

Evaluation of antihistamine-related daytime sleepiness

A double-blind, placebo-controlled study with terfenadine

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The daytime sleepiness potentially associated with antihistamines was evaluated by the multiple sleep latency test (MSLT) in a study comparing terfenadine with placebo. According to a double-blind, randomized, cross-over design, 12 healthy men were given either 120 mg terfenadine or placebo once daily in the morning, for 3 consecutive days with a 5-day interval. EEG-polygraphic recordings were made each study day at 9.30 and 11.30 a.m., and 1.30, 3.30, and 5.30 p.m., and the tendency to fall asleep was measured. All mean stage-I sleep latencies throughout the study failed to show any significant difference between terfenadine and placebo. Accordingly, psychomotor performance assessed by visual and auditory reaction time did not change after treatment. The results of this study confirmed that terfenadine does not induce daytime sleepiness as objectively measured by MSLT.

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The introduction of second-generation antihistamines in the treatment of allergic diseases has dramatically lessened the incidence of adverse effects associated with classic histamine H₁-receptor blockers. Comparative studies have shown that the sedation potentially induced by the so-called "nonsedating" antihistamines, such as terfenadine, did not differ from that by placebo (10). The major criticism of such studies, i.e. that data based on subjective assessment give limited indication of the potential impairment in real-life situations, has been overcome by numerous trials specifically evaluating psychomotor performance. Several tests have been used, including EEG, driving performance, reaction time, critical flicker frequency, and the visuomotor coordination test. All the currently available nonsedating antihistamines, such as terfenadine, loratadine, cetirizine, and astemizole, did not differ from placebo in that respect (1, 2, 6-9, 11, 12, 20). The recently developed multiple sleep latency test (MSLT), which objectively measures the degree of daytime sleepiness, has been used in three studies (15, 18, 19). This technique is the most commonly used to evaluate daytime sleepiness in humans, both experimentally and clinically. This method was developed at the Stanford University Sleep Research Center (3) and has probably achieved such widespread acceptance because of its simple intuitive approach to sleepiness (the sleeper one is, the faster

one falls asleep). Exhaustive series of studies have shown MSLT scores to be related to ingestion of drugs (5, 16, 17). The main advantages of this tool are the direct and objective assessment of sleepiness, the minimized sources of variance inherent in performance tests, and the simple methodology used. Overall results showed increased sleep tendency with diphenhydramine, hydroxyzine, and triprolidine, but not terfenadine, loratadine and cetirizine. Whereas the loratadine study (18) was conducted according to the most recent standardized MSLT technique, terfenadine was evaluated by a single day administration, with EEG recordings performed only during early and late daytime hours, and sleep accumulation allowed by four consecutive 60-min naps (15). In the investigators' opinion, such a procedure did not allow an absolute statement regarding the degree of sleepiness associated with the test drugs.

The aim of the present study was to evaluate by MSLT standard technique (4) the objective daytime sleepiness associated with repeated terfenadine administration in comparison with placebo.

Material and methods

Subjects

Twelve healthy men aged between 28 and 30 years (mean age 28) volunteered for the study by signing an informed consent form. The protocol was ap-

proved by the local ethics committee and conducted according to the Helsinki declaration and its subsequent amendments.

Prior to inclusion in the study all subjects underwent a physical examination, laboratory tests, and a general questionnaire regarding sleep habits. Absence of any sensitivity to antihistamine drugs in their medical history qualified subjects to enter the study. Neither alcoholic nor caffeinated beverages were allowed for at least 2 days before and during the study.

Procedure

According to a double-blind, placebo-controlled, randomized cross-over design, subjects were given for 3 consecutive days with a 5-day interval terfenadine 120 mg q.i.d. and placebo. The length of the drug administration period was based on the kinetic characteristics of the active compound, in order to ensure steady-state plasma levels, and it was judged short enough to avoid developing the tolerance to the sedation potentially associated with antihistamines.

Each study day subjects received medication in the morning in the investigator's presence. The MSLT recordings took place in our sleep laboratory unit during the 3 days of each treatment period. Only the latency tests recorded during day 2 and day 3 of drug intake were considered for analysis of results, the first day of each treatment period serving as training in the experimental conditions. Standard electroencephalograms derived from electrodes placed on F4, C4, O2, F3, C3, O1, in accordance with the 10–20 International System. Right and left electrooculograms (EOG) and submental electromyograms (EMG) were recorded during each session, starting 30 min after drug administration. At 9.30 and 11.30 a.m., and 1.30, 3.30, and 5.30 p.m. on each study day, subjects retired to a quiet, dark room, lay down on a bed, closed their eyes, and were instructed to try to sleep. The sleep latency (SL) was taken as the interval from the start of the test to the first signs of stage 1 (at least two 30-s periods).

Each recording was terminated 1 min after the first signs of stage-1 sleep or after 20 min of wakefulness.

Sleep stages were scored according to the criteria of Rechtschaffen & Kales (13). If the subject did not fall asleep during a particular recording that session was given a latency score of 20 min. Between sessions, subjects were out of bed and kept awake by the investigators' observation.

Each study day, before drug intake, subjects rated their own subjective degree of sleepiness/alertness by completing the Stanford sleepiness scale (SSS) (18). In addition, individual psychomotor perform-

ance was assessed at the same time by visual and auditory simple reaction time.

Any adverse reaction spontaneously reported by the subject throughout the study was carefully noted and followed-up. Statistical analysis of results was made by analyses of variance.

Results

Sleep latency assessed by the MSLT, and calculated as the average between the 2 days of actual recording, did not reveal any significant difference between treatments, as shown in Table 1. Separate analyses of each of the 5 latency tests throughout the study days did not demonstrate any difference between placebo and terfenadine. The shortest latencies were experienced with either terfenadine and placebo at 3.30 p.m., and in this respect they paralleled the usual daytime nadir in sleepiness (14). For both treatments, the longest sleep latency was recorded consistently at 9.30 a.m.

Table 2 presents the data of visual and auditory reaction time recorded during the 3 days of each treatment period before drug intake. No statistical difference between placebo and terfenadine was detected at any time during the study.

The self-rating of sleepiness by SSS is shown in Table 3. The subjects' self-evaluated level of sleepiness during the 3 days of each treatment demonstrated no significant difference between placebo and terfenadine, and were therefore consistent with both MSLT and reaction-time results.

Throughout the study the subjects tolerated the test compounds well, and made no complaints of adverse effects.

Discussion

The consolidated clinical experience of a greatly reduced incidence of adverse effects related to second-generation antihistamine drugs has been definitely confirmed by a number of studies (6) which objectively measured the impairment of psychomotor performance. The recently introduced MSLT for the

Table 1. Daytime sleep latency ($n=12$). Data are mean (95% confidence interval) min of the 2 days of each MSLT recording

	Terfenadine (120 mg)	Placebo
Latency		
9.30 a.m.	18.4 (16.6–20.0)	16.9 (14.3–19.5)
11.30 a.m.	14.8 (11.7–17.9)	16.2 (13.6–18.8)
1.30 p.m.	14.6 (11.3–17.9)	15.9 (13.3–18.5)
3.30 p.m.	12.8 (9.7–15.9)	13.6 (10.5–16.7)
5.30 p.m.	17.5 (15.3–19.7)	16.8 (14.8–18.8)
Mean latency	15.6 (13.0–18.2)	15.8 (13.2–18.4)

Table 2. Visual and auditory reaction time. Data are mean (95% confidence interval) ms of the 3 days of each treatment

	Terfenadine (120 mg)	Placebo
Visual SRT		
Day 1	210.1 (199.2–221.4)	218.3 (183.0–253.1)
Day 2	205.5 (198.3–212.8)	210.2 (197.1–223.4)
Day 3	201.3 (192.4–210.0)	191.4 (182.6–200.1)
Auditory SRT		
Day 1	165.4 (145.2–185.8)	161.7 (150.0–172.4)
Day 2	151.7 (140.2–162.7)	152.0 (145.1–159.3)
Day 3	144.1 (135.3–153.8)	153.3 (140.1–166.2)

SRT=simple reaction time.

Table 3. Self-rating of sleepiness by SSS. Data are mean (95% confidence interval) scores of the 3 days of each treatment

	Terfenadine (120 mg)	Placebo
Rating		
Day 1	1.7 (1.1–2.4)	1.8 (0.9–2.7)
Day 2	1.7 (1.3–2.1)	1.6 (1.2–2.0)
Day 3	1.7 (1.0–2.4)	1.8 (1.1–2.5)
Mean rating	1.7 (1.0–2.4)	1.8 (1.1–2.5)

direct evaluation of sleepiness/alertness associated with antihistamines has shown the lack of sedative effects following terfenadine, loratadine, and cetirizine (15, 18, 19), in comparison with the older compounds.

The results of our study, using the standard MSLT procedure, paralleled those obtained by Roehrs et al. (15), thus demonstrating that terfenadine is completely devoid of sedative effects at the dose recommended for clinical use. In this respect, the data obtained by repeated latency tests were consistent with those obtained by reaction time and self-assessment of sleepiness/alertness. Our chosen length of drug administration period, i.e. 3 consecutive days, seemed adequate enough to detect any potential sedation associated with terfenadine, since by that time stable plasma concentrations of the drug are usually reached (10). In this study the amount of sleep and wakefulness during the nights preceding the test was not controlled. Nevertheless, in our opinion the monitoring of daytime sleepiness during the 2 consecutive days and then averaging the results, minimized any interference by possible sleep irregularities prior to the study.

In conclusion, this study demonstrated that 1) repeated administration of terfenadine 120 mg once daily is devoid of sedative daytime effects, as objectively evaluated, and 2) that the MSLT can be regarded as a reliable, direct, and objective method for

the assessment of daytime sleepiness related to antihistamines.

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References

- BETTS T, MARKMAN D, DEBENHAM S, MORTIBOY D, McKEVITT T. Effects of two antihistamine drugs on actual driving performance. *Br Med J* 1984; 288: 281–2.
- BRANDON ML, WEINER M. Clinical investigation of terfenadine, a non-sedating antihistamine. *Ann Allergy* 1980; 44: 71–5.
- CARSKADON MA, DEMENT WC. Sleep tendency: an objective measure of sleep loss. *Sleep Res* 1977; 6: 200.
- CARSKADON MA. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. In: KRYGER MH, ROTH T, DEMENT WC, eds. *Principles and practice of sleep medicine*. Philadelphia: Saunders, 1989: 685–8.
- DEMENT WC, SEIDEL W, CARSKADON MA. Daytime alertness, insomnia, and benzodiazepines. *Sleep* 1984; 7: 18–26.
- DRUCE H. Impairment of function by antihistamines. *Ann Allergy* 1990; 64: 403–5.
- GENGO FM, DABRONZO J, YURCHAK A, LOVE S, MILLER K. The relative antihistaminic and psychomotor effects of hydroxyzine and cetirizine. *Clin Pharmacol Ther* 1987; 42: 265–72.
- GUILLARD AWK, GRUISEN A, DE JONG R. The influence of antihistamines on human performance. *Eur J Clin Pharmacol* 1988; 35: 249–53.
- LORING DW, MEADOR KJ. Central nervous system effects of antihistamines on evoked potentials. *Ann Allergy* 1989; 63: 604–8.
- McTAVISH D, GOA KL, FERRILE M. Terfenadine. An updated review of its pharmacological properties and therapeutic efficacy. *Drugs* 1990; 39: 552–74.
- NICHOLSON AN, STORN BM. Performance studies with the H₁-histamine receptor antagonists, astemizole and terfenadine. *Br J Clin Pharmacol* 1982; 13: 199–202.
- O'HANLON JF. Antihistamines and driving safety. *Cutis* 1988; 42: 10–13.
- RECHTSCHAFFEN A, KALES A. A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects. Bethesda, MD: National Institute of Health, publication no. 204, 1968.
- RICHARDSON G, CARSKADON M, ORAV E, DEMENT W. Circadian variation of sleep tendency in elderly and young adult subjects. *Sleep* 1982; 5: S82.
- ROEHRS TA, TIETZ EI, ZORICK FJ, ROTH T. Daytime sleepiness and antihistamines. *Sleep* 1984; 7: 137–41.
- ROEHRS TA, LUMLY M, ASKER D, ZORICK F, ROTH T. Ethanol and caffeine effects on daytime sleepiness. *Sleep Res* 1986; 15: 41.
- ROTH T, ROEHRS T, KOSHOREK G, SICKLESTEEL J, ZORICK F. Central effects of antihistamines. *Sleep Res* 1986; 15: 43.
- ROTH T, ROEHRS T, KOSHOREK G, SICKLESTEEL J, ZORICK F. Sedative effects of antihistamines. *J Allergy Clin Immunol* 1987; 80: 94–8.
- SEIDEL WF, COHEN S, BLIWISSE NG, DEMENT WC. Cetirizine effects on objective measures of daytime sleepiness and performance. *Ann Allergy* 1987; 59: 58–62.
- SHUCARD DW, CREER TL. The effects of antihistamines on electrophysiologic and behavioral measures of cognition. *J Allergy Clin Immunol* 1989; 84: 284–5.

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