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VII. 6. A Simulated Car-driving Performance on the Effects of Administration of Levocetirizine, Fexofenadine, and Diphenhydramine in Healthy Japanese Volunteers

Inami A.1,2, Matsuda R.1, Grobosch T.3, Komamura H.1, Yamada Y.1, Ito T.1, Koike D.1, Takeda K.1, Miyake M.1, Hiraoka K.1, Maurer M.3, Yanai K.1,2, and Tashiro M.1

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Introduction

Histamine H1 receptor (H1R) antagonists, known as antihistamines, have sedative side effects, which are caused by the block of H1R in brain. First-generation antihistamines such as diphenhydramine (DIP) can easily cross the blood-brain barrier (BBB), and they are known to cause strong sedation. The second-generation antihistamines, such as cetirizine, loratadine, and ebastine, may cause little or mild impairment of performance compared with the first-generation antihistamines1). Levocetirizine (LEV) has a high affinity and selectivity for H1R, and it has been reported to show little sedation as well as fexofenadine (FEX)2). However, our previous [11C]doxepin PET study revealed that H1R occupancy of LEV 5mg administration was 8.1%. For elderly patients aged ≥65 years, the US label recommends starting at lower dosages. We performed the examination using a driving simulator to young and elderly groups in order to determine the effect of LEV on driving performance. Here, we report the results of our early analysis on young group.

Materials and Methods

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). This study uses a double-blind, placebo-controlled, four-way, crossover design. Single doses of LEV 5 mg, FEX 60 mg, DIP 50 mg, and placebo (PLA) were administered orally with 100 mL water. Driving tests were performed before oral administration (baseline: Driving 1) and at 90 min (Driving 2) and 180 min (Driving 3) post-
administration (Fig. 1) 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). All subjects performed a simple brake reaction time (SBRT) test, a choice brake reaction time test (CBRT), a lateral tracking (LT) test, and multiple test, using a commercially available simulator (DS-3000, Mitsubishi Precision Ltd., Tokyo, Japan) (Fig. 2). 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. The mean deviation from the center of the lane was calculated 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 test whose results were analyzed independently of the relevant single tests. The results of the multiple test were calculated separately as the tracking error (mean deviation from the center of the road) and brake reaction time.

The Stanford Sleepiness Scale (SSS) is a seven-point self-report measure of how alert an individual feels, with proven sensitivity in a number of studies. 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 and has been used to detect sedation in response to many different classes of compounds. 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. The higher the score, the less alert and more drowsy the subject felt. Plasma concentration of levocetirizine, fexofenadine and diphenhydramine were determined by high performance liquid chromatography and mass spectrometry as we noted in detail on our published paper3).

For the statistical analyses of subjective sedation, the SSS and LARS scores were examined using the Friedman test. 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 LEV, FEX, DIP, and PLA. Significant findings were further examined by post hoc Bonferroni testing in order to examine differences between two drug
conditions (two-tailed; \( p \leq 0.05 \)). For the LT test data, a nonparametric Friedman test was applied. 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; \( p \leq 0.05 \))

**Results and Discussion**

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 tests. 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 PLA treatment was significantly smaller than after DIP both at 90 and 180 min post-administration (\( p < 0.001 \)) (Fig. 3). In addition, at 90 min (\( p = 0.001 \)) and 180 min (\( p = 0.037 \)), the mean deviation values after LEV treatment were significantly smaller than those after DIP treatment (Fig. 3). At 90 min (\( p = 0.001 \)) and 180 min (\( p = 0.004 \)), the mean deviation values after FEX treatment were also significantly smaller than those after DIP treatment (Fig. 3). 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 PLA treatment was significantly smaller than that for DIP at 90 min (\( p = 0.006 \)) post-administration (Fig. 4). In addition, at 90 min (\( p = 0.017 \)) and 180 min (\( p = 0.03 \)), the mean deviation values after LEV treatment were significantly smaller than those after DIP treatment (Fig. 4). At 90 min (\( p = 0.017 \)) and 180 min (\( p = 0.03 \)), the mean deviation values after FEX treatment were also significantly smaller than those after DIP treatment (Fig. 4). SSS and LARS showed similar results (Fig. 5). Post hoc tests revealed that subjects given DIP felt significantly more sedated compared with those given LEV, FEX, or a PLA at 90 and 180 min post-administration (Fig. 5). The mean plasma concentrations (ng/mL) ± 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 point3). These results are not consistent with the prescribing information, and there was no particular abnormality.
The results indicated no significant impairment in the car-driving test parameters after oral administration of an acute dose of LEV 5 mg. Verster et al. in healthy volunteers, in which the standard deviation of lateral position after LEV 5 mg was equivalent with that of the PLA. These results suggest that it is safe to drive a car when taking LEV 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 LEV, while those with cetirizine were 6.38 for the subjective measure and 1.31 for the objective measure. In the present study, DIP significantly impaired car-driving ability, demonstrating that the sensitivity of our driving test was sufficient. Statistical examination showed that the LT results after DIP treatment were significantly different from those after PLA treatment. The subjective assessment was also consistent with the objective findings of the significant impairment of car-driving performance, especially for LT. The observed pattern was that the LT test was more sensitive than reaction time tests 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 LEV 5 mg once daily. Our results show that after acute oral administration of LEV 5 mg, performance in the car-driving test was not significantly affected in healthy Japanese volunteers. In addition, people using sedative antihistamines, such as DIP, should be warned against driving, because our results clearly show the impairment of LT.

Acknowledgements

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References

Figure 1. Schematic diagram of the study protocol (reproduced from Ref. 3).

Figure 2. Car-driving simulator (DS-3000, Mitsubishi Precision Ltd).

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 (reproduced from Ref. 3).
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 (reproduced from Ref. 3).

Figure 5. Box plot of subjective sedation measured by the Stanford Sleepiness Scale (SSS) and line analog rating scale (LARS). *p<0.05, **p<0.001 for the post hoc Wilcoxon signed rank test. Pla: placebo, Fex: fexofenadine, Lev: levocetirizine, Dip: diphenhydramine (reproduced from Ref. 3).