

Sleepiness and performance during three-day administration of cetirizine or diphenhydramine

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Objective: *The sedative effects of cetirizine (10 mg once daily), diphenhydramine (50 mg three times daily), and placebo, each administered during a 3-day period, were compared with objective measures of sleepiness and performance.*

Methods: *Twelve atopic subjects received each of the three treatments for 3 consecutive days in a double-blind Latin square design. Subjects received either cetirizine at 8:00 AM and placebo at 3:00 PM and 10:00 PM; diphenhydramine at 8:00 AM, 3:00 PM, and 10:00 PM; or placebo at all three times. Sleepiness was measured on days 1 and 3 with the multiple sleep latency test at 9:00 AM, 11:00 AM, 1:00 PM, 3:00 PM, and 5:00 PM. Performance was assessed with a 60-minute simulated assembly line task at 9:30 AM, 11:30 AM, 1:30 PM, and 3:30 PM. Nightly sleep duration was estimated with actigraphy.*

Results: *Compared with placebo and cetirizine, diphenhydramine produced marked impairment only on the first day of drug administration. The multiple sleep latency test and the simulated assembly line task values remained stable across days with cetirizine and placebo but improved with diphenhydramine, resulting in no differences among the three conditions on the third day.*

Conclusion: *Unlike cetirizine, diphenhydramine produced acute impairment of alertness and performance. By the third day of administration, however, this impairment was no longer present, apparently because of development of tolerance to the sedative effects. (J ALLERGY CLIN IMMUNOL 1994;94:716-24.)*

Key words: *Sleepiness, performance, cetirizine, diphenhydramine*

The ubiquity of sleepiness in the United States, resulting from sleep disorders, sleep deprivation, central nervous system (CNS)-active medications and other factors, is detailed in the report of the National Commission on Sleep Disorders Research.¹ As the commission report details, the transportation industry provides particularly dramatic examples of the serious nature of sleepiness in society. For example, the National Transportation Safety Board estimates that 200,000 automobile accidents each year are sleep-related, and fatigue accounts for nearly one third of all fatal-to-the-driver truck accidents. Moreover, sleepi-

Abbreviations used

CNS: Central nervous system
MSLT Multiple sleep latency test
SALT: Simulated assembly line task
VAS: Visual analog scale

ness affects virtually all components of life. A variety of CNS depressant compounds contribute to the sleepiness that places individuals at risk for accidents, poor performance, and overall decreased well-being.

Until the relatively recent development of second-generation histamine (H₁) antagonists, sedation was a common side effect of antihistamine therapy. Available evidence indicates that newer drugs such as astemizole and terfenadine are significantly less sedating at therapeutic doses. Another compound that appears to have a reduced sedative effect at therapeutic doses is cetirizine. Cetirizine does not consistently increase

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subjective ratings of sleepiness,^{2,6} and a single study examining physiologic sleep tendency found an absence of sedation associated with this compound.⁷ Most studies of human performance with cetirizine show no significant decremental effect on tasks of brief,^{2, 5, 8, 9} moderate,⁷ or long¹⁰ duration, although some conflicting data exist.^{11, 12}

This study was designed to extend our knowledge of the sedating characteristics of cetirizine and the first-generation compound, diphenhydramine. Several aspects of this study differentiate it from the majority of studies of the sedating characteristics of H₁ antagonists. First, an objective physiologic measure of sleepiness was used, the multiple sleep latency test (MSLT); most studies rely on subjective reports (which are influenced by demand characteristics and environmental stimuli) or infer sleepiness from performance measures. Long-duration psychomotor performance was assessed with a simulated assembly line task (SALT), which is more likely than brief tasks to accurately represent "real world" performance in the workplace. Further, sleepiness and performance were assessed on the first and third days of drug administration, as opposed to the more typical one-time administration. Finally, all subjects were documented to be hypersensitive to an environmental allergen, because it is at least theoretically possible that atopic individuals may respond differently to the sedative properties of H₁ antagonists.

METHODS

Subjects

Twelve individuals, six men and six women with a mean age of 31.3 years (SD: 8.1 years) and a mean body weight of 184.3 lb (range, 126 to 286 lb), recruited through media advertisements, completed study participation. All participants had a history of hypersensitivity to at least one environmental allergen, which was documented by positive skin prick test results. Testing for 14 common allergens was conducted by the study investigators for 11 of the subjects within 2 weeks before entry into the study. Testing for one subject was conducted by her personal physician 1 month before study entry. On average, subjects had positive test results for 5.9 allergens (range, 1 to 12; median, 5). All subjects denied sleep difficulty and daytime sleepiness and were required to adhere to a regular sleep-wake schedule for 14 days before entry into the study. Participants were free of significant sleep disturbances as determined by a screening nocturnal polysomnogram. In addition, they were required to have a mean sleep latency greater than 5.0 minutes during a screening daytime MSLT. The mean latency for all 12 subjects was 12.6 minutes (SD, 5.5 minutes; range, 5.5 to 20.0

minutes). Other than atopy, subjects were free of medical and psychiatric disorders and were not taking CNS-active medications as determined by physical examination, laboratory analyses, and medical history. Subjects did not use antihistamines or any sedating or alerting medications for at least 14 days before randomization. None had used long-acting medications such as astemizole, flurazepam, diazepam, fluoxetine, or sertraline for at least 3 months. Individuals consuming more than six caffeinated beverages per day were excluded from the study. Female participants were accepted if they were surgically sterile, 2 years postmenopause, or using a reliable contraceptive procedure and if they were not breast-feeding. All subjects signed an informed consent form, and the experimental protocol was approved by the institutional review board.

Procedures

The study was a randomized, double-blind Latin square design, comparing cetirizine (10 mg once daily), diphenhydramine (50 mg three times daily) and placebo. Each subject participated in three 3-day treatment periods, separated by 5 to 14 days of washout (mean, 5.6 days). The two washout periods for each individual did not vary by more than 2 days, except for one subject whose washout periods varied by 7 days. Multiple sleep latency and SALT tests were conducted on days 1 and 3 of each treatment period. On day 2, participants adhered to their usual daytime activities at home but took medication as scheduled. Medications were given with a double-dummy technique three times each day, with the exception that on day 3, the last dose was omitted because testing concluded at 5:30 PM. During the cetirizine treatment period, 10 mg of cetirizine was administered at 8:00 AM and placebo was given at 3:00 PM and 10:00 PM; during the diphenhydramine treatment period, diphenhydramine was administered at 8:00 AM, 3:00 PM, and 10:00 PM; placebo was administered at all three times during the placebo condition. Subjects were instructed to maintain a regular sleep schedule, spend 8 hours in bed each night, and avoid napping, caffeine, alcohol, antihistamines, and other CNS-active medications.

The MSLT was conducted on days 1 and 3 at 9:00 AM, 11:00 AM, 1:00 PM, 3:00 PM, and 5:00 PM. The validity of the MSLT is well documented,¹³ and the procedures are standardized.¹⁴ Briefly, electrophysiologic recordings were made to identify sleep onset on five occasions during the day at 2-hour intervals. Subjects were asked to relax and allow themselves to fall asleep as they lay in a quiet, sleep-conducive environment. High levels of physiologic sleepiness result in rapid sleep onset (i.e., short sleep latencies), whereas low levels of sleepiness produce a delay in sleep onset (i.e., longer sleep latencies).

Four 60-minute SALT sessions were conducted at 9:30 AM, 11:30 AM, 1:30 PM, and 5:30 PM. The SALT is a computer-driven, continuous measure designed to be sensitive to variations in sleepiness and to have face

TABLE 1. Mean and standard deviation for the MSLT at each test time for each treatment day for the three conditions

Condition	Time					Mean
	9:00 AM	11:00 AM	1:00 PM	3:00 PM	5:00 PM	
Cetirizine						
Day 1						
Mean	9.13	5.46	5.96	6.33	10.42	7.46
SD	7.77	3.93	3.22	5.08	7.08	4.43
Day 3						
Mean	7.67	5.58	6.38	7.92	12.29	7.97
SD	6.59	6.03	6.42	6.91	7.23	5.08
Diphenhydramine						
Day 1						
Mean	7.08	3.33	4.54	5.21	7.13	5.46
SD	5.70	2.37	4.23	5.33	7.10	4.27
Day 3						
Mean	9.13	4.79	7.33	8.42	11.96	8.33
SD	6.40	5.35	5.12	4.24	6.48	4.79
Placebo						
Day 1						
Mean	7.54	4.42	6.96	8.67	11.54	7.83
SD	6.58	5.27	5.33	7.64	7.71	5.35
Day 3						
Mean	9.75	6.42	7.00	7.42	10.67	8.25
SD	7.98	5.45	4.77	5.30	8.36	5.55

validity with respect to "real world" job demands. Previous studies have shown that the SALT is sensitive to circadian changes in sleepiness throughout the night, as well as changes in sleepiness level with increased prior sleep or caffeine ingestion.¹⁵⁻¹⁷ The task involves presentation of images of electronic circuit boards that pass across a video monitor as objects might travel on an assembly line conveyor belt. Subjects perform quality control inspections on each circuit board, discarding or repairing faulty items, depending on the nature of the flaw. Subjects are also required to respond as quickly as possible to "alarms" that represent assembly line malfunctions. Four 60-minute SALT sessions were included each day in this study. Approximately 15% of the circuit boards contained one of seven possible errors. All participants were trained to a minimal criterion of 80% correct responses on the SALT during two to four training sessions, each of 2 to 5 hours in duration, within 2 weeks of randomization. Three SALT variables are reported here: (1) correct responses, the percentage of discardable or repairable boards correctly handled; (2) correction time, the mean time from appearance of a faulty board until appropriate action was taken; and (3) alarm response time, the mean time from alarm onset until operator intervention.

Subjects rated their subjective sleepiness level each day just before each of the five MSLT subtests by using

a visual analog scale (VAS). The scale consisted of a 100 mm line with one pole labeled "very sleepy" and the other labeled "very alert." Subjects also rated their overall sleepiness at the end of each treatment day. Similarly, a VAS labeled "very poorly" and "excellently" was administered at the end of each laboratory day to obtain a subjective rating of global performance on the SALT during that day.

On the 3 nights of each treatment period, beginning with the night before laboratory day 1, subjects wore a wrist activity monitor (actigraph; Ambulatory Monitoring, Inc., Ardsley, N.Y.) to estimate nocturnal sleep duration. Actigraphs were set to store movements in 1-minute periods, and data were scored with software validated in our laboratory. Actigraphs were also worn during polysomnographic screening to assess accuracy of sleep duration estimates in this group of subjects.

Data analyses

Before analysis, all variables from the SALT performance measure underwent transformations to adjust for proportions or normalize distributions. Correct response rate underwent arcsine transformation, and reciprocal transformation was applied to correction time and alarm response time. Untransformed data are presented in tables and figures for ease of understanding. All data were analyzed with repeated measures analysis of variance with factors for drug treatment, day,

time of day, and their interactions with the multivariate general linear hypothesis module of SYSTAT statistical software (SYSTAT, Inc., Evanston, Ill.). The multivariate statistics were used to assess significance. Follow-up comparisons were made when statistically appropriate.

RESULTS

The mean correct response rate for all subjects during the last 2 hours of training on the SALT was 92.0% (range, 82% to 100%). Thus subjects were performing well above the minimum criterion at the end of training. Sleep duration estimated by actigraphy did not differ significantly on any of the 3 nights under any of the conditions. Mean estimated sleep durations were 344.4 minutes (SD 94.1 minutes), 347.1 minutes (SD, 71.0 minutes), and 339.5 minutes (SD, 95.0 minutes) for the cetirizine, diphenhydramine, and placebo conditions, respectively. Comparison of total sleep time from the screening polysomnogram and actigraph-estimated sleep duration from the same night suggests that sleep durations during the study nights were somewhat higher than the actigraph estimates.

MSLT

Analyses of the MSLT revealed a significant drug by day by time of day interaction ($F(8,4) = 12.824, p < 0.013$) and a main effect for time of day ($F(4,8) = 6.036, p < 0.015$). MSLT data can be found in Table I and Fig. 1. Mean latencies for cetirizine, diphenhydramine, and placebo, respectively, were 7.5, 5.5, and 7.8 minutes on treatment day 1 and 8.0, 8.3, and 8.3 minutes on treatment day 3. On day 1, diphenhydramine produced significant sedation at 1:00 PM and 5:00 PM relative to placebo ($p < 0.05$) and at 11:00 AM ($p = 0.056$) and 1:00 PM ($p < 0.05$) compared with cetirizine. There were no differences between placebo and cetirizine on treatment day 1 and no differences among the three conditions on treatment day 3. There was a significant decrease in physiologic sleepiness during the diphenhydramine condition on treatment day 3 compared with treatment day 1 ($p < 0.05$). During both treatment days, physiologic sleepiness was maximal at 11:00 AM and generally decreased as the day progressed for all conditions.

SALT

Table II and Fig. 2 display the percent of correct responses for the three treatment conditions on

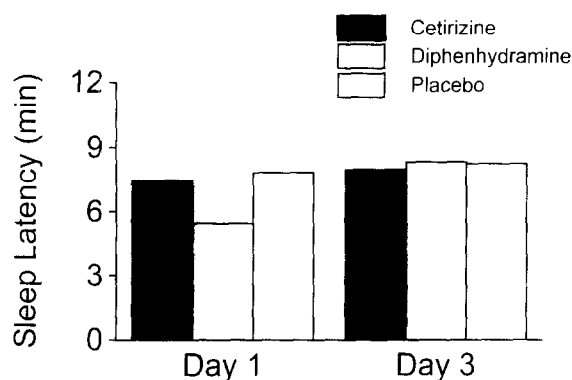


FIG. 1. MSLT. Mean sleep latency for days 1 and 3 of each treatment period.

each day. Data analysis revealed a drug by day interaction ($F(2,10) = 8.704, p < 0.006$) and a drug by day by time interaction ($F(6,6) = 5.342, p < 0.031$). There was also a main effect for day ($F(1,11) = 6.166, p < 0.030$), as well as a trend for a main drug effect ($F(2,10) = 3.94, p = 0.055$). On day 1, subjects made fewer correct responses during the diphenhydramine condition (83.1%) than during the cetirizine (87.8%) or placebo (88.9%) conditions ($p < 0.05$ for both), which did not differ from each other. On day 3, correct response rate was equivalent among the three conditions. Compared with day 1, performance improved on day 3 in the diphenhydramine condition ($p < 0.05$), whereas performance remained stable on day 3 in the other two conditions. Performance was most impaired on day 1 during the two morning test periods after diphenhydramine administration and was impaired to a lesser extent in the afternoon after the second diphenhydramine dose.

Analyses of alarm response time (Fig. 3) revealed a drug by day interaction ($F(2,10) = 14.595, p < 0.001$) and a main effect for day ($F(1,11) = 9.015, p < 0.012$). On treatment day 1, subjects responded twice as quickly to assembly line malfunctions (alarms) in the cetirizine and placebo conditions (1.3 seconds and 1.2 seconds, respectively) compared with diphenhydramine (2.6 seconds, $p < 0.05$ for both). However, response time with diphenhydramine improved on day 3 (1.7 seconds, $p < 0.05$ compared with day 1), resulting in equivalent performance for all three treatments on that day.

Subjects took approximately 1 second longer to make corrections during diphenhydramine treatment day 1 (8.2 ± 3.2 seconds) compared with cetirizine (7.4 ± 3.2 seconds) or placebo

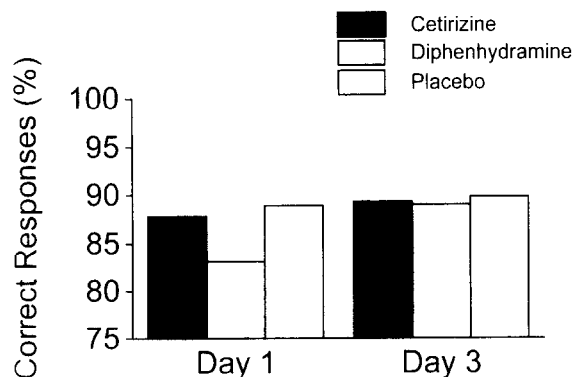


FIG. 2. SALT. Mean percent of correct responses for days 1 and 3 of each treatment period.

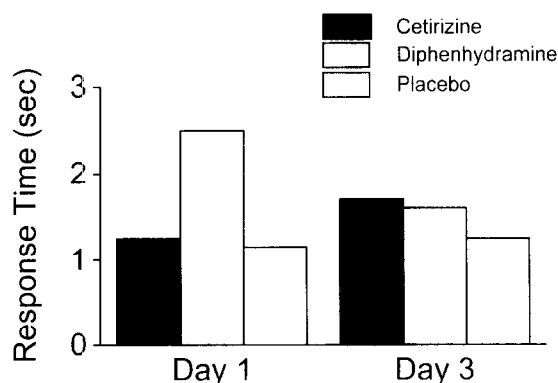


FIG. 3. SALT. Mean response time (in seconds) to alarms for days 1 and 3 of each treatment period. Subjects are required to respond as quickly as possible to alarms, which represent assembly line downtime.

TABLE II. Mean and standard deviation for the percent of correct responses on the SALT performance measure at each test period on each treatment day for the three drug conditions

Condition	Time				Mean
	9:30 AM	11:30 AM	1:30 PM	3:30 PM	
Cetirizine					
Day 1					
Mean	88.4	87.3	88.3	87.3	87.8
SD	17.8	19.2	15.3	16.1	16.9
Day 3					
Mean	88.8	89.6	88.0	90.8	89.3
SD	18.3	18.9	17.5	13.8	16.7
Diphenhydramine					
Day 1					
Mean	81.4	81.0	86.4	83.6	83.1
SD	22.4	22.5	16.3	19.6	19.2
Day 3					
Mean	89.8	88.7	89.4	88.0	89.0
SD	17.9	16.0	21.0	16.4	17.3
Placebo					
Day 1					
Mean	88.1	89.3	88.8	89.6	88.9
SD	19.5	15.1	14.0	14.8	15.4
Day 3					
Mean	92.0	89.4	88.1	89.7	89.8
SD	13.7	15.4	17.1	14.3	14.8

(7.0 ± 2.6 seconds; $p < 0.05$), with most of the difference occurring during the first two test periods. Correction time on diphenhydramine improved on day 3 (6.3 ± 2.0 seconds), with the result that no treatment differences were noted on this day (cetirizine = 6.8 ± 2.1 seconds; placebo = 6.8 ± 3.0 seconds).

VAS sleepiness ratings

Subjective VAS sleepiness ratings (Table III), obtained just before each MSLT subtest, showed significant main effects for day ($F(1,10) = 5.95$, $p < 0.035$) and time of day ($F(4,7) = 6.134$, $p < 0.019$) and approached significance for treatment ($F(2,10) = 3.647$, $p < 0.065$). Across days with diphenhydramine, subjects rated themselves

TABLE III. Mean and standard deviation (in millimeters) for the VAS for sleepiness/alertness at each test time for each treatment day for the three drug conditions

Condition	Time					Mean
	8:55 AM	10:55 AM	12:55 PM	2:55 PM	4:55 PM	
Cetirizine						
Day 1						
Mean	59.67	49.17	56.50	51.92	60.55	55.61
SD	25.64	25.78	24.99	24.65	24.66	21.13
Day 3						
Mean	63.17	55.17	58.50	51.50	59.00	57.47
SD	23.44	23.74	26.82	31.55	27.13	23.80
Diphenhydramine						
Day 1						
Mean	52.50	32.75	40.67	36.50	51.00	42.68
SD	20.89	18.31	16.41	24.41	26.31	16.32
Day 3						
Mean	55.00	47.17	55.08	56.58	58.33	54.43
SD	22.78	25.25	17.69	19.74	24.70	19.78
Placebo						
Day 1						
Mean	59.25	47.58	60.58	54.67	69.42	58.30
SD	24.44	28.64	25.03	25.04	22.83	20.48
Day 3						
Mean	70.92	55.33	63.67	46.58	74.50	62.20
SD	20.94	26.05	20.39	25.19	12.86	17.15

TABLE IV. Mean and standard deviation for the global VASs

Ratings (mm)	Cetirizine	Diphenhydramine	Placebo
Sleepiness/alertness			
Day 1	53.2 (24.2)	41.5 (21.0)	61.3 (25.8)
Day 3	51.3 (29.4)	57.2 (24.7)	59.2 (21.5)
Mean	52.3 (25.5)	49.4 (21.9)	60.3 (23.1)
Performance			
Day 1	66.7 (21.6)	54.3 (18.2)	66.8 (23.3)
Day 3	58.7 (29.0)	65.9 (21.6)	65.2 (20.1)
Mean	62.7 (24.3)	60.1 (19.0)	66.0 (20.0)

Standard deviations are given in parentheses.

as approximately 20% sleeper compared with placebo ($p < 0.05$) and approximately 14% sleeper compared with cetirizine ($p = 0.08$). Subjective ratings of sleepiness did not differ between cetirizine and placebo. Across conditions, subjects rated themselves as slightly more alert on day 3 compared with day 1. Overall, subjects judged that they were sleepest at 11:00 AM and 3:00 PM. On day 1, diphenhydramine produced significantly more subjective sleepiness than placebo at 11:00 AM, 1:00 PM, 3:00 PM, and 5:00 PM ($p < 0.05$).

Global sleepiness and performance ratings

Global ratings of sleepiness/alertness and performance at the end of each treatment day are presented in Table IV. Analyses of the global sleepiness/alertness ratings revealed a significant drug by day interaction ($F(2,8) = 7.522$, $p < 0.015$). Subjects rated themselves as being more sleepy at the end of diphenhydramine treatment day 1 (41.5) compared with cetirizine (53.2) and placebo (61.3) treatment day 1 ($p < 0.05$ for both), which did not differ from each other. On treatment day 3, there were no significant differ-

ences among the three conditions, with mean ratings of 57.2, 51.3, and 59.2 for diphenhydramine, cetirizine, and placebo, respectively. Subjects rated themselves as being significantly more alert at the end of day 3 in the diphenhydramine condition compared with treatment day 1 ($p < 0.001$), whereas alertness ratings were similar on both treatment days for cetirizine and placebo.

Global performance ratings analyses revealed a trend for a drug by day interaction ($F(2,8) = 3.559, p < 0.078$). Performance was judged to be poorer on day 1 with diphenhydramine (54.3) compared with cetirizine (66.7), $p < 0.01$ and placebo (66.8, $p = 0.083$), which did not differ from each other. Compared with day 1, performance ratings improved on day 3 with diphenhydramine ($p < 0.01$). Performance ratings during the cetirizine and placebo conditions were similar on both treatment days. There were no significant differences among the three conditions on treatment day 3.

DISCUSSION

The results of this investigation revealed that diphenhydramine produced significant sleepiness and decremental effects on performance on the first day of administration. However, this impairment had resolved by the third day. Cetirizine, on the other hand, showed no impairment on either day. All dependent measures in the cetirizine condition demonstrated stability from day 1 to day 3 and did not differ from placebo. Thus the prior observation that cetirizine is nonsedating or minimally sedating, when objective measures are used on a single day, can be extended to a 3-day period.

Our day-1 observations are consistent with published data showing significant negative CNS effects with the acute administration of diphenhydramine^{2, 18-21} but little or no sleepiness or performance impairment with the acute use of cetirizine.^{2, 5, 7-10} Furthermore, the SALT data and the global estimates of sleepiness and performance at the end of day 1 in this study were remarkably similar to the data from our earlier study with a different group of subjects.¹⁰ Correct response rates in the first and second studies, respectively, were 88.0% and 87.8% for cetirizine, and 87.8% and 88.9% for placebo.

To our knowledge, this is the first report to demonstrate amelioration of objectively measured diphenhydramine-induced sleepiness and perfor-

mance deficits. The stability of all measures from day 1 to day 3 in the placebo condition indicates that systematic learning, motivation, or other non-pharmacologic influences between day 1 and day 3 were absent. In addition, sleep duration estimates did not differ among conditions or within a condition, and no subject reported napping. Thus tolerance to the CNS effects of diphenhydramine appears to be the most probable explanation for the consistently observed increase in performance and alertness on day 3 in the diphenhydramine condition, given the pharmacokinetics of this compound. With a plasma elimination half-life of about 8 hours,²² the 50 mg three times daily dosing schedule is very likely to have produced plasma levels on day 3 that were similar to or higher than those on day 1, assuming first-order linear pharmacokinetics. Manning et al.²³ have recently presented data that are consistent with the development of tolerance to the CNS effects of diphenhydramine after 3 doses of dimenhydrinate (of which diphenhydramine is the active moiety responsible for CNS effects) ingested on a single day. Similar data exist for triprolidine, administered in repeated doses²⁴ or sustained release form.²⁵ In addition, Seppala et al.²⁶ have reported tolerance to subjectively assessed sedation with twice daily dosing of brompheniramine, carbinoxamine, and clemastine.

The sedative properties of diphenhydramine and cetirizine in the atopic subjects in this study appear to be similar to those described in studies of unselected individuals, at least during the first day of administration. Whether the change in sedative characteristics observed for diphenhydramine over the 3 days of this study represents a pharmacodynamic property of the drug in atopic persons, which differs from that in nonallergic individuals, is uncertain.

The diphenhydramine-induced impairment in performance of the SALT on day 1 became apparent about 2 hours after the first dose (during the first performance testing session). Subjective sleepiness was increased by diphenhydramine shortly thereafter, whereas the MSLT did not show significant drug effects until 3 to 5 hours after the first dose. These data are consistent with previous reports demonstrating maximal impairment with diphenhydramine 2 to 3 hours after administration.^{18, 21} SALT performance decrements persisted for at least 4 hours after the first dose of diphenhydramine and were present for at least 1 to 2 hours after the second

dose. Subjective sleepiness persisted throughout the day.

In general, irrespective of drug effects, group data indicated that performance was poor when sleepiness was high. However, correlations between mean MSLT and mean SALT performance measures were not consistently high. These correlations ranged from 0.18 to 0.45, and none were statistically significant. On the other hand, subjective assessments of sleepiness and performance were highly correlated. Sixteen of the 18 correlations among ratings of mean VAS sleepiness, global sleepiness, and global performance were statistically significant. These correlations ranged from 0.49 to 0.96. These findings support results of previous studies,^{8, 27, 28} which demonstrated that the relationship between sleepiness and performance is not straightforward. The data from this study provide further support for the hypothesis that sleepiness/alertness level provides a basic capacity for performance, which is then modified by factors such as motivation and task familiarity. In our previous study¹⁰ we suggested that performance was poorest at the presumed trough of alertness. In this study we demonstrated that performance was poorest at the trough of alertness.

Although the data of this study can be interpreted as evidence of fairly rapid development of tolerance to the CNS effects of diphenhydramine when administered three times daily, the potential for impairment with diphenhydramine cannot be discounted. Because many patients do not take antihistamines on a daily basis or on a multiple-dosing schedule, sedation might be a concern with each initiation of therapy. In fact, Roehrs et al.²⁸ demonstrated objective sleepiness and performance deficit on the second day of diphenhydramine administration when a single 50 mg dose was taken each morning. In addition, in a study by Roth et al.,²⁹ MSLT data averaged over 2 days during which diphenhydramine 50 mg was administered at 8:00 AM, 12:00 PM, and 4:00 PM, revealed significant impairment compared with placebo. Further research is required to replicate our findings and to determine the dosing strategies and subject characteristics that affect the development of tolerance to the sedating effects of diphenhydramine.

In summary, these data demonstrate that diphenhydramine produces significant sleepiness and impairs performance with acute administration. Tolerance to these sedating effects developed with three times daily dosing over a 3-day

period. Cetirizine, on the other hand, did not cause increased sleepiness or performance deficits with either acute or short-term use.

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