Desloratadine Shows No Effect on Performance During 6 h at 8,000 ft Simulated Cabin Altitude

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Valk PJL, Van Roon DB, Simons RM, Rikken G. ***Desloratadine shows no effect on performance during 6 h at 8,000 ft simulated cabin altitude.*** **Aviat Space Environ Med 2004; 75:433–8.**

Introduction: Sustained vigilance is required by pilots and crew during flight; therefore, the use of antihistamines with sedating properties is widely prohibited. The purpose of this study was to determine the effects of desloratadine, a long-acting, nonsedating antihistamine, on healthy volunteers placed under conditions of simulated cabin pressure. ***Methods:*** In a double-blind crossover study, 21 subjects randomly received single doses of desloratadine 5 mg, diphenhydramine 50 mg (active control), and placebo on different days separated by washout periods of 7 d. On test days, predose levels of alertness and fatigue were determined, as were post-dose levels at 1, 2, 3, 5, and 6 h. Measurements included vigilance and tracking, a multi-attribute task battery, the Stanford Sleepiness Scale, and pulse oximetry. ***Results:*** Desloratadine had no detrimental effects on sleepiness or performance of tasks associated with flying ability. Conversely, diphenhydramine (active control) caused significantly more sleepiness than did the placebo [$F(2,40) = 6.52$, $p < 0.01$], as well as impaired performance (tracking performance $p < 0.05$ at 3 h post dose), and an increased percentage of omissions ($p < 0.05$ at 2 h post dose). ***Conclusion:*** A single dose of desloratadine 5 mg did not cause sleepiness and did not impair the performance of tasks associated with flying ability.

Keywords: aviation, cognitive performance, H_1-receptor antagonist, desloratadine.

ANTIHISTAMINES ARE widely used to treat allergic rhinitis (AR), but many of these agents cause sedation and have been shown to impair in-flight performance (10,19). Pilots may be particularly vulnerable to the sedative effects of antihistamines because they are required to sustain attention and vigilance under relatively monotonous conditions (18,26). Other crewmembers, such as navigators, tactical crew, and air traffic controllers, must also maintain vigilance and are, therefore, also vulnerable to the sedating effects of antihistamines. It is not surprising that the use of antihistamines with sedative properties in crew during flight is widely prohibited.

Desloratadine is a long-acting, peripheral H_1-receptor antagonist with antiallergic, anti-inflammatory, and decongestant activity (9). In clinical trials, desloratadine has been shown to relieve the nasal and nonnasal symptoms of seasonal AR (22), including nasal congestion (16), as well as the symptoms of asthma in patients with AR and concomitant asthma (2), and the symptoms of chronic idiopathic urticaria (21). In clinical trials, desloratadine has demonstrated an adverse event profile similar to that of placebo (9,21). The objective of this study was to determine the effects of desloratadine on sleepiness and performance (vigilance, tracking, communicating, and managing resources) in healthy volunteers placed under conditions of simulated cabin pressure.

METHODS

Study Design/Medication

This was a randomized, double-blind, placebo-controlled, single-center crossover study. A computer-generated randomization schedule was used to randomly assign doses of desloratadine 5 mg, diphenhydramine 50 mg (active control), and placebo to qualifying subjects. Each dose of study drug was administered orally in the morning with 200 ml of water at approximately the same time each day (9:30 a.m.). All subjects received all three treatments with at least a 7-d washout period between treatment phases. Use of caffeine-containing products was prohibited on the day of testing and was limited to three portions on the day before testing.

Subjects

Healthy male subjects between the ages of 18 and 40 were considered for inclusion. All subjects were nonsmokers, had a negative urine screen for drug abuse, and were free of clinically significant disease. Previous flight/hypobaric experience was not required. Results of standard laboratory biochemistry, hematology, and urinalysis tests obtained at screening were within normal limits. All included subjects displayed an adequate adaptation toward the differences in cabin pressure and were able to complete the tests adequately. An institutional review board approved the study protocol, and

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all subjects signed consent forms after being thoroughly informed about the study and study medications.

Subjects were excluded if they had active seasonal and/or perennial allergic rhinitis; had a history of allergies to more than two classes of medication; were allergic to or could not tolerate antihistamines; had a condition that might impair the absorption, metabolism, or excretion of desloratadine or diphenhydramine; had an upper respiratory tract infection, sinus infection, or viral upper respiratory infection within 7 d before screening; or were not within 10% of normal average body weight. Additional exclusion criteria included use during the study of any central nervous system medication or medications with sedative effects; use of an investigational drug within 1 mo before the screening visit; use of a sedative/hypnotic, antihistamine, or anticholinergic drug during the 2 wk before the first treatment phase; and consumption of alcoholic beverages within 24 h before the start of the study or during treatment study days.

Study Procedures

At a screening visit, the eligibility of subjects and their vital signs were assessed, a medical history and physical examination were conducted, and laboratory tests and an electrocardiogram were performed. On the same day, subjects were trained on the performance tests several times until a stable performance level was achieved. An ear sinus check was completed in the hypobaric chamber to familiarize subjects with the decrease and increase in cabin pressure.

On study days, 1 h before treatment, subjects completed the Groningen Sleep Quality Scale (GSQS) to provide information on the quality of their sleep during the night before the trial day. Subjects with a bad night's sleep were rescheduled. Subjects were placed in a hypobaric chamber; over a period of 15 min, the ambient pressure in the hypobaric chamber was decreased to a pressure of 564 mmHg (75 kPa), equivalent to 2,438 m in the Standard Atmospheric. This pressure was chosen to represent pressurized cabins, which are normally maintained in the range of 1800–2400 m (6000–8000 ft) during cruising flight.

The Vigilance and Tracking Test (VigTrack), the Multi-Attribute Task Battery (MAT), the Stanford Sleepiness Scale (SSS), and pulse oximetry were performed after this level of ambient pressure was reached. Study drug was administered following completion of these assessments. VigTrack, MAT, SSS, and pulse oximetry were also performed 1, 2, 3, 5, and 6 h after administration of the study treatment. Physical exercise was prohibited while subjects were in the hypobaric chamber, but activities (including playing games, reading magazines and books, and participating in active discussions) were provided so that daytime somnolence could be avoided. At the end of the study, ambient pressure was increased to that of sea level (simulating descent), and subjects were discharged to their homes after they had been medically evaluated. Adverse events, which were monitored throughout the study, included those that were spontaneously reported, as well as those revealed through answers to general questioning and/or results of laboratory tests.

VigTrack, MAT, and SSS are used in aviation research to determine pilot alertness and fatigue. VigTrack is an instrument that measures vigilance performance under the continuous load of a compensatory tracking task that is used in field studies to assess the effects of fatigue and sleepiness in pilots (27,28). The task was developed on a Psion 3a palmtop computer. With arrow keys and a response button, subjects simultaneously track and respond to movement on a computer display. Data are gathered on tracking and vigilance performance.

MAT provides a benchmark set of tasks for use in a wide range of laboratory studies of operator performance and workload (1,6). This battery incorporates tasks analogous to activities that aircraft crewmembers perform in flight, and it provides a high degree of experimenter control and performance data on each subtask. Features include a system monitoring task, a tracking task, a communications task, and a resource management task, all of which are performed simultaneously. Performance measurements include the following: 1) root mean squared (RMS) tracking error; 2) numbers of false reactions and omissions, as well as mean reaction time; 3) numbers of adequate responses, false reactions, and omissions, as well as decision and response times; and 4) RMS deviation from fuel level target.

The SSS is a subjective rating scale used to assess sleepiness (12). Scale measures have been highly correlated with flying performance and threshold of information processing speed during periods of intense fatigue (18). The SSS consists of seven statements (ranging from "feeling active and vital" to "sleep onset soon"); subjects indicate how they feel at the moment by indicating which description best fits their condition. The GSQS consists of 14 different sleep quality statements; subjects must determine which statements are applicable to their sleep during the previous night (15). A score of 6 points or greater reflects a bad night's sleep.

The peripheral hemoglobin-oxygen saturation (S_{aO_2}) value in the peripheral blood of each subject was determined with the use of a pulse oximeter with a finger clip sensor. The S_{aO_2} of subjects staying at a simulated altitude of 8,000 ft has been shown to range from 89% to 93% (25). This mild hypoxia has been associated with performance impairment in some studies (25); however, others suggest that greater hypoxia (e.g., that experienced at 10,000 ft) is necessary to produce detectable performance impairment (25).

Data Analysis

To compensate for differences at baseline, difference scores were computed for all subjects during all three treatments by subtracting baseline scores from scores obtained in the five test sessions (1, 2, 3, 5, and 6 h post dose). Repeated measures of analysis of variance (ANOVA) were used to assess changes from baseline in VigTrack, MAT, SSS, and S_{aO_2} values. Within-subject factors included treatment and time of day. Comparisons between treatment at different time points were

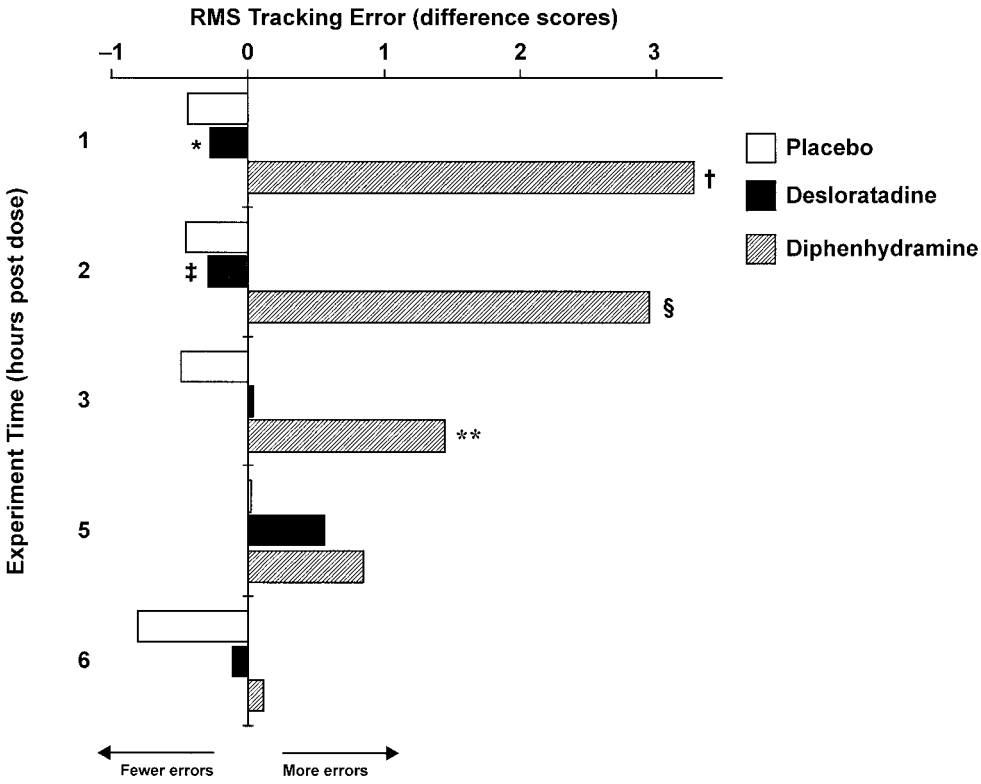

Fig. 1. Effects of desloratadine 5 mg, diphenhydramine 50 mg, and placebo on tracking performance as measured on the VigTrack. RMS = root mean squared. *$p < 0.01$ vs. diphenhydramine; † $p < 0.001$ vs. placebo; ‡ $p < 0.001$ vs. diphenhydramine; § $p < 0.01$ vs. placebo; ** $p < 0.05$ vs. placebo. Desloratadine showed no significant difference vs. placebo at any time point.

performed using Tukey's Honest Significant Difference method. Differences in SSS and GSQS scores were tested by means of the Wilcoxon matched-pairs signed-rank test. The significance level was set at 0.05.

RESULTS

A total of 21 healthy white men received all 3 treatments. The average age of the subjects was 22.6 yr; average weight and height were 73.4 kg and 181.4 cm, respectively. No significant differences were noted among the three treatments with respect to subjective sleep quality during the night before the trial day, as determined according to the GSQS.

A significant treatment × session interaction was found [$F(10,200) = 5.20$, $p < 0.001$]. No significant differences were seen between desloratadine and placebo in tracking and vigilance as measured on VigTrack. Conversely, diphenhydramine impaired tracking performance ($p < 0.05$ vs. placebo up to 3 h post dose). The diphenhydramine group showed impaired performance immediately following administration of the drug. This was followed by a linear improvement in performance at a level that was comparable with the desloratadine and placebo groups at the end of the day (**Fig. 1**).

On tests of vigilance, no significant difference in the number of false reactions was observed between treatments; however, the treatment × session interaction was significant [$F(10,200) = 3.16$, $p < 0.001$] and it was found that diphenhydramine produced a significant increase in the percentage of omissions vs. placebo ($p < 0.05$ at 2 h post dose). The diphenhydramine group showed impaired performance immediately after administration of the drug. This was followed by a linear improvement in performance that reached a level comparable with that seen in the desloratadine and placebo groups at the end of the day (**Fig. 2**).

On the subtask of tracking, a significant treatment × session interaction was found [$F(10,200) = 3.86$, $p < 0.001$]. No significant differences in tracking performance between desloratadine and placebo as measured on MAT were noted at any time point. Diphenhydramine significantly impaired tracking performance early on ($p < 0.001$ at 1 h), at most time points throughout the study, and up to the final evaluation time point (6 h) compared with desloratadine and placebo.

On the subtask of resource management, a significant session effect [$F(5,100) = 4.45$, $p < 0.001$] was found. The effect was similar for desloratadine and for placebo; each demonstrated overall improvement across the study period. In contrast, diphenhydramine produced significant impairment at the first assessment ($p < 0.05$) compared with desloratadine; this also occurred after dosing over the duration of the study [$F(1,20) = 6.12$, $p < 0.05$] compared with placebo (**Fig. 3**).

On the subtask of system monitoring, no significant differences were seen between groups in the number of omissions and the number of false reactions, and no significant difference in reaction time was observed between either of the antihistamines and placebo at any time point. However, regarding reaction time, a significant treatment × session interaction was found [$F(10,200) = 1.91$, $p < 0.05$]. Reaction time in the desloratadine group was significantly shorter over the course of the study compared with diphenhydramine ($p < 0.01$).

On the subtask of communication, each group performed similarly with no significant differences in the

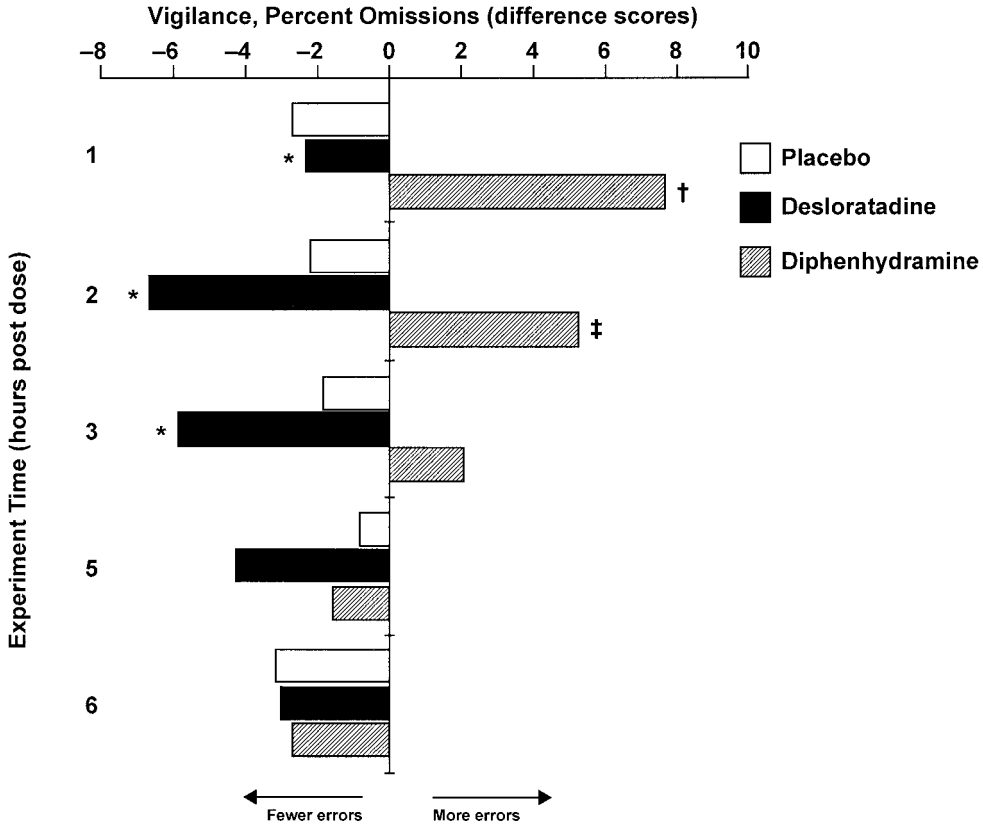

Fig. 2. Effects of desloratadine 5 mg, diphenhydramine 50 mg, and placebo on vigilance as measured on the VigTrack. * $p < 0.05$ vs. diphenhydramine; † $p < 0.01$ vs. placebo; ‡ $p < 0.05$ vs. placebo. Desloratadine showed no significant difference vs. placebo at any time point.

number of adequate responses, number of omissions, number of false reactions, or response time. Daytime sleepiness—measured with the SSS—was comparable between desloratadine and placebo groups throughout the entire test period of 6 h. As was expected, diphenhydramine treatment was associated with a greater increase in sleepiness scores and significantly more sleepiness than was placebo [$F(2,40) = 6.52$, $p < 0.01$] (**Fig. 4**). No significant differences in S_{aO_2} values were seen between treatments. During the study, values remained at around 94% (range, 90%–98%) until ambient pressure was increased to that of sea level.

No subjects in the placebo or desloratadine treatment groups reported any adverse events. There were three diphenhydramine-treated subjects who reported mild adverse events. Dizziness/wooziness, which occurred in one diphenhydramine-treated subject, was the only adverse event considered possibly related to a study drug; all other adverse events were considered unlikely to be related to a study drug.

DISCUSSION

The sedative properties of first-generation antihistamines are well recognized. Consequently, use of these agents in crewmembers during flight is generally prohibited. Compared with first-generation H_1-receptor antagonists, second-generation antihistamines are larger and less lipophilic, and they have a higher affinity for protein binding. These agents are associated with lower penetration of the blood-brain barrier and, at therapeutic doses, are associated with less sedation than are first-generation antihistamines. Studies using the second-generation antihistamines fexofenadine (80 mg, 120 mg, and 180 mg) and loratadine (10 mg) have shown that neither cognitive function nor psychomotor function is impaired (5,11). However, some agents [e.g., cetirizine, levocetirizine (R-enantiomer of cetirizine)] have been shown to have a higher sedative potential than other second-generation antihistamines (13,20,23), although some recent studies of levocetirizine have not uncovered evidence of sedation (8,29). The literature describing the sedative potential of cetirizine and its R-enantiomer is inconsistent; this discrepancy may derive from shortcomings in the experimental design of some studies that do not allow assessment of the delayed effects of cetirizine (6 h or longer after dosing) on performance and sleepiness.

The doses of desloratadine (5 mg) and diphenhydramine (50 mg) used in this study are consistent with those used to treat AR in clinical practice. Diphenhydramine can be administered at lower doses (25 mg); however, 50-mg doses have been employed in previous studies of flying task performance (5) and in a recent study of cognitive and psychomotor performance with repeated doses of various antihistamines (8).

In addition to the sedating effects of antihistamines, the in-flight cabin pressure can affect flight performance (25). Lower ambient pressure in the cockpit during flight (range, 81.2–75.2 kPa) has been associated with mild hypoxia (oxygen saturation of hemoglobin of 89–93%) and may result in impaired performance (7,14). Therefore, for accurate prediction of the true effect of treatment on crewmembers during flight, tests must be performed under conditions that mimic the in-flight

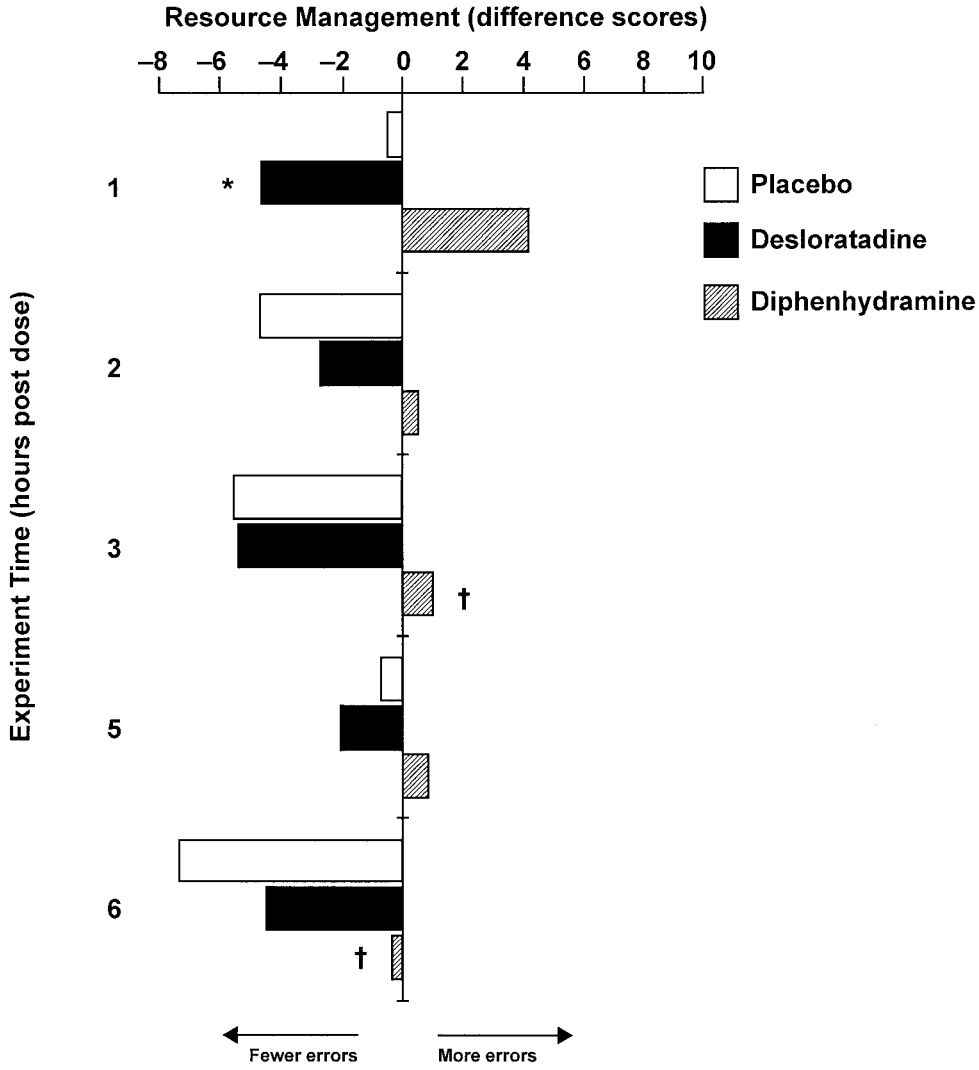

Fig. 3. Resource management scores at 1, 2, 3, 5, and 6 h after administration of desloratadine 5 mg, diphenhydramine 50 mg, and placebo as measured on the MAT. * $p < 0.05$ vs. diphenhydramine; † $p < 0.05$ vs. placebo. Desloratadine showed no significant difference vs. placebo at any time point.

environment. Although it was conducted in healthy volunteers, the present study was performed under conditions of simulated cabin pressure; therefore, it likely predicts the effects of desloratadine on performance and sleepiness in crewmembers during actual flight. As has been noted, this study was conducted in healthy male volunteers. We cannot predict if similar results would have been observed in women or in patients with AR.

The results of this study are consistent with those of other clinical studies that assessed the effects of desloratadine on the central nervous system. Scharf and associates demonstrated that a single 7.5-mg dose of desloratadine did not impair wakefulness or psychomotor performance (24). Vuurman and colleagues demonstrated that a single 5-mg dose of desloratadine did not impair the driving performance of healthy volunteers (30). A recent report by Nicholson and colleagues (17) similarly found no adverse effects of desloratadine 5 mg on multiple measures of psychomotor performance, daytime sleep latencies, or subjective reports of sleepiness. The authors concluded that desloratadine could be suitable for persons involved in skilled activity and transport.

No adverse events were observed with desloratadine treatment in this study. Previous single- and multiple-dose clinical studies have also demonstrated that desloratadine has a placebo-like adverse event profile (21). Unlike some other antihistamines, desloratadine is not associated with adverse cardiovascular effects (3,4).

This study demonstrates that a single dose of desloratadine 5 mg has no detrimental effects on sleepiness

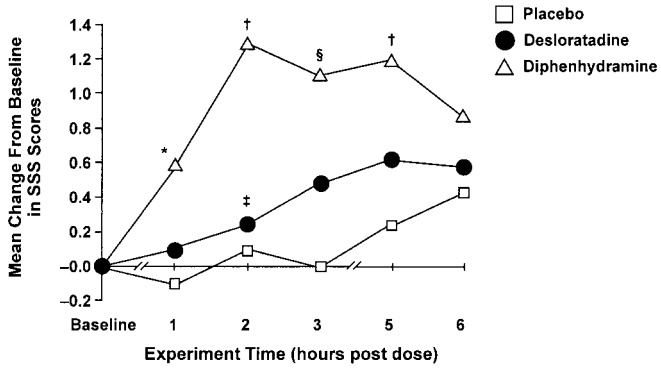

Fig. 4. Effects of desloratadine 5 mg, diphenhydramine 50 mg, and placebo on sleepiness as measured by the SSS. * $p < 0.05$ vs. placebo; † $p < 0.01$ vs. placebo; ‡ $p < 0.01$ vs. diphenhydramine; § $p < 0.001$ vs. placebo. Desloratadine showed no significant difference vs. placebo at any time point.

and performance of tasks associated with flying ability in healthy volunteers under conditions of simulated cabin pressure for up to 6 h after dosing. Conversely, the active control diphenhydramine is associated with significant sleepiness and impaired performance on flying tasks across this time period, confirming the sensitivity of the tests used.

The results of this study indicate that after a single dose, desloratadine does not impair one's ability to process information, coordinate complex psychomotor tasks, or sustain attention and vigilance—activities that are vital for maintenance of flight safety. Further studies are warranted to assess the effects on performance of multiple administrations of desloratadine.

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