

Sedating Effects of AM/PM Antihistamine Dosing with Evening Chlorpheniramine and Morning Terfenadine

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Abstract

To save costs, some healthcare providers advocate a treatment plan for allergic rhinitis that combines sedating and nonsedating antihistamines. This AM/PM dosing includes an over-the-counter (OTC) sedating antihistamine in the evening and a prescription nonsedating antihistamine in the morning. We investigated the potential carryover sedation effects of the OTC antihistamine on daytime alertness in 29 healthy volunteers over 7 days. Treatment groups included: PM dose of chlorpheniramine 12 mg with AM dose of terfenadine 60 mg (CP12/TF, n=9), PM dose of chlorpheniramine 8 mg with AM dose of terfenadine 60 mg (CP8/TF, n=9), and placebo morning and evening (n=11). Multiple Sleep Latency Test and Stanford Sleepiness Scale test results showed that the AM/PM dosing regimen increased daytime sleepiness and decreased alertness. These effects were more pronounced and prolonged in participants who received the higher CP dose. Those who received AM/PM dosing also demonstrated a carryover sedation effect; they fell asleep more quickly and described themselves as less able to concentrate during the following day compared with placebo subjects.

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An estimated 22% of Americans suffer from allergic rhinitis, making antihistamines (H₁-receptor antagonists) one of the most widely used class of drugs. Sedating antihistamines (eg, chlorpheniramine maleate and diphenhydramine HCl) are not selective

for the H₁-receptor site. They readily cross the blood-brain barrier and tend to induce dopaminergic, serotonergic, and cholinergic responses, causing significant central nervous system (CNS) adverse effects. In contrast, the newer, generally nonsedating antihistamines (eg, loratadine, terfenadine, astemizole, and fexofenadine) achieve peripheral H₁-receptor blockade without CNS effects. These medications do not carry labels warning of drowsiness or the need to use caution when driving or operating machinery.

To save costs, some healthcare providers recommend placing patients on an over-the-counter sedating antihistamine at night and a prescription nonsedating antihistamine in the morning. The rationale for this AM/PM dosing regimen is that the sedative effects of the sedating antihistamine are presumed to be limited to the hours of sleep, and that the patient will not experience sedation while awake.

However, no efficacy and safety data exist to support this practice, and DuBuske has recommended against AM/PM dosing until further safety and efficacy studies are conducted.¹ A particular concern is that the CNS depressant effects from the evening dose may carry over to the following day. Sedating antihistamines are known to cause adverse effects such as sleepiness,² diminished learning performance in children,³ decreased driving safety,⁴ mood and motivation alterations,⁵ diminished performance of clerical tasks,⁶ and altered cognitive functions such as divided attention, working memory, and vigilance.⁵ There are also subjective reports of drowsiness the morning after evening use of a sedating antihistamine.⁷ Carryover effects are most likely due to the long half-lives of sedating antihistamines; the mean elimination half-lives of chlorpheniramine, brompheniramine maleate, and hydroxyzine HCl are 24.2, 24.9, and 20 hours, respectively.⁸

We investigated the carryover effects of AM/PM dosing on daytime sleepiness and level of alertness.

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... METHODS ...

We screened all participants with a brief medical history, physical examination, and laboratory tests including a drug abuse screen, liver enzyme, urea nitrate, and creatinine tests. Subjects were required to be in good general physical health, could not be pregnant (ie, confirmed by negative serum β -hCG test), and could not have known sensitivity to the study drugs. Participants had to be free of allergies at the time of the study and had no sleep or neurological disorders. Subjects with a history of a serious medical illness, asthma, or substance abuse in the year prior to the study were excluded. The Investigational Review Board of Georgetown University School of Medicine approved the protocol, and we obtained written informed consent from each participant.

Subjects were assigned randomly, in a double-blind fashion, to one of three parallel treatment groups: evening (10:00 PM) dose of 12 mg chlorpheniramine (CP) plus morning (7:30 AM) dose of 60 mg terfenadine (TF); evening dose of 8 mg CP plus morning dose of 60 mg terfenadine (TF); or morning plus evening placebo doses. Blinded drug treatments were in blister pack cards that appeared identical and were labeled by dosing day and subject number.

Subjects arrived at the test site at 6:30 PM on day 1, and we conducted a nocturnal polysomnogram according to the guidelines of the American Society of Sleep Centers in our accredited sleep center. Placebo was administered to all subjects at 10:00 PM. Subjects were prohibited from the use of alcohol, illicit drugs, or any medication other than aspirin or acetaminophen 48 hours prior to and during the study.

On day 1, a board certified polysomnographer reviewed results from the prior night's polysomnogram. Polysomnograms were considered abnormal and subjects were excluded if their scores surpassed threshold levels for any of eight parameters (ie, sleep efficiency, latency of sleep onset, apnea, and hypopnea index). Participants with normal nocturnal polysomnograms were randomized and remained in the study. Placebo was administered to all subjects at 7:30 AM. Baseline test procedures were conducted during the remainder of day 1. At 10:00 PM on day 1, subjects received CP-8 mg, CP-12 mg, or placebo and slept in Georgetown University's Clinical Research Center.

We repeated the final sleep latency test period on day 2. Subjects were instructed to resume their normal activities, and they were reminded to take their study medications according to schedule. They were instructed to keep a diary of the times they took medications and any adverse events. Subjects were also instructed to return to the sleep center on day 4 at 7:30 PM with their study medication packs and completed diaries. Scalp electrodes were attached and subjects slept at the Clinical Research Center that evening. The following morning and afternoon (day 5), we repeated the baseline (day 1) study procedures. At 6:00 PM, electrodes were removed, subjects were questioned about adverse events and concomitant medication use, and then dismissed.

... TEST PROCEDURES ...

Multiple Sleep Latency Test (days 1, 2, and 5)

We used an objective physiological measure of sleepiness, the Multiple Sleep Latency Test (MSLT), to assess daytime sleepiness. The MSLT is a common diagnostic tool used in sleep disorder clinics and is accepted internationally for quantifying daytime sleepiness after drug treatment, including antihistamines.⁹ The sensitivity of the MSLT to carryover effects of evening doses of medication has been demonstrated with benzodiazapene hypnotics.¹⁰

We conducted the MSLT according to the guidelines of the American Society of Polysomnographers in Georgetown University's accredited sleep center. The only non-standard aspect of the MSLT procedure was discontinuation of nap periods after 15 minutes of continuous wakefulness, rather than 20 minutes. Testing began approximately 2 hours after awakening, with naps at 9:30 AM, 11:30 AM, 1:30 PM, 3:30 PM, and 5:30 PM. Subjects were instructed to recline on their bed,

Table 1 Standard Sleepiness Scale Ratings

1. Feeling active and vital
2. Functioning at a high level, but not at peak; able to concentrate
3. Feeling relaxed, awake, responsive, but not at full alertness
4. Feeling a little foggy, let down, not at peak
5. Feeling foggy, slowed down, beginning to lose interest in remaining awake
6. Feeling sleepy, woozy, prefer to be lying down, fighting sleep
7. Feeling sleep onset coming on, losing struggle to remain awake

relax, and try to fall asleep. Electroencephalogram (EEG) was recorded and the session ended when the subject either fell asleep according to standard EEG criteria or after 15 minutes if no sleep was observed.

Stanford Sleepiness Scale (days 1, 2, and 5)

We also administered the Stanford Sleepiness Scale,¹¹ a measure of subjective sleepiness and alertness, at 8:30 AM and at 2:30 PM. The Stanford Sleepiness Scale is a 7-point self-report measure used to assess subjective sleepiness and level of alertness (Table 1). Subjects were instructed to select the statement best reflecting their current level of sleepiness.

Adverse Events

We questioned participants about health problems, and they maintained a diary throughout the study. All adverse events were recorded by the physician investigator (K.E.P.), who evaluated the relationship between the event and the study drug.

Statistical Analysis

MSLT results were analyzed by analysis of variance using daily average sleep latency values. Categorical demographic variables were analyzed with Fisher's exact test. The Kruskal-Wallis and Wilcoxon 2 sample tests were used to evaluate overall and pairwise differences, respectively, between treatment groups for the Stanford Sleepiness Scale.

sleep latencies for all treatment groups at baseline (day 1) reflect mild daytime sleepiness. We believe the cause of this mild daytime sleepiness to be related to the novelty and discomfort of having undergone a polysomnogram in the hospital on the night prior to baseline MSLT testing. There were no differences between treatment groups on day 1.

On days 2 and 5, subjects in the placebo group had normal sleep onset latencies (Figure 1). In contrast, subjects who received either regimen of CP/TF the previous evenings exhibited increased daytime sleepiness on day 2 ($P \leq 0.05$). Subjects who received CP 8 mg had a mean sleep onset of 6.33 minutes, and those who received CP 12 mg had a mean sleep onset of 6.87 minutes. These sleep onset latencies were significantly shorter than the mean latency for the placebo group (10.89 minutes) ($P = 0.003$ for CP 8 mg and $P = 0.007$ for CP 12 mg).

Day 5 results show that subjects who received CP 8 mg had sleep latencies just within normal limits (10 minutes). In contrast, subjects who received CP 12 mg continued to demonstrate mild but abnormal daytime sleepiness (8 minutes). Pairwise comparisons demonstrate a statistically significant difference between subjects who received CP 12 mg and those who received placebo ($P = 0.03$).

Daytime sleepiness (mean sleep latency onset values ≤ 10 minutes) occurred more frequently in CP patients. On day 2, 36% of placebo subjects had mean sleep onset latencies < 10 minutes. By comparison,

... RESULTS ...

Demographic Variables

Three volunteers were excluded because of sleep apnea, insomnia, and periodic leg movements, respectively. Twenty-nine patients (25-47 years of age) were randomized into the study and completed at least one post-baseline day. Demographic variables for the three treatment groups are presented in Table 2. There were no significant differences between the three groups for any of the demographic variables.

Multiple Sleep Latency Test

Table 3 shows the MSLT results. Values > 10 minutes are considered to reflect normal daytime sleepiness.¹² Mean

Table 2. Demographic Characteristics

	Placebo	CP 8 mg	CP 12 mg
Number of Subjects	11	9	9
Mean Age in Years (SD)	34.6 (± 5.6)	33.0 (± 3.4)	35.9 (± 5.9)
Sex (%)			
Male	3 (27)	2 (22)	5 (56)
Female	8 (73)	7 (78)	4 (44)
Race (%)			
Caucasian	7 (64)	6 (67)	6 (67)
African American	4 (36)	3 (33)	3 (33)
Mean Weight in Pounds (SD)	162.2 (± 39.55)	162.3 (± 33.97)	169.3 (± 40.05)

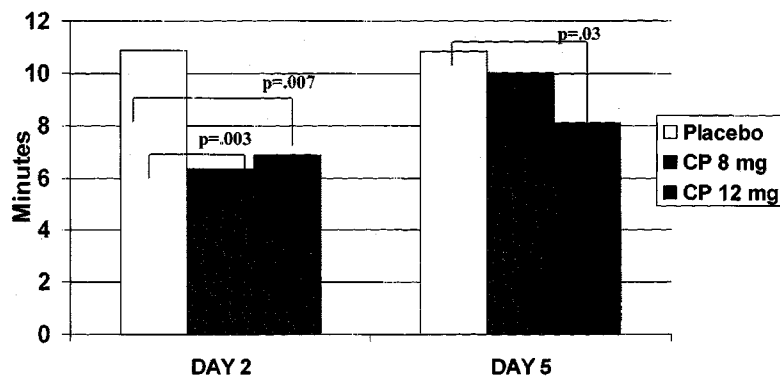
No significant between-group differences. Fisher's Exact Test was used to compare sex and race. One-way analysis of variance (ANOVA) was used to compare age and weight. CP = chlorpheniramine maleate.

Table 3. Mean Sleep Latency Test Values (SD)

	9:30 AM	11:30 AM	1:30 PM	3:30 PM	5:30 PM	Mean
Day 1						
Placebo	10.82 (±4.98)	10.82 (±4.85)	5.55 (±4.03)	7.27 (±5.2)	11.45 (±4.5)	9.18 (±3.72)
CP 8 mg/TF	7.67 (±3.39)	9.33 (±4.74)	6.67 (±5.24)	5.67 (±4.44)	7.89 (±5.04)	7.44 (±3.86)
CP 12 mg/TF	9.67 (±5.07)	9.67 (±3.5)	7.13 (±3.6)	7.44 (±4.16)	8.56 (±4.48)	8.44 (±3.33)
Day 2						
Placebo	10.45 (±4.34)	11.73 (±4.69)	8.55 (±4.87)	10.45 (±5.73)	13.27 (±2.53)	10.89 (±3.13)
CP 8 mg/TF	5.67 (±3.84)	7.22 (±2.59)	3.89 (±1.54)	4.11 (±2.76)	10.78 (±3.73)	6.33 (±2.48)
CP 12 mg/TF	6.89 (±4.83)	7.11 (±4.23)	5.44 (±3.84)	6.00 (±3.67)	8.88 (±4.88)	6.87 (±3.44)
Day 5						
Placebo	10.40 (±4.93)	12.40 (±3.24)	7.20 (±3.71)	10.10 (±4.23)	14.10 (±1.91)	10.84 (±2.17)
CP 8 mg/TF	12.33 (±3.71)	11.00 (±4.72)	6.78 (±4.82)	8.67 (±4.69)	11.44 (±4.13)	10.04 (±2.42)
CP 12 mg/TF	6.67 (±3.57)	8.33 (±4.3)	7.22 (±5.19)	6.00 (±3.91)	12.22 (±3.19)	8.09 (±3.07)

CP = chlorpheniramine maleate.

Figure 1. Multiple Sleep Latency Test Findings for Days 2 and 5: Mean Sleep Latencies by Treatment Group*



*One-way analysis of variance was used to compare sleep latencies. CP = chlorpheniramine maleate.

88% of subjects who received the 8 mg dose and 88% of subjects who received the 12 mg dose of CP/TF on day 2 had mean sleep onset latencies <10 minutes. On day 5, 30% of placebo subjects, compared with 44% of the 8 mg CP subjects and 88% of the 12 mg CP sub-

jects, had mean sleep onset latencies <10 minutes (Figure 2).

Stanford Sleepiness Scale

There were no between-group differences in the Stanford Sleepiness Scale results at baseline. Analyses of the morning scores for days 2 and 5 (Figure 3) indicate that there were statistically significant differences between the sleepiness ratings of CP 12 mg subjects and placebo-treated subjects on day 2 ($P = 0.015$) and day 5 ($P = 0.004$). Responses to the sleepiness scale suggest a dose relationship between the evening CP dose and self-reported sleepiness.

Adverse Events

The incidence of adverse events was similar across treatment groups. Adverse events occurred in 60% of CP 8 mg and 12 mg subjects

and in 64% of placebo subjects. The most frequently reported adverse event was headache (CP 8 mg = 30%; CP 12 mg = 40%; placebo = 36%). No participant discontinued the study due to adverse events.

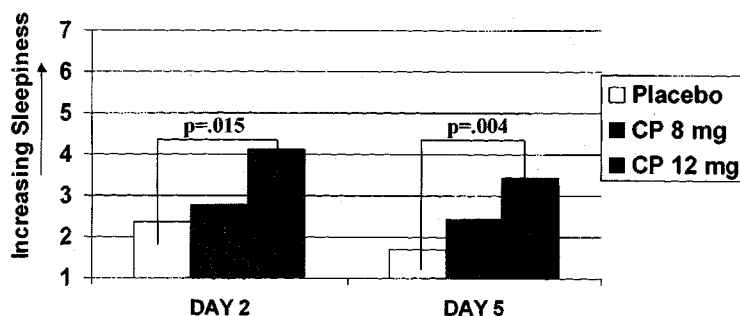
... DISCUSSION ...

AM/PM antihistamine dosing significantly influenced daytime sleepiness and level of alertness. Subjects who received evening doses of CP in combination with morning doses of TF fell asleep more quickly during the following day and described themselves as feeling less alert and less able to concentrate than placebo patients. Even after 4 nights of antihistamine dosing, a significantly higher proportion of patients receiving CP, especially those receiving the higher dose, had abnormal daytime sleepiness compared with placebo patients. These results demonstrate that the CNS depressant effects of evening administration of a sedating antihistamine persist throughout the following day and are still evident after 4 days of continuous AM/PM dosing.

One might expect the adverse effects of AM/PM dosing to diminish or disappear with continuous dosing due to tolerance. While this study only partially addresses this issue, our results suggest that carryover sleepiness may diminish with time only in some patients, especially in those receiving lower doses of the sedating antihistamine. After 4 nights of continuous AM/PM dosing, subjects receiving CP 8 mg demonstrated normal daytime sleepiness on MSLT testing, although 44% of the subjects in this group still had sleep latencies at levels considered clinically abnormal.

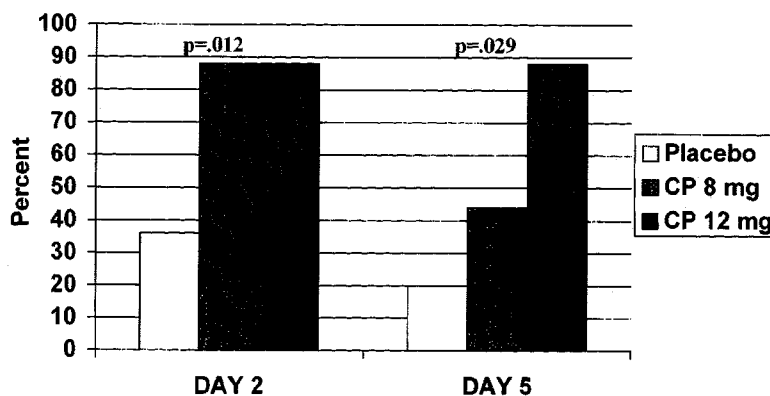
Several factors suggest that a high level of tolerance will not develop. First, we did

Figure 2. Percent of Subjects with Mean Sleep Onset Latency <10 Minutes on Days 2 and 5 by Treatment Group*



*Chi Square tests were used to compare percent of subjects in each treatment group with sleep onset latency less than 10 minutes.
CP = chlorpheniramine maleate.

Figure 3. Stanford Sleepiness Scale Results for Days 2 and 5 (AM): Mean Sleepiness Rating by Treatment Group*



*Wilcoxon 2-sample test was used to compare sleep ratings of CP groups with placebo group
CP = chlorpheniramine maleate

not observe tolerance-like effects among patients receiving the 12 mg dose. Second, poor compliance with sedating antihistamines¹ is likely to interfere with the development of tolerance. Compliance with sedating antihistamines is presumed to be poor because patients want to avoid drowsiness, lightheadedness, and anticholinergic effects of these medications.⁷

This study did have some limitations. First, since we did not have a treatment group receiving nighttime CP and daytime placebo, we cannot attribute all adverse CNS depressant effects to CP. However, it is unlikely that TF contributed to CNS depressant effects; numerous studies with TF have shown no association with impairment of psychomotor performance¹² or increased daytime sleepiness.¹³ Second, the sample size was not sufficient for analysis of treatment group differences at individual sleep latency tests. Third, as stated earlier, fatigue experienced by subjects on day 1 appeared to be the result of the polysomnogram conducted the previous evening and appeared to be responsible for greater than expected daytime sleepiness at baseline. As a result, change-from-baseline comparisons did not provide expected contrasts. Finally, since the subject sample was limited to healthy, allergy-free subjects without sleep disorders, the impact of the carryover sedation effect may be underestimated. Sedation effects are likely to be even greater on the elderly, on patients with sleep disorders, and on other individuals who are not well rested.

In sum, our findings suggest that AM/PM dosing can result in decreased alertness and increased daytime sleepiness. Patients often do not recognize their level of sedation from sedating antihistamines. This is exemplified by the marked incongruity between self-reported sleepiness and sleep latency results for the CP8 group after the first night of AM-PM dosing. As a result, patients may fail to take necessary safety precautions and place themselves at an increased risk for traumatic work related injuries,¹⁴ poor school and work performance,^{3,6} and increased risk of impaired driving.⁴

Although an AM/PM dosing regimen can result in cost advantages, managed care organizations and prescribing physicians need to seriously weigh the potential disadvantages and risks of this regimen. The adverse safety consequences that could result from the levels of sleepiness demonstrated in this study may be significant, and the societal and personal costs associated with these safety risks may outweigh the apparent cost savings of AM/PM dosing.

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