

A simulated car-driving study on the effects of acute administration of levocetirizine, fexofenadine, and diphenhydramine in healthy Japanese volunteers

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Objective Antihistamines are often used for treating allergic rhinitis. However, many older antihistamines cause sedative side effects. The sedative effects of antihistamines on car-driving have been investigated. This has not been investigated for levocetirizine, a new-generation antihistamine, in Asian populations, and so we evaluated its sedative effects in healthy Japanese subjects.

Methods In this double-blind, placebo-controlled, four-way crossover study, healthy volunteers received single doses of levocetirizine 5 mg, fexofenadine 60 mg, diphenhydramine 50 mg, and placebo at intervals of at least 6 days. Simple brake reaction time and choice brake reaction time task (CBRT), a lateral tracking (LT) task, and a multiple task, a mixture of CBRT and LT task, were used to compare driving performance between the four drugs. Subjective sedation was also assessed.

Results The simple brake reaction time and CBRT, and the CBRT component of the multiple task, did not show any significant differences between the drugs. In contrast, the LT, both as a single parameter and as a component of the multiple task, showed significant differences between diphenhydramine and the newer-generation antihistamines in a manner that corresponds with subjective sedation.

Conclusions Levocetirizine and fexofenadine did not impair psychomotor performance in subjects performing simulated car-driving tasks, while diphenhydramine did impair psychomotor performance in the subjects. Copyright © 2016 John Wiley & Sons, Ltd.

KEY WORDS—antihistamines; sedation; simulated car-driving; levocetirizine; fexofenadine; diphenhydramine

INTRODUCTION

Histamine is a chemical mediator that induces allergic reactions, as observed in allergic rhinitis, urticaria, and other reactions. Histamine also plays a major role in various central nervous system (CNS) functions, such as arousal, maintenance of attention, the sleep–wake cycle, and cognition (Haas and Panula, 2003; Theunissen *et al.*, 2004). In the brain, histamine is synthesized in the tuberomammillary nucleus, a cluster of histaminergic neurons in the posterior hypothalamus. The neurons project into various regions of the brain in order to maintain neuronal activity. Most effects of histamine are mediated through H₁-receptor interactions (White, 1990).

First-generation antihistamines inhibit histamine action at the H₁-receptor sites of mast cells and used to

be the first treatment option for managing the symptoms of allergic disorders. However, these antihistamines cause undesirable side effects such as sedation and impairment of psychomotor functions. The main cause of these adverse effects is the ability of antihistamines to cross the blood–brain barrier (BBB) and thus block neuronal transmission in the histaminergic nervous system in the brain. Newer generations of antihistamines have therefore been introduced that are mildly sedative or non-sedating, although most of them may show some level of CNS impairment, especially at supraclinical doses (Casale *et al.*, 2003; Holgate *et al.*, 2003; Kay, 2000; Kay and Harris, 1999; Ridout *et al.*, 2003a; Roberts and Gispert, 1999; Rosenzweig and Patat, 1999; Simons *et al.*, 1996; Tagawa *et al.*, 2002; Theunissen *et al.*, 2004; Verster *et al.*, 2003a).

Although first-generation antihistamines have the greatest sedative effects, they are the most common over-the-counter antihistamines in Japan, the USA, and many other countries. Impaired psychomotor performance can lead to impairment in everyday tasks,

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including car-driving, increasing the risk of injury (Ridout *et al.*, 2003b). In an extensive literature review, Verster and Volkerts (2004) noted that first-generation antihistamines, such as triprolidine, diphenhydramine, and d-chlorpheniramine, significantly impaired car-driving performance. Furthermore, diphenhydramine is one of the top-selling over-the-counter drugs for allergic rhinitis (RedBook, 1998), but data have shown that it has a greater effect on car-driving performance than alcohol does (Weiler *et al.*, 2000). Several newer-generation antihistamines, such as cetirizine, loratadine, and ebastine, may cause little or mild impairment of performance compared with the first-generation antihistamines (Verster and Volkerts, 2004).

Levocetirizine, which is the levo-enantiomer of cetirizine, has been recently introduced in Japan as an antihistamine with minimal sedative side effects. Its daily recommended dose is 5 mg. Levocetirizine has a high affinity and selectivity for H₁ receptors (twofold that of cetirizine), whereas the dextro-enantiomer of cetirizine is inactive (Gillard *et al.*, 2002). The potency in inhibiting histamine-induced wheals and flares with levocetirizine 5 mg has been shown equivalent to that of cetirizine 10 mg (Clough *et al.*, 2001; Wang *et al.*, 2001) and diphenhydramine 50 mg. In a study by Hindmarch *et al.* (2001), the acute and subchronic effects on cognitive and psychomotor functions of levocetirizine 5 mg were examined in 20 healthy volunteers, and they found that levocetirizine, cetirizine, and loratadine did not significantly impair psychomotor performance. Another study by Gandon and Allain (2002) compared the effects on various tests of levocetirizine 5 mg and diphenhydramine 50 mg after acute and subchronic administration. Levocetirizine did not significantly affect performance in any tests, whereas diphenhydramine significantly impaired performance in some cognitive tests.

In addition, it has been reported that levocetirizine, after both acute (day 1) and sub-chronic (day 4) use of the standard 5 mg daily dose, does not affect the performance of subjects on a standardized driving test (Verster *et al.*, 2003b). Racemic cetirizine has also been reported not to impair driving performance after standard doses (Theunissen *et al.*, 2006), with an interesting case reported where cetirizine was taken at a dose of 50 mg (five times the standard) without impairing routine daily functions, including driving (Nordness and Zacharisen, 2003). Additionally, a study using an automobile driving simulator has reported that three single doses of cetirizine (5, 10, and 20 mg) had no effect on driving performance (Gengo *et al.*, 1990). Although one study with cetirizine has reported no interactions and impairment when the drug

was combined with alcohol (Patat *et al.*, 1995), another report has suggested that cetirizine may cause mild impairment in driving, especially when combined with alcohol (Ramaekers *et al.*, 1992). Although no data have been published on levocetirizine in higher than standard doses and/or in combination with alcohol, caution is advisable in such cases.

Fexofenadine does not impair performance and is non-sedating even at doses higher than those recommended (Hindmarch *et al.*, 1999; Hindmarch *et al.*, 2002; Kamei *et al.*, 2003; Mason *et al.*, 1999; Ridout and Hindmarch, 2003; Ridout *et al.*, 2003b; Tashiro *et al.*, 2004). Fexofenadine does not impair the car-driving performance of volunteers after oral administration, even at supraclinical dose levels up to 360 mg (Meeves and Appajosyula, 2003; Potter *et al.*, 2003; Ridout *et al.*, 2003b; Vermeeren and O'Hanlon, 1998; Verster and Volkerts, 2004; Weiler *et al.*, 2000). Furthermore, recent positron emission tomography studies have shown that fexofenadine does not cross the BBB and bind to H₁-receptors, whereas other second-generation antihistamines may still occupy a certain proportion of H₁-receptors in the brain (Hiraoka *et al.*, 2015; Tashiro *et al.*, 2002; Tashiro *et al.*, 2004). Brain histamine H₁-receptors occupancy values following oral treatment have been reported for fexofenadine 60–120 mg (−8.0% to −0.1%), levocetirizine 5 mg (8.1%), cetirizine 10 mg (12.6%), cetirizine 20 mg (25.2%), and diphenhydramine 30 mg (56.4%). Antihistamines with values higher than 50% have been classified as “sedative,” and those with values lower than 20% have been classified as “minimally sedative” (Hiraoka *et al.*, 2015; Tashiro *et al.*, 2002; Tashiro *et al.*, 2004; Tashiro *et al.*, 2008; Tashiro *et al.*, 2009).

Because histamine plays a major role in maintaining vigilance and attention, blocking of histamine-binding receptors during antihistamine use may harm an individual's driving performance, making it important to examine whether an antihistamine may affect driving performance. In this study, we determined the effects of levocetirizine 5 mg and fexofenadine 60 mg on the car-driving performance of healthy Japanese volunteers using a driving simulator.

MATERIALS AND METHODS

Subjects

Subjects were recruited through advertisements on Tohoku University campuses. The medical ethics committee of the Tohoku University Graduate School of Medicine approved the study protocol. Subjects were

treated according to guidelines for Good Clinical Practice and the Declaration of Helsinki and its 1996 amendments. Each subject was informed beforehand about the possible risks of the simulated car-driving test and the possible adverse effects of antihistamines. Written informed consent was obtained before inclusion in the study, and subjects were paid to cover costs related to the study.

Upon recruitment, study candidates were medically screened for abnormalities in blood chemistry, hematology, urinalysis, 12-lead electrocardiogram, chest X-ray, and brain MRI T1 tests. They had no past history of allergy, asthma, or H1 antagonist use. They also used no concomitant medication and had no history of alcohol or drug abuse. Subjects had possessed a valid driver's license for at least 1 year and reported having driven at least once per week during the last 1 year. In addition, all candidates were asked to drive on the simulator to exclude subjects with a risk of simulator sickness. Twenty healthy volunteers (11 men and 9 women) participated in and completed the study. Their mean age and standard deviation was 26.7 ± 5.9 years (men: 25.8 ± 4.7 years; women: 27.7 ± 7.4 years). All subjects were trained on the simulated car-driving test beforehand to become familiar with test procedures.

Study design

The current study uses a double-blind, placebo-controlled, four-way, crossover design. Single doses of levocetirizine 5 mg, fexofenadine 60 mg, diphenhydramine 50 mg, and placebo were administered orally with 100 mL water. They were concealed in four envelopes, labeled with treatment period (1, 2, 3, or 4) and the subject's randomization number. Treatment periods were separated by a washout period of at least 6 days. Driving tests were performed before oral administration (baseline: Driving 1) and at 90 min (Driving 2) and 180 min (Driving 3) post-administration (Figure 1) (Verster and Volkerts, 2004; Verster *et al.*, 2003a). The use of alcohol was

prohibited the day before and on treatment days, and nicotine was prohibited 24 h prior to the experiment and on the treatment day. Products containing caffeine, grapefruit juice, or any supplement drink containing active agents, such as amino acids, vitamins, and catechin, were prohibited on treatment days. Only water was allowed during testing. Food consumption was controlled, and it included a light lunch prepared by the investigators.

On the treatment day, subjects were re-familiarized with the driving task for around 30 min prior to the pre-treatment baseline measurement to ensure a performance plateau. Following a simple physical examination of blood pressure and pulse rate, the baseline examination (Driving 1) was conducted, which took 25 min (Figure 1). Soon after the completion of the Driving 1 phase, the subjects took the medication. The order of test drugs was determined based on the Latin Square method to eliminate the order effect.

Assessments

The primary assessment was the driving test, including brake reaction time, lateral stability, and the multiple task, and the secondary assessment was subjective sedation. Subjective sedation was measured prior to and immediately after the driving test at each time point (six times in each test; Checks 1 to 6: 25 and 0 min pre-administration; 180, 205, 270, and 295 min post-administration) (Figure 1).

Simulated car-driving study. Driving performance is a relatively sensitive indicator of the side effects of psychoactive drugs. All subjects performed a simple brake reaction time (SBRT) test, a choice brake reaction time test (CBRT), a lateral tracking (LT) test, and a multiple task, using a commercially available simulator (DS-3000, Mitsubishi Precision Ltd., Tokyo, Japan) (Horiuchi *et al.*, 2008). This simulator was in use for evaluation of a sedating agent (low-dose propofol) intravenously administered to subjects who underwent

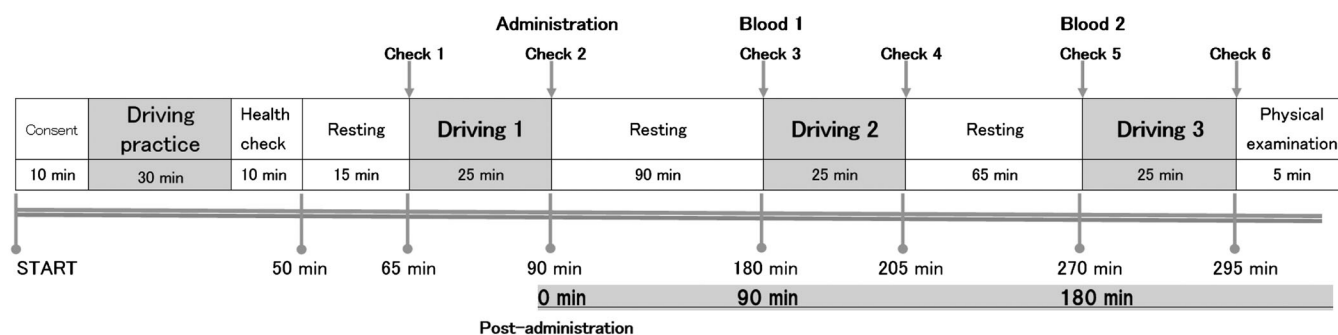


Figure 1. Schematic diagram of the study protocol

esophagogastroduodenoscopy (Horiuchi *et al.*, 2008). They used a different driving simulator model (DS-300), but the same driving simulation program was used in the simulator. The subjects sat in front of a monitor and used a steering wheel, accelerator, and brakes to control the vehicle. The image of the road changed in accordance with the subject's actions. During the SBRT, crossing pedestrians appeared randomly on the screen and attempted to cross the road from the left side only (Figure 2, top). During the CBRT, crossing pedestrians appeared randomly on the screen and attempted to cross the road from both sides. To measure the reaction time, the subjects were required to identify and respond to the behavior of the pedestrians properly. During the SBRT and CBRT, the mean brake reaction time was calculated. In the LT test, the object of the test was to steer an image of a car hood down the center of a winding road as accurately as possible using a steering wheel, and the ability to track continuously was measured (Figure 2, bottom). The mean deviation from the center of the lane was calculated



Figure 2. Images projected on the monitor of a car-driving simulator used in the present study. General view of the simple brake reaction time task (top) and lateral tracking task (bottom) captured from an instruction program for study volunteers

as a percentage, taking the deviation to either edge of the lane as 100%.

Subjects were also asked to perform the CBRT and the LT tests a second time, as part of a multiple task whose results were analyzed independently of the relevant single tests. The results of the multiple task were calculated separately as the tracking error (mean deviation from the center of the road) and brake reaction time.

Subjective sedation assessment. The Stanford Sleepiness Scale (SSS) is a seven-point self-report measure of how alert an individual feels (Hoddes *et al.*, 1973), with proven sensitivity in a number of studies (Mochizuki *et al.*, 2002; Okamura *et al.*, 2000; Tagawa *et al.*, 2002). For example, subjects may indicate feeling active, vital, alert, wide awake, somewhat foggy, sleepy, or asleep. The higher the score, the less alert and more drowsy the subject felt.

The line analog rating scale (LARS) is a measure of the subjective effects of psychoactive drugs (Hindmarch, 1975) and has been used to detect sedation in response to many different classes of compounds (Hindmarch *et al.*, 1999; Hindmarch and Shamsi, 2001; Hindmarch *et al.*, 2001; Ridout and Hindmarch, 2003; Ridout *et al.*, 2003b). Subjects were asked to mark a series of 100-mm line analog scales, indicating their present state of mind. This score was compared with a midpoint that represented their pretreatment state of mind. Mean ratings of drowsiness and alertness were taken as a measurement of perceived sedation (Sherwood and Hindmarch, 1993). The higher the score, the less alert and more drowsy the subject felt.

Measurement of plasma concentration of levocetirizine, fexofenadine, and diphenhydramine.

Plasma concentrations of levocetirizine, fexofenadine, and diphenhydramine were determined by high-performance liquid chromatography and mass spectrometry. A Luna C8 (2) analytical column was used (30×2.1 mm, 5 µm particle size) for levocetirizine and fexofenadine, and a Kinetex C18 column (100×3.0 mm, 2.6 µm particle size) was used for diphenhydramine. To prevent rapid deterioration of the analytical columns, a C18 guard column (4×3.0 mm; all from Phenomenex, Aschaffenburg, Germany) was used. The temperature of the column oven was 60 °C. The mobile phase consisted of a mixture of solvent A (0.2% acetic acid) and solvent B (MeOH).

The following parameters were used for elution: levocetirizine and fexofenadine: 0–0.5 min, 20% B; 0.5–0.8 min, 20–50% B (linear); 0.8–2.5 min, 50–80% B (linear); 2.5–2.7 min, 80–98% B (linear); 2.7–3.5 min, 98% B; 3.5–4.1 min, 98–20% B

(linear); 4.1–4.5 min, 20% B. The flow rate was 0.5 mL/min, and the total run time was 4.5 min. Diphenhydramine: 0–1.5 min, 5–98% B (linear); 1.5–2.5 min, 98% B; 2.5–3.0 min, 98–5% B (linear); 3.0–4.0 min, 5% B. The flow rate was 0.6 mL/min, and the total run time was 4.0 min (Peters *et al.*, 2007, 2009).

The high-performance liquid chromatography system (Shimadzu, Duisburg, Germany) was coupled to a triple quadrupole mass spectrometer (5500 QTrap; AB SCIEX, Darmstadt, Germany) with a turbo electrospray ion source operated in positive ionization mode (ESI+). The source temperature was 350 °C, and the ion source voltage was set to 5500 V. Compounds were quantified in multiple reaction mode (*m/z*): levocetirizine: 389.1 → 201.0/165.0; internal standard (IS; cetirizine-D₈): 397.1 → 201.1; fexofenadine: 502.1 → 466.3/484.1; IS (fexofenadine-D₆): 508.3 → 472.1; diphenhydramine: 256.0 → 167.0/152.0; IS (phencyclidine-D₅): 249.0 → 164.0. The retention time for levocetirizine/cetirizine-D₈ was 2.63 min; for fexofenadine/fexofenadine-D₆, it was 2.34 min; and for diphenhydramine/phencyclidine-D₅, it was 2.55/2.50 min (Peters *et al.*, 2007, 2009).

Samples were prepared for measurements by adding 400 µL IS solution to 100 µL of plasma. Subsequently, samples were vortexed, centrifuged for 5 min at approximately 16 000 × *g*, and 100 µL of the supernatant was transferred into a 1.5 mL glass vial with a 200 µL insert and measured with an injection volume of 1 µL. To determine the analyte concentration, samples with a defined amount of analyte (calibrators) were used to create a standard curve for both analytes in the plasma. For calculating the concentration, a linear standard curve based on nine different calibrators (levocetirizine and fexofenadine: 1, 5, 10, 25, 50, 100, 250, 500, and 750 ng/mL; diphenhydramine: 0.8, 4, 8, 20, 40, 80, 125, 250, and 500 ng/mL) and three quality control samples (20, 200, and 400 ng/mL) were used. Validation tests were performed following the guidelines published by Peters *et al.* (2007, 2009) and the guidelines of the Society of Toxicological and Forensic Chemistry. The inter-day bias of Quality control (QC) samples for levocetirizine and fexofenadine was < 3%, and it was -9, 7.9, and 4.5% for diphenhydramine (20, 200, and 400 ng/mL).

The linear range of measurements for levocetirizine and fexofenadine was 0.2–750 ng/mL and that for diphenhydramine was 2.5–500 ng/mL (*R* > 0.999). The lower limit of quantification of levocetirizine and fexofenadine was 0.2 ng/mL and that of diphenhydramine was 2.5 ng/mL (Peters *et al.*, 2007, 2009).

Statistical analysis

For the statistical analyses of subjective sedation, the SSS and LARS scores were examined using the Friedman test, which is a non-parametric analog of analysis of variance, because the subjective data were scores (SPSS 15.0 [Japanese version]). Significant findings were additionally examined by *post hoc* multiple pairwise treatment comparisons using a Wilcoxon signed rank test (two-tailed; *p* ≤ 0.05).

Brake reaction time data were examined using repeated measures analysis of variance with factors for levocetirizine, fexofenadine, diphenhydramine, and placebo because most data sets were well-modeled by a normal distribution, as confirmed by performing a Shapiro–Wilk test. Significant findings were further examined by *post hoc* Bonferroni testing in order to examine differences between two drug conditions (two-tailed; *p* ≤ 0.05). For the LT test data, a non-parametric Friedman test was applied because a Shapiro–Wilk test showed that no data sets were well-modeled by a normal distribution. Significant findings were further examined by multiple *post hoc* pairwise Wilcoxon signed rank tests in order to examine differences between two drug conditions (two-tailed; *p* ≤ 0.05).

RESULTS

Brake reaction time tasks. No significant treatment effect was detected for the mean brake reaction time and accuracy in SBRT and CBRT, as well as in the CBRT component of the multiple task. *Post hoc* testing revealed no significant difference between diphenhydramine, fexofenadine, levocetirizine, and placebo.

Lateral tracking test. A significant main effect was found for mean deviation in the LT test when the Friedman test was applied to the 90 and 180 min post-administration data sets (*p* < 0.001 and *p* = 0.003, respectively). A *post hoc* Wilcoxon signed rank test revealed that the mean deviation value after placebo treatment was significantly smaller than after diphenhydramine both at 90 and 180 min post-administration (*p* < 0.001) (Figure 3). In addition, at 90 min (*p* = 0.001) and 180 min (*p* = 0.037), the mean deviation values after levocetirizine treatment were significantly smaller than those after diphenhydramine treatment (Figure 3). At 90 min (*p* = 0.001) and 180 min (*p* = 0.004), the mean deviation values after fexofenadine treatment were also significantly smaller than those after diphenhydramine treatment (Figure 3).

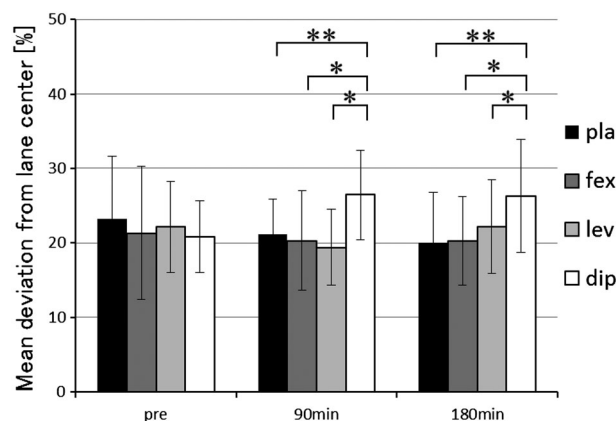


Figure 3. Lateral tracking test results showing the mean deviation from the center of the lane. Values are means (%), and standard deviation is shown by the error bars. * $p < 0.05$, ** $p < 0.001$ for the *post hoc* Wilcoxon signed rank test. Pla, placebo; Fex, fexofenadine; Lev, levocetirizine; Dip, diphenhydramine

Lateral tracking test component of the multiple task. A significant effect was found for the mean deviation in the LT test component of the multiple task when a Friedman test was applied to the 90 min ($p=0.011$) and 180 min ($p=0.044$) post-administration data sets. A *post hoc* Wilcoxon signed rank test revealed that the mean deviation value after placebo treatment was significantly smaller than that for diphenhydramine at 90 min ($p=0.006$) post-administration (Figure 4). In addition, at 90 min ($p=0.017$) and 180 min ($p=0.03$), the mean deviation values after levocetirizine treatment were significantly smaller than those after diphenhydramine treatment (Figure 4). At 90 min ($p=0.017$) and 180 min ($p=0.03$), the mean deviation values after fexofenadine treatment were also significantly smaller than those after diphenhydramine treatment (Figure 4).

Subjective sedation assessment

In general, there were no significant differences between drug treatments at the baseline, except for SSS and LARS measured immediately after the baseline driving test (Driving 1; Check 2), which showed significant differences in subjective sedation between diphenhydramine and the other drugs (Figure 5).

Stanford sleepiness scale. The SSS assessment revealed a significant main effect of treatment ($p < 0.01$) when the Friedman test was applied at 90, 115, 180, and 205 min post-administration. *Post hoc* tests revealed that subjects given diphenhydramine were significantly less alert at 90 and 180 min post-administration compared with those given levocetirizine, fexofenadine, or placebo (Figure 6). No significant difference in alertness was found in subjects

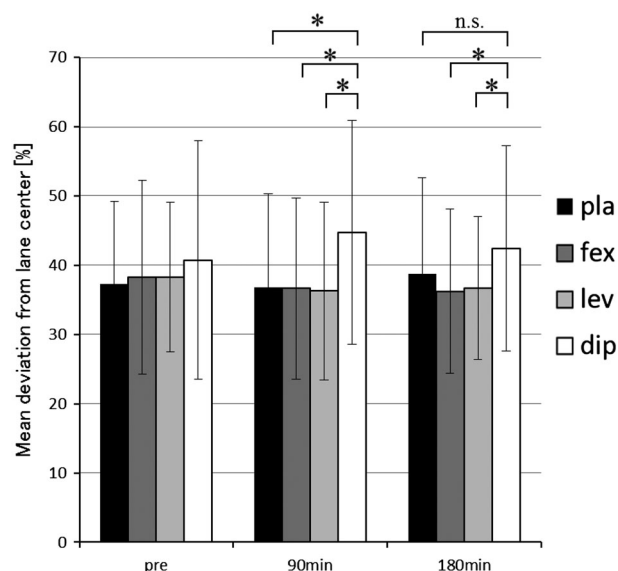


Figure 4. Results of the lateral tracking test component of the multiple task. Values are mean deviation (%), and standard deviation is illustrated by the error bars. * $p < 0.05$, ** $p < 0.001$ for the *post hoc* Wilcoxon signed rank test. Pla, placebo; Fex, fexofenadine; Lev, levocetirizine; Dip, diphenhydramine

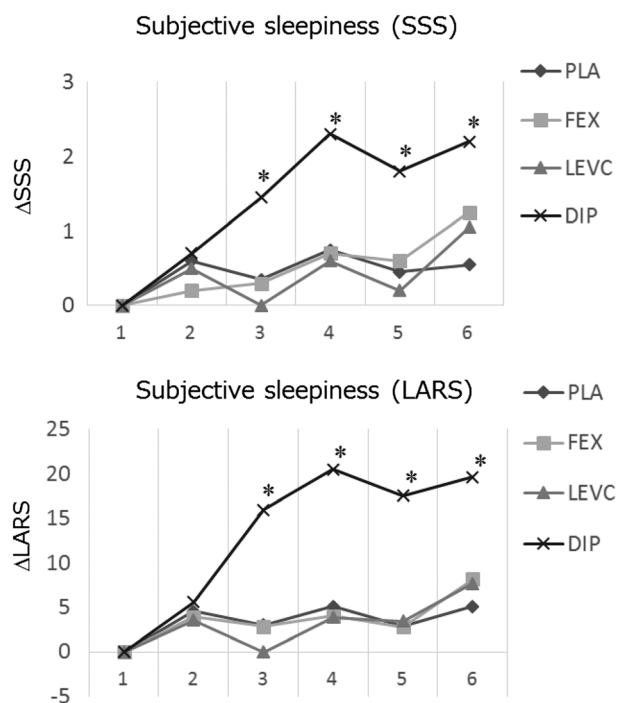


Figure 5. Time course of mean subjective sedation measured on the Stanford Sleepiness Scale (SSS) (top) and line analog rating scale (LARS) (bottom). Pla, placebo; Fex, fexofenadine; Lev, levocetirizine; Dip, diphenhydramine. Asterisks (*) indicate statistical significance as characterized by the Friedman test (* $p < 0.01$). Statistical significances examined by *post hoc* Wilcoxon signed rank test are shown in Figure 6

EFFECT OF ANTIHISTAMINES ON SIMULATED CAR-DRIVING

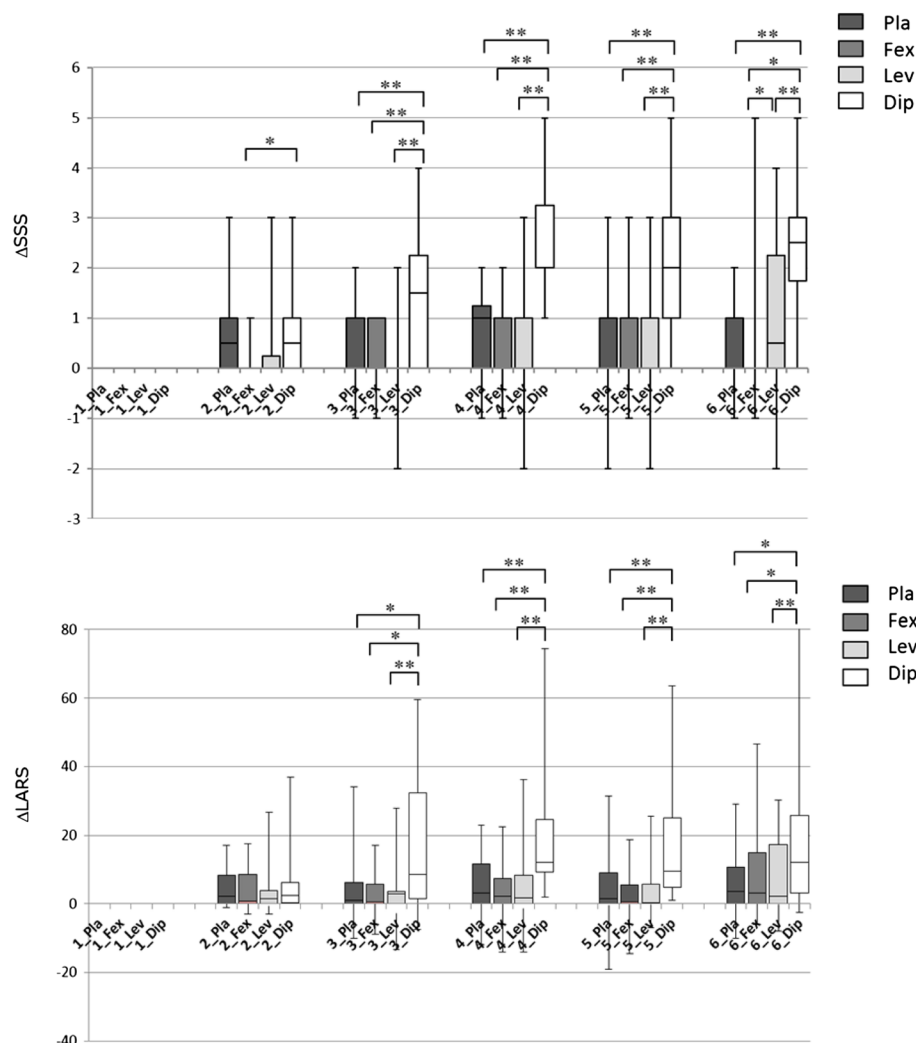


Figure 6. Box plot of subjective sedation measured by the Stanford Sleepiness Scale (SSS) and line analog rating scale (LARS). * $p < 0.05$, ** $p < 0.01$ for the *post hoc* Wilcoxon signed rank test. Pla, placebo; Fex, fexofenadine; Lev, levocetirizine; Dip, diphenhydramine

given fexofenadine and levocetirizine compared with placebo. Significant difference was found between fexofenadine and levocetirizine at 210 min post-administration (Check 6, Figure 6) and between fexofenadine and diphenhydramine at baseline (Check 2, Figure 6), both of which could be attributed to chance because the differences between levocetirizine and placebo and between diphenhydramine and placebo were not significant at either occasion.

Line analog rating scale. The LARS results also showed a significant treatment effect ($p < 0.01$), as judged by the Friedman test for 90, 115, 180, and 205 min post-administration. *Post hoc* tests revealed that subjects given diphenhydramine felt significantly more sedated compared with those given levocetirizine, fexofenadine, or a placebo at 90 and 180 min post-

administration (Figure 6). No significant difference in alertness was found for subjects given levocetirizine or fexofenadine compared with those given placebo at 90 and 180 min post-administration (Figure 6).

Plasma concentration of levocetirizine, fexofenadine, and diphenhydramine

The mean plasma concentrations (ng/mL) $\pm$ standard deviation at 90 and 180 min post-administration, respectively, were levocetirizine 171.2 ± 46.0 , 156.3 ± 30.3 ; fexofenadine 165.4 ± 62.1 , 137.8 ± 42.8 ; and diphenhydramine 48.2 ± 31.7 , 69.8 ± 22.9 . The peak plasma concentrations were achieved for levocetirizine and fexofenadine at around 90 min post-administration, whereas the peak plasma concentration of diphenhydramine was achieved at a later time point.

Adverse events

There were no spontaneous reports of adverse events.

DISCUSSION

Sedation can be a direct result of antihistamine treatment for allergic reactions, especially with first-generation drugs. The increased impairment of cognitive and psychomotor performance may sometimes be more uncomfortable than the allergic reaction itself (Vuurman *et al.*, 1993, 1996). The impairment of cognitive and psychomotor performance has been measured in various ways (Marshall and Colon, 1993), through decreased productivity, and impaired cognition and learning (Vuurman *et al.*, 1993, 1996). These results led to the development of a number of new compounds, the second-generation antihistamines, which have equal efficacy as antihistaminic agents compared with first-generation antihistamines, although they have an improved safety profile with less brain penetration.

Levocetirizine is the active isomer of the second-generation antihistamine cetirizine. The oral dose of levocetirizine, 5 mg, has been shown to be clinically equivalent to cetirizine 10 mg (Clough *et al.*, 2001; Wang *et al.*, 2001). Levocetirizine demonstrates rapid absorption after oral administration, and $T_{\max}$ is approximately 0.9 h post administration. Peak plasma concentrations of 270 ng/mL have been reported following a single oral dose of 5 mg levocetirizine. The peak plasma concentration in the present study was around 170 ng/mL at 90 min, which is later than $T_{\max}$, at 0.9 h.

Cetirizine is regarded as a mildly sedative antihistamine (together with most of the other second-generation antihistamines) that may cause sedation and impaired psychomotor activity at doses greater than 20 mg (Tashiro *et al.*, 2005). We reported the brain histamine H1 receptor occupancies of cetirizine 10 mg and 20 mg using placebo data for the same subjects (12.6% and 25.2%, respectively) (Tashiro *et al.*, 2005). We also demonstrated a dose dependency in the brain H1 receptor occupancy of oral cetirizine, although the sample size was small ($n=6$) (Tashiro *et al.*, 2008). In contrast, brain penetration of levocetirizine is lower than that of cetirizine. Recently, our data suggest that the brain histamine H1 receptor occupancy of 5 mg levocetirizine (8.1%) is lower than that of cetirizine 10 mg (Hiraoka *et al.*, 2015; Tashiro *et al.*, 2008). Therefore, in this study, we examined the effects of levocetirizine 5 mg on simulated car-driving.

The results indicated no significant impairment in the car-driving test parameters after oral administration of an acute dose of levocetirizine 5 mg. In addition, the present results are consistent with a previous study by Verster *et al.* (2003b) in healthy volunteers, in which the standard deviation of lateral position after levocetirizine 5 mg was equivalent with that of the placebo (-0.66 cm; $+1.12$ cm). The standard deviation of lateral position after diphenhydramine treatment was significantly different from that of the placebo treatment ($p < 0.0001$) (Verster *et al.*, 2003b). Impaired lateral instability after oral treatment with d-chlorpheniramine was also observed among study subjects of simulated car-driving study in our previous study (Tashiro *et al.*, 2008). These results suggest that it is safe to drive a car when taking levocetirizine 5 mg once daily. The present results seem to agree with a recent meta-analysis using the proportional impairment ratio (PIR), where the PIRs for both objective and subjective measures were 0.0 for levocetirizine, while those with cetirizine were 6.38 for the subjective measure and 1.31 for the objective measure (Isomura *et al.*, 2014).

In the present study, only one of the three principal measures showed significant impairment due to diphenhydramine. However, the simple reaction time and choice reaction time tasks do not seem sensitive enough, in the opinion of the authors, to detect sedative side effects of antihistamines in young volunteers (those in their early 20s). For this, very difficult tasks, such as a visual discrimination task with an ultra-short exposure duration (4 to 6 ms) are more sensitive (Tashiro *et al.*, 2005). Therefore, not finding significant impairment in brake reaction time tasks was not surprising, and the impairment in the steering task is important.

Hindmarch *et al.* (2001) reported acute effects on cognitive and psychomotor functions for levocetirizine 5 mg, cetirizine 10 mg, and promethazine 30 mg in healthy volunteers. Levocetirizine and cetirizine did not significantly impair psychomotor performance. Another study compared the effects of acute administration of levocetirizine 5 mg and diphenhydramine 50 mg with those of placebo on cognitive and psychomotor performance. Levocetirizine did not significantly affect performance in any test. In contrast, diphenhydramine significantly impaired performance on the critical flicker fusion and choice reaction tests (Gandon and Allain, 2002).

Currently, fexofenadine is regarded as one of the least sedative antihistamines, partly because it is non-sedating at regular doses and even at supraclinical doses (Hindmarch *et al.*, 1999; Hindmarch *et al.*,

2002; Kamei *et al.*, 2003; Mason *et al.*, 1999; Meeves and Appajosyula, 2003; Potter *et al.*, 2003; Ridout and Hindmarch, 2003; Ridout *et al.*, 2003b; Tashiro *et al.*, 2004; Vermeeren and O'Hanlon, 1998; Verster and Volkerts, 2004; Weiler *et al.*, 2000). Recent positron emission tomography studies have shown that fexofenadine does not cross the BBB and bind to H₁ receptors (Hiraoka *et al.*, 2015; Tashiro *et al.*, 2002; Tashiro *et al.*, 2004), which would explain why no CNS impairment is observed.

Subjective sedation assessment and driving performance results revealed no significant differences between subjects who were administered fexofenadine and those who received placebo under any test conditions. These findings are consistent with previous studies, which have reported that fexofenadine did not show sedative effects and did not impair cognitive, psychomotor, and driving performance (Hindmarch *et al.*, 1999; Hindmarch *et al.*, 2002; Kamei *et al.*, 2003; Ridout and Hindmarch, 2002; Ridout and Hindmarch, 2003; Ridout *et al.*, 2003b; Vermeeren and O'Hanlon, 1998; Weiler *et al.*, 2000).

In the present study, diphenhydramine significantly impaired car-driving ability, demonstrating that the sensitivity of our driving test was sufficient. Statistical examination showed that the LT results after diphenhydramine treatment were significantly different from those after placebo treatment. The subjective assessment was also consistent with the objective findings of the significant impairment of car-driving performance, especially for LT.

As with every study, our methodology is not without limitations. First, the number of subjects was relatively small, although it is comparable with other studies of similar design. Second, the validation of the simulator used in the present study is still in progress. The simulator was relatively new at the time of testing and has been previously used to demonstrate the impairment of driving ability of patients who underwent esophagogastroduodenoscopy after sedation by an intravenous injection of low-dose propofol (40–80 mg for < 70 years and 30 mg for > 70 years) or midazolam 4 mg (Horiuchi *et al.*, 2008). In the Horiuchi *et al.* previous experiment, both the CBRT task and tracking task showed statistically significant impairment due to sedation caused by low-dose propofol or midazolam, tested in 30 subjects. Thus, with a different therapeutic agent, the sensitivity of the simulator was demonstrated. We therefore consider it sufficient to detect sedation due to sedative antihistamines, too. Here, the observed pattern was that the LT task was more sensitive than reaction time tasks under the influence of sedative antihistamine.

CONCLUSION

The findings of the present and previous car-driving studies suggest that it is safe to drive a car when taking levocetirizine 5 mg once daily. Our results show that after acute oral administration of levocetirizine 5 mg, performance in the car-driving test was not significantly affected in healthy Japanese volunteers. In addition, people using sedative antihistamines, such as diphenhydramine, should be warned against driving, because our results clearly show the impairment of LT.

CONFLICT OF INTEREST

M. Tashiro and K. Yanai received speaker honoraria from GlaxoSmithKline K.K., and they also received research supports from GlaxoSmithKline K.K. for the present study.

ACKNOWLEDGEMENTS

The study was supported by research funding from GlaxoSmith Kline (to Tashiro M). Further support was provided by the Japan Foundation for Clinical Pharmacology (to M. Tashiro). The authors thank Ms. Nami Miyabayashi for her contribution as a clinical research coordinator and Ms. Michiko Sato and Ms. Chieko Ogata for performing medical procedures and attending to study subjects. The authors also thank Prof. Masatoshi Itoh of Sendai Medical Imaging Clinic, Sendai, Japan, for his support and encouragement.

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