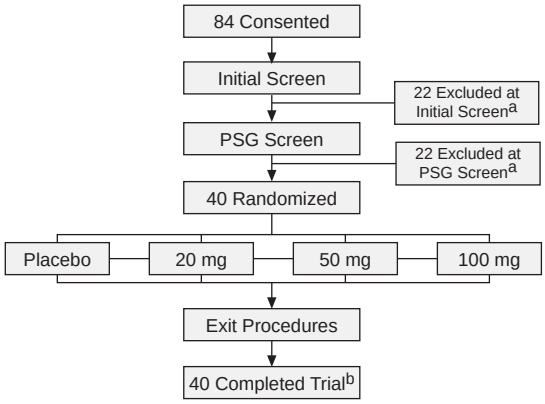
Figure 1. The Efficacy and Safety of the Melatonin Agonist β-Methyl-6-Chloromelatonin in Primary Insomnia: A Randomized, Placebo-Controlled, Crossover Trial



[a]See text for details of excluded subjects.
[b]Trial completions were subjects who completed all 4 weeks of double-blind treatment, including physical examination and laboratory evaluation at study completion.
Abbreviation: PSG = polysomnography.

employing acute melatonin agonist administration, and none studied subjects with primary insomnia.[3–5] Therefore, we are not aware of any study of the direct soporific effect of a melatonin agonist in subjects with primary insomnia.

Second, melatonin side effects are a complication in assessing whether melatonin agonists have a direct versus indirect soporific effect. Melatonin produces hypothermia, bradycardia, and decreased blood pressure.[6,7,8] The sleep-inducing effects of melatonin agonists are reportedly correlated with their hypothermic properties, suggesting that the sleep-inducing properties of melatonin may be secondary to hypothermia.[9]

β-Methyl-6-chloromelatonin is a melatonin agonist with high affinity for melatonin receptors.[10] Previous research indicates that β-methyl-6-chloromelatonin demonstrates no significant effect on body temperature, heart rate, or blood pressure.[11] Therefore, the present study examined the effect of acute administration of β-methyl-6-chloromelatonin to assess whether melatonin agonists have a direct effect on sleep in subjects with primary insomnia.

A preliminary double-blind, placebo-controlled polysomnographic study[10] indicated that β-methyl-6-chloromelatonin demonstrates a dose-response–related effect on sleep onset. A 20-mg β-methyl-6-chloromelatonin dose resulted in a decrease in sleep latency in subjects with primary insomnia, while a 5-mg dose produced a nonsignificant trend in the appropriate direction.[10] It is not known if doses of β-methyl-6-chloromelatonin greater than 20 mg produce greater reductions in sleep latency than those observed with 20 mg. Therefore, the present study examined the acute effect of β-methyl-6-chloromelatonin at doses up to 100 mg on sleep onset in order to confirm and extend previous studies.

METHOD

Subjects

Men and nonfertile women between the ages of 21 and 55 years, within 25% of ideal body weight, meeting criteria for primary insomnia according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR), and in otherwise good health were enrolled in the study. This study was conducted according to the current revision of the Declaration of Helsinki and 45 Code of Federal Regulations (CFR) part 46 and 21 CFR parts 50 and 56 concerning the protection of human subjects. This study was approved for all sites by a central institutional review board.

Eighty-four subjects signed informed consent for the present study, of which 40 subjects were randomly assigned to the treatment conditions (Figure 1). Of the 44 subjects who did not proceed to randomization, 22 were excluded at the initial screen (9 excluded for evidence of significant active major organ disease, 4 excluded for age/weight not meeting study criteria, 3 excluded for sleep log abnormalities, and 6 voluntary withdrawals), and an additional 22 were excluded at the 2-night double-blind placebo polysomnography (PSG) screen (19 excluded for out-of-range sleep latencies and 3 for clinically significant leg movement). The remaining 40 subjects received treatments of 20 mg, 50 mg, or 100 mg of β-methyl-6-chloromelatonin or matching placebo in a randomized order for 2 consecutive nights with a 5-day washout period between treatments. One hundred milligrams was used as the upper dose limit, as no safety data are available for doses greater than 100 mg.

Study Design

This was a multicenter, 4-period, randomized, placebo-controlled, 4-dose crossover study of β-methyl-6-chloromelatonin ((R)-*N*-[2-(6-chloro-5-methoy-1*H*-indol3yl) propyl]acetamide). The study was conducted in conformance with guidelines for good clinical practice. Subjects who provided signed informed consent underwent screening procedures consisting of a 2-week sleep log, physical and psychiatric examinations, laboratory testing (hematology, chemistry, and urinalysis), urine drug screen, and pregnancy test (initial screen, Figure 1). Eligible subjects (i.e., those in general good health whose habitual bedtime varied by no more than 1 hour during the 2-week diary) underwent a 2-consecutive-night PSG screening evaluation after receiving single-blind placebo treatment both nights (PSG screen, Figure 1). On all PSG evaluation nights, drug or placebo was administered 1 hour before "lights out." For the purposes of the study, "lights out" oc-

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curred 1 hour prior to the subjects' usual bedtimes as determined from the sleep logs. For study inclusion, subjects needed to demonstrate a mean screening sleep onset latency between 30 and 90 minutes, with no night less than 30 minutes or greater than 90 minutes. Subjects were also excluded if they demonstrated evidence of clinically significant leg movement or sleep apnea (> 10 episodes per hour), clinically significant laboratory abnormalities, significant variation in habitual bedtime, evidence of significant active major organ disease, history of significant caffeine use or drug abuse, or use of psychotropic drugs.

The primary outcome variable was latency to persistent sleep. Secondary outcome measures consisted of other PSG sleep parameters (wake after sleep onset, total sleep time, sleep efficiency, time in stage 1, time in stage 2, time in stages 3 and 4, rapid eye movement sleep [REM], REM latency, and total wake time), items on a questionnaire capturing subjective data on the previous night's sleep quality, and psychomotor assessments (symbol copy and digit symbol substitution tests) upon awakening. PSG recordings from the randomized portion of the study were scored by a central reader blinded to the subjects' treatment condition.

Safety measures (vital signs) were obtained at each polysomnography session before study drug administration, 1 hour after study drug administration, and upon awakening the following morning. Adverse events were captured throughout the study by solicited and spontaneous subject reports at each visit. A physical examination and laboratory evaluation were performed at study completion.

Statistical Analysis

Sample size estimation was based on the primary outcome variable, time to persistent sleep. The employment of effect size data from a preliminary study of β-methyl-6-chloromelatonin on latency to persistent sleep, with $\alpha = .05$ 2-tailed test and $\beta = 0.90$, resulted in an estimated sample size of 40.[10] The efficacy and safety analysis includes all randomized subjects (intent-to-treat analysis).

Subjects, site investigators, and all study personnel were blinded to the subjects' treatment. Randomization was maintained by F.P.Z., who was not involved with the clinical execution of the study except for responsibility to unblind the medical monitor in case of a serious adverse event that required immediate medical intervention. No serious adverse events occurred during the study; therefore, the medical monitor remained blinded throughout the study.

Data were analyzed employing SAS statistical software, version 8.3 (SAS Institute, Cary, N.C.). The preselected primary outcome measure was latency to persistent sleep determined by PSG. Univariate analyses revealed that latency to persistent sleep scores as well as all other PSG variables were not normally distributed as has been previously observed.[12] Sleep latency and other PSG variables were normalized by log transformation and analyzed by repeated-measures analysis of variance (ANOVA) employing the SAS procedure Proc Mixed to determine if there was any significant difference between drug-treatment and placebo groups. As latency to persistent sleep was not normally distributed, these data are reported as geometric means and 95% confidence limits that were taken from the Proc Mixed output. Individual comparisons employed the method of Dunnett and were 2-tailed with a preselected level of significance of $\alpha = .05$. The secondary PSG outcome measures were analyzed and reported similarly (wake after sleep onset, total sleep time, sleep efficiency, time in stage 1, time in stage 2, time in stages 3 and 4, time in stage REM, and REM latency).

Subjective measures of sleep included the estimated time to fall asleep the preceding night, time asleep, number of wakenings, time awake, difficulty falling back to sleep, quality of sleep, and restorative nature of sleep. Frequency data (number of wakenings) were analyzed by the Proc Freq procedure, which tested whether there was any difference in the number of wakenings in drug versus placebo groups. The dependent variables time to fall asleep, time awake, difficulty falling back to sleep, quality of sleep, and restorative nature of sleep were analyzed by repeated-measures ANOVA employing Proc Mixed procedures to determine if statistically significant differences occurred between drug-treatment and placebo groups. Psychomotor performance was assessed employing the Digit Symbol Substitution Test (DSST) and Symbol Copying Test (SCT). Differences between placebo and drug treatment on DSST and SCT scores were assessed by repeated-measures ANOVA employing Proc Mixed procedures. Subjective measures of sleep as well as DSST and SCT scores were normally distributed; therefore, means and standard deviations were employed to describe the central tendency and variance of these measures.

RESULTS

Subject Demographics and Treatment Compliance

The 40 randomized subjects consisted of 25 white and 15 African American subjects, 33 women and 7 men, and were as a group 39.2 ± 8.9 years old (mean ± SD). These demographics are consistent with the general subject population seen at each of the clinical sites. All randomized subjects completed the study. Study medication was administered by study team members while the subjects were in the sleep laboratory, and thus treatment compliance was 100%.

Polysomnography

The primary efficacy measure in the present study was latency to persistent sleep determined from the PSG record (time to the first 20 epochs of nonwake). Analysis

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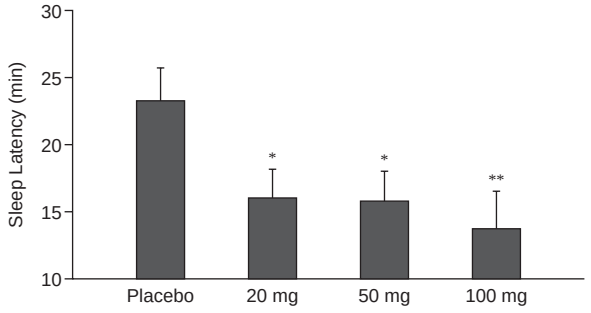
Table 1. Effect of β-Methyl-6-Chloromelatonin on Sleep Performance as Measured by Polysomnography (PSG) in a Randomized Crossover Study[a,b]

PSG Sleep Variable	Dose (mg)	Geometric Mean	95% Confidence Limits	p Value
Latency to				.0003[a]
persistent	0	23.2	18.3 to 29.3	
sleep (min)	20	16.0	12.6 to 20.2	.0082
	50	15.8	12.5 to 20.0	.0062
	100	13.7	10.8 to 17.3	< .0001
Wake after				.0753
persistent	0	32.2	26.0 to 40.0	
sleep (min)	20	38.7	31.2 to 47.9	
	50	37.4	30.2 to 46.4	
	100	39.9	32.1 to 49.5	
Total sleep				.5439
time (min)	0	402.8	390.2 to 415.8	
	20	410.8	398.0 to 424.1	
	50	403.8	391.1 to 416.8	
	100	409.2	396.4 to 422.4	
Sleep efficiency				.5095
(%)	0	83.8	81.2 to 86.5	
	20	85.5	82.8 to 88.3	
	50	84.0	81.4 to 86.7	
	100	85.2	82.5 to 88.0	
Time in stage 1				.6461
(min)	0	40.4	35.9 to 45.5	
	20	41.1	36.5 to 46.2	
	50	42.4	37.7 to 47.7	
	100	40.8	36.3 to 45.9	
Time in stage 2				.1999
(min)	0	234.3	222.8 to 246.4	
	20	242.4	230.5 to 255.0	
	50	241.2	229.4 to 253.7	
	100	244.8	232.7 to 257.5	
Time in stages				.1259
3 and 4 (min)	0	14.7	9.4 to 23.0	
	20	11.6	7.4 to 18.1	
	50	13.7	8.8 to 21.4	
	100	15.2	9.7 to 23.6	
REM duration				.2260
(min)	0	87.5	79.9 to 95.9	
	20	91.2	83.2 to 99.9	
	50	82.4	75.2 to 90.3	
	100	86.4	78.8 to 94.7	
REM latency				.8267
(min)	0	67.3	58.5 to 77.4	
	20	65.5	56.9 to 75.3	
	50	66.9	58.2 to 76.9	
	100	69.9	60.8 to 80.3	
Wake time				.9107
(min)	0	60.5	51.1 to 71.6	
	20	57.8	48.8 to 68.4	
	50	58.6	49.5 to 69.3	
	100	57.6	48.6 to 68.2	

[a]Result of overall repeated-measures analysis of variance. p Values associated with individual drug doses refer to drug versus placebo statistical comparisons.
[b]N = 40 all doses.
Abbreviation: REM = rapid eye movement sleep.

revealed a significant overall effect of β-methyl-6-chloromelatonin dose on latency to persistent sleep (p = .0003; Table 1 and Figure 2). At the 20-mg β-methyl-6-chloromelatonin dose, latency to persistent sleep decreased 31% compared with placebo treatment, which was highly significant (p = .0082). A similar 32% improvement in latency to persistent sleep was observed at the 50-mg

Figure 2. Effect of β-Methyl-6-Chloromelatonin on Sleep Latency Determined by Polysomnography in Subjects With Primary Insomnia[a,b]



[a]Values are mean and SD of log-transformed sleep latencies.
[b]N = 40 all doses.
*p < .01.
**p < .0001.

Table 2. Effect of β-Methyl-6-Chloromelatonin on Subjective Evaluation of Time to Fall Asleep in a Randomized Crossover Study[a]

	Time to Fall Asleep (min)		
Dose (mg)	Mean	SD	p Value[b]
0	39.9375	25.1514	
20	34.7250	22.9900	.0582
50	34.1250	21.9576	.0350
100	33.5000	18.0260	.0198

[a]N = 40 all doses.
[b]The overall repeated-measures analysis of variance resulted in a p value of .0050. p Values for each dosage amount are results of drug versus placebo comparisons.

β-methyl-6-chloromelatonin dose (p = .0062). At the 100-mg β-methyl-6-chloromelatonin dose, a 41% improvement in latency to persistent sleep was observed, which was also highly significant (p < .0001). No significant effect of β-methyl-6-chloromelatonin on other PSG variables was observed (Table 1).

Subjective Sleep Measures and Psychomotor Performance

Subjective sleep latency assessed on the morning after β-methyl-6-chloromelatonin administration paralleled the results observed for PSG sleep latency (Table 2). Subjects' subjective assessments of time to fall asleep the previous night were significantly lower in the drug-treatment groups compared with placebo (p = .0050). Perceived time to fall asleep was significantly lower at both the 50-mg and 100-mg doses (p = .0350 and p = .0198, respectively), while a trend toward significance was observed at the 20-mg dose (p = .0582). No significant drug effects were observed on other subjective measures of sleep performance (sleep duration, number of wakenings, time awake, difficulty falling asleep again, and overall quality and restorative nature of the sleep). Psychomotor

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Table 3. Effect of β-Methyl-6-Chloromelatonin on Psychomotor Assessments Performed the Morning After Treatment in a Randomized Crossover Study[a]

		Number Correct		
Psychomotor Test	Dose (mg)	Mean	SD	p Value[b]
Digit Symbol Substitution Test				.6523
	0	65.6875	13.0380	
	20	67.5375	13.9728	
	50	64.9500	14.2969	
	100	65.4375	13.5468	
Symbol Copy Test				.2862
	0	126.6500	28.4654	
	20	128.1125	27.1204	
	50	128.0750	30.1476	
	100	125.2625	26.9875	

[a]N = 40 all doses.
[b]Drug versus placebo.

Table 4. Number of Patients Experiencing an Adverse Event (AE) by Body System and COSTART Designation at Each β-Methyl-6-Chloromelatonin Dose[a,b]

Body System	AE Code	Placebo, N (%)	20 mg, N (%)	50 mg, N (%)	100 mg, N (%)
Digestive	Nausea	2 (5)	2 (5)	2 (5)	1 (2.5)
	Diarrhea	1 (2.5)	0 (0)	0 (0)	1 (2.5)
Body as a whole	Headache	2 (5)	1 (2.5)	0 (0)	3 (7.5)
Respiratory	Rhinitis	0 (0)	1 (2.5)	1 (2.5)	0 (0)
	Pharyngitis	0 (0)	0 (0)	1 (2.5)	1 (2.5)
Special senses	Amblyopia	1 (2.5)	1 (2.5)	0 (0)	0 (0)

[a]Adverse events shown are all those (both drug-related and non–drug-related) with an incidence ≥ 5%. Adverse events that occur more than once for a particular subject at a particular dose are counted 1 time.
[b]N = 40 all doses. The same 40 patients were crossed over in random fashion to each treatment.
Abbreviation: COSTART = Coding Symbols for a Thesaurus of Adverse Reaction Terms.

testing the morning after β-methyl-6-chloromelatonin administration revealed no significant difference between drug and placebo treatments (Table 3).

Safety

No subject deaths or other serious adverse events occurred during this study. Overall, 40 subjects were exposed to 320 doses of study drug. Seventeen subjects experienced a total of 35 adverse events. All adverse events were mild to moderate in severity; there were no severe adverse events. The frequency and severity of adverse events did not differ as a function of β-methyl-6-chloromelatonin dose and were similar to placebo for all doses of β-methyl-6-chloromelatonin. Adverse events that occurred in 5% or more of the subject population are displayed by body system and Coding Symbols for a Thesaurus of Adverse Reaction Terms[25] in Table 4 as a function of study drug dose.

DISCUSSION

The present study demonstrates that β-methyl-6-chloromelatonin significantly reduces latency to persistent sleep compared with placebo. Not only was the overall comparison of β-methyl-6-chloromelatonin with placebo highly significant for the primary efficacy variable, but all the individual dose comparisons were also highly significant. This included the 31%, 32%, and 41% improvement in sleep latency observed at 20-mg, 50-mg, and 100-mg β-methyl-6-chloromelatonin doses, respectively. These results are consistent with those of a prior pilot study examining 5-mg and 20-mg β-methyl-6-chloromelatonin doses.[10] In that study, the 5-mg dose produced a nonsignificant 16% reduction in sleep latency, while the 20-mg dose produced a significant 38% reduction in sleep latency. Taken together, these studies indicate that β-methyl-6-chloromelatonin produces a dose-response–related decrease in sleep latency over a dose range of 5 mg to 100 mg. The 41% reduction in latency observed with the 100-mg β-methyl-6-chloromelatonin dose is comparable to that produced by the widely used omega benzodiazepine zolpidem when used at approved doses.[13] These observations suggest that β-methyl-6-chloromelatonin may be a clinically effective treatment for individuals with primary insomnia.

The effect of β-methyl-6-chloromelatonin on subjective reports of time to fall asleep paralleled its effect on PSG-determined sleep latency. The overall comparison of β-methyl-6-chloromelatonin versus placebo on this secondary efficacy measure was significant. Individual comparisons revealed that both the 50-mg and 100-mg β-methyl-6-chloromelatonin doses significantly decreased subjects' perceived time to fall asleep, with a trend toward improvement at the 20-mg dose (p = .0582). Subjective time to fall asleep is an important dimension, as individuals are more likely to be compliant with a drug that produces a perceived improvement in sleep performance.

While significant improvement was observed for the primary PSG outcome measure, latency to persistent sleep, no significant β-methyl-6-chloromelatonin effects were observed on the secondary outcome PSG measures nor on subjective sleep measures other than time to fall asleep. One possible reason for this may have been that study subjects were selected for problems with sleep onset and not sleep maintenance. For example, subjects' performance in the present study on PSG sleep maintenance measures was similar to that reported for normal subjects.[14,15] Therefore, the potential effect of β-methyl-6-chloromelatonin on sleep maintenance may not have been observed due to a "floor" effect. An additional implication of the present PSG data is that β-methyl-6-chloromelatonin does not disrupt sleep architecture at doses up to 100 mg, as no β-methyl-6-chloromelatonin effect was observed on any sleep stage or REM measures.

Evaluations performed upon waking the morning after taking β-methyl-6-chloromelatonin revealed no significant changes in psychomotor performance at any drug dose. This suggests that β-methyl-6-chloromelatonin used

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at doses up to 100 mg lacks the morning-after psychomotor impairment associated with many sleep medications.[16–18] Adverse event and other safety analyses showed similar frequency and severity across all doses of β-methyl-6-chloromelatonin as well as placebo. Therefore, β-methyl-6-chloromelatonin appears to be safe and well tolerated at doses up to 100 mg when acutely administered.

The purpose of the present study was to determine if treatment with a melatonin agonist has a direct soporific effect in subjects with primary insomnia. In order to address this question, the present study employed acute β-methyl-6-chloromelatonin administration. Many prior studies have administered melatonin agonists over 1 to 3 weeks.[19–22] It is difficult to distinguish soporific effects from circadian rhythm effects of a melatonin agonist when administered chronically. When only acute melatonin agonist studies are considered, the evidence for a direct soporific effect is equivocal. For example, Attenburrow et al.[3] found that acute administration of 0.3 mg or 1 mg of melatonin had no effect on sleep latency in healthy subjects with no history of insomnia. Similarly, James et al.[4] found no significant effect of 1 or 5 mg of melatonin on sleep latency in young adults with no evidence of a sleep disorder. Zhdanova et al.[5] reported a significant effect of 0.3 mg or 1.0 mg of melatonin on sleep latency in normal young subjects without a sleep disorder. Waldhauser et al.[6] found that 80 mg of melatonin produced a significant decrease in sleep latency in young healthy adults with no evidence of a sleep disorder. While these studies represent those published on the acute effect of melatonin agonists on sleep onset, they do not address the present study's hypothesis because none of these studies were performed in subjects with primary insomnia.

There is only 1 brief published report[23] of the acute effect of a melatonin agonist on sleep onset in subjects with primary insomnia. This abstract reported the effects of the melatonin agonist TAK-375 on sleep parameters in subjects with primary insomnia.[23] A significant overall effect of TAK-375 (4 mg, 8 mg, 16 mg, and 32 mg) was observed on PSG sleep latency, whereas no significant overall effect on subjective time to fall asleep occurred. TAK-375 and β-methyl-6-chloromelatonin differ in that TAK-375 is a selective MT1 agonist while β-methyl-6-chloromelatonin demonstrates high affinity for both MT1 and MT2 melatonin receptors.[10,23] The present results in combination with the TAK-375 study suggest that MT1 receptor activation is sufficient for PSG sleep induction, whereas activation of MT1 and MT2 receptors is required for subjective sleep induction.

Side effects are a serious complication in determining whether melatonin agonists have a direct rather than an indirect soporific effect. Melatonin produces hypothermia, bradycardia, and decreased blood pressure at doses greater than 1 mg.[7,8,24] Some authors suggest that the soporific effect of melatonin is secondary to melatonin's hypothermic effect. For example, Gilbert et al.[24] demonstrated that a single 5-mg dose of melatonin produced a significant decrease in core body temperature, heart rate, and sleep latency. Statistical analysis revealed that, within subjects, the decrease in core body temperature and sleep latency were correlated, leading the authors to suggest that melatonin's soporific effect may be secondary to its hypothermic effect.

The present study is the first that suggests that melatonin agonists may exert a direct soporific effect. Previous studies[10,11] indicate that β-methyl-6-chloromelatonin does not demonstrate the major side effects of melatonin. In these studies, β-methyl-6-chloromelatonin did not decrease body temperature, did not decrease heart rate, and did not decrease blood pressure when used at doses up to 100 mg. Therefore, the soporific effect of β-methyl-6-chloromelatonin demonstrated in the present study would appear to be a direct effect of β-methyl-6-chloromelatonin on sleep latency and not a secondary effect due to drug-induced hypothermia, bradycardia, and hypotension.

The present study has several limitations. The size of the randomized subject population was limited, and the inclusion criteria focused on sleep onset insomnia. Although β-methyl-6-chloromelatonin appears to have no significant effect on body temperature, heart rate, or blood pressure, other unknown effects may have mediated β-methyl-6-chloromelatonin's observed effect on objective and subjective sleep measures. Further studies enrolling a larger subject population and employing a chronic dose regimen are required to better understand the soporific effects of β-methyl-6-chloromelatonin.

In summary, the present study provides evidence that β-methyl-6-chloromelatonin is a safe and effective treatment for reducing sleep latency in subjects with primary insomnia. The reported absence of a significant effect of β-methyl-6-chloromelatonin on body temperature, heart rate, or blood pressure suggests that these melatonin-associated side effects did not mediate β-methyl-6-chloromelatonin's soporific effects observed in the present study and that β-methyl-6-chloromelatonin may have a direct soporific effect.

Drug name: zolpidem (Ambien).

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