The Effect of Loratadine on Psychomotor Function in Healthy Japanese Subjects : Comparison with *d*-Chlorpheniramine Maleate and Placebo in a Double-Blind 4-Way Crossover Study

Shigeyuki NAKANO^{*1,2} Yukiko SUNAMI^{*3} Shin IRIE^{*1,3}
Kyoko MATSUGUMA^{*3} and Hiroshi TSUKIKAWA^{*3}

^{*1} Department of Pharmaceutical Medicine, Oita University Faculty of Medicine, Oita, Japan

^{*2} International University of Health and Welfare Graduate School, Tokyo, Japan

^{*3} Kyushu Clinical Pharmacology Research Clinic, Medical Co. LTA, Fukuoka, Japan

The effect of loratadine, a new antihistamine, on psychomotor function was investigated in healthy Japanese volunteers using accuracy of typing figures into a personal computer as the index in a Latin-square double-blind crossover study with *d*-chlorpheniramine maleate as positive control and placebo as negative control. Twenty subjects typed figures for 15 minutes at 2 hours after receiving a single dose of 10 mg or 20 mg of loratadine after breakfast. The number of correct entries was counted automatically per subject as the primary variable. In the chlorpheniramine group the number of correct entries was significantly less than in the placebo and loratadine 10 mg and 20 mg groups ($p < 0.05$, $p < 0.05$, and $p < 0.01$, respectively). No significant difference was observed between the placebo, loratadine 10 mg, and loratadine 20 mg groups. The results suggest that loratadine, unlike *d*-chlorpheniramine maleate, does not affect psychomotor function at either the usual dose of 10 mg or at twice the usual dose (20 mg).

Key words : antihistamine drug, loratadine, *d*-chlorpheniramine, psychomotor performance, typing accuracy

Introduction

Classic antihistamines are known to induce sedation¹. Even when there are no complaints of subjective symptoms, psychomotor function decrement to some degree which may interfere with daily activities is observed in various tests. The quality of life of patients is also reported to be affected by even the so-called second-generation antihistamines², and sleepiness is reported to be induced by these drugs at the above clinical doses³.

Loratadine is a novel antihistamine drug which has been marketed since 2002 in Japan ; it is indicated for the treatment of itching associated with allergic rhinitis, urticaria and dermatological disorders (dermatitis and eczema, pruritus cutaneous). Clinical pharmacological studies of loratadine including the time to sedation⁴, motiva-

tion to perform activities during the workday⁵, effect on driving performance⁶, effect on pilot performance⁷, and influence on children's learning⁸, have already been conducted outside Japan. The results have confirmed that 10 mg/day, the usual dose of loratadine, does not affect psychomotor function.

Although many clinical pharmacological studies have already been conducted outside Japan to examine the sedative effect of loratadine, none have been performed in Japan. The incidence of sleepiness with loratadine was almost the same as that with low dose loratadine and placebo in phase III studies conducted in Japan in patients with chronic urticaria and perennial allergic rhinitis^{9,10}. A clinical pharmacological study is generally considered to provide strong supporting evidence in the interpretation of the results of phase II and phase

Address for correspondence : NAKANO S. Department of Pharmaceutical Medicine, Oita University Faculty of Medicine, 1-1 Idaigaoka, Hasama-machi, Yufu-city, Oita 879-5593, Japan
(Manuscript received March 22, 2007 ; revised June 30, 2007 ; accepted July 5, 2007)

III studies conducted in patients. The present study was therefore performed in healthy Japanese subjects to evaluate the effect of loratadine on psychomotor function at 10 mg/day, the usual dose, as well as 20 mg/day, double the usual dose, by Latin-square double-blind method using *d*-chlorpheniramine maleate as the positive control and placebo as the negative control.

Methods

The accuracy of typing figures into a personal computer was selected as the index to investigate the sedative effect of loratadine. Additionally, to assess changes in drowsiness of subjects, measurement by visual analogue scale (VAS) was also conducted. Assessment by VAS has been conducted in a clinical pharmacological study of a similar drug¹¹⁾, and this method is considered useful for interpreting the results obtained from the figure-typing. This study was conducted from November 2002 to February 2003 in compliance with the Helsinki Declaration and in accordance with GCP as well as various laws and regulations in Japan. The protocol of this study was approved by the Institutional Review Board of Kyushu Clinical Pharmacology Research Clinic, the medical institution which conducted this study.

1. Subjects

Nine male and eleven female healthy volunteers who were assessed by the investigators to satisfy the criteria for participation were selected. Written informed consent was obtained from each subject before enrollment in the study. Inclusion criteria were 1) Japanese living in Japan, 2) at least 20 years of age at the time of informed consent, 3) body weight of 40.0 to 80.0 kg with body mass index [body weight (kg)/height (m)²] of 18.5 to less than 25.0 at the time of screening, and 4) capable of typing 600 or more correct figures within 15 minutes on the day of figure-typing practice conducted between screening and the day of hospitalization. Exclusion criteria were 1) women who were pregnant, nursing or possibly pregnant, or who wished to become pregnant, 2) subjects who work mainly during the night, 3) subjects who had received loratadine in the past, and 4) subjects with an error rate of at least 5% on the day of figure-typing practice.

2. Study design

The effect of loratadine on psychomotor function was investigated in healthy male and female subjects in a Latin-square double-blind, 4-way crossover study by the double-dummy method using *d*-chlorpheniramine maleate 6 mg and placebo as control with efficiency of typing figures into a personal computer in the morning as the index. A combination of loratadine 10 mg tablet, *d*-chlorpheniramine maleate tablet (Polaramine® repetabs 6 mg), and matching placebos was administered orally, 3 tablets after breakfast and one tablet after supper. The combinations of study drugs for each treatment group are shown in Figure 1. Loratadine tablets and *d*-chlorpheniramine maleate tablets together with matching placebo were provided by Schering-Plough Ltd. (Osaka).

3. Study protocol

1) Preliminary study

A preliminary study was conducted prior to the main study to confirm the nature of data obtained in the figure-typing test and the target number of subjects planned for this study. The same inclusion and exclusion criteria were used as in the main study, and *d*-chlorpheniramine maleate tablet or its matching placebo was administered to 8 subjects by a single-blind 2×2 crossover method.

2) Main study

The subjects received the test drugs at 9:00 in the morning and 19:00 in the evening on Day 3 of hospitalization. Figure-typing was performed at 2 hours after drug administration.

3) Management of subjects

Alcohol and caffeine-containing drinks were prohibited. Subjects consumed the standard meal of the study site during the hospitalization period. Naps were prohibited on figure-typing days other than the practice day. Lying down, smoking, and activities inducing eye strain such as watching TV, reading books, and playing video games were also prohibited on figure-typing days other than the practice day from 2 hours before the start of the test until the completion of the test. The subjects were asked to rest in sitting position from 15 minutes before the start of the test.

4. Figure-typing

A figure-typing program software developed by

Treatment group	After breakfast			After supper
Loratadine 10mg	● + ○ + ○	Active	Placebo	Placebo
Loratadine 20mg	● + ● + ○	Active	Active	Placebo
Chlorpheniramine	○ + ○ + ●	Placebo	Placebo	Active
Placebo	○ + ○ + ○	Placebo	Placebo	Placebo

● : Loratadine 10mg tablet, ○ : Loratadine placebo tablet
 ● : *d*-chlorpheniramine maleate tablet (Polaramine® repetabs 6 mg),
 ○ : *d*-chlorpheniramine maleate placebo tablet

Fig. 1 Combination of study drugs for each treatment group

the Department of Clinical Pharmacology and Therapeutics of Oita University was used. Subjects performed continuous typing of 10-digit figures on a monitor display, using a single finger (index finger of the dominant hand). No corrections were allowed. After completion of typing the first 10-digit figure, the next 10 digits were shown on the screen, with the cursor automatically moving to the next typing column. The amount of correct typing in 15 minutes was counted automatically for each subject after each figure-typing test. The numeral keys on the top of keyboard were used for figure-typing. Subjects practiced using the figure-typing program software at the time of screening, on the practice day, and on the first day of hospitalization from the first to fourth periods. The results of typing during hospitalization were not disclosed to the subjects. The value obtained on Day 2 (drug-free state) of hospitalization in the first period was used as the baseline value.

5. Subjective feeling : drowsiness

The subjects recorded their drowsiness on VAS record forms¹²⁾ using a 100 mm scale at 7 time points, that is, before study drug administration (9 : 00) and at 11 : 00, 13 : 00, 15 : 00, 17 : 00, 19 : 00 and 21 : 00. The distance of each item at each time point was determined and recorded in millimeter (mm) units.

6. Sample size estimation

The target number of subjects was determined based on the results of the preliminary study. When analysis of normal distribution by frequency data was performed using the data obtained from the

preliminary study, the variation coefficient was the smallest and skewness was close to zero (0) with logarithmic transformation. Therefore, the value obtained by logarithmic transformation was used in the sample size calculation. Assuming two-sided 5% level of significance and 80% power, the sample size required to verify a difference between the placebo group and *d*-chlorpheniramine maleate group in a crossover study (4 drugs×4 periods) was estimated to be 19. Since there are 4 sequences in this study, 20, a multiple of 4, was established as the target number of subjects.

7. Statistical analysis

1) Figure-typing

ANOVA in a mixed effect model was performed using "the number of correct figures in the morning" as an index. When no significant difference was observed for sequence ($p > 0.1$) and a significant difference was observed for the drug groups, paired comparisons were performed between drug groups using the error variance from the model. Multiplicity was not taken into account.

2) Subjective feeling : drowsiness

ANOVA in a mixed effect model was performed using VAS as the value of drowsiness. When a significant difference was observed among drug groups, paired comparisons were performed between drug groups using the error variance from model.

3) Level of significance

The level of significance was set at two-sided 5%.

Results

Twenty subjects were randomized and 5 each

Table 1 The study design

Sequence	1st period	2nd period	3rd period	4th period
A group (5 cases)	Loratadine 10 mg	Placebo	Chlorpheniramine	Loratadine 20 mg
B group (5 cases)	Loratadine 20 mg	Loratadine 10 mg	Placebo	Chlorpheniramine
C group (5 cases)	Chlorpheniramine	Loratadine 20 mg	Loratadine 10 mg	Placebo
D group (5 cases)	Placebo	Chlorpheniramine	Loratadine 20 mg	Loratadine 10 mg

Study drugs were allocated in a Latin square design (A to D groups). All 4 drugs were given to each subject with at least a 1-week wash-out period.

were assigned to sequence A to D (Table 1). The demographic features and baseline values of figure-typing for the 20 subjects are shown in Table 2.

1. Figure-typing

Figure 2 shows the number of correct figures typed in the morning by each group. A significant difference was observed among the drug groups ($p < 0.01$) but no significant difference was noted among the sequences. A significant difference was also observed for the administration period ($p < 0.001$), indicating the presence of a learning effect. The subjects in the placebo group and loratadine 10 mg and 20 mg groups typed significantly more correct figures than those in the chlorpheniramine group ($p < 0.05$, $p < 0.05$, and $p < 0.01$, respectively). On the other hand, no significant differences were observed between the placebo, loratadine 10 mg, and 20 mg groups (Figure 2). In the evening, results similar to that in the morning were observed (data not shown).

2. Subjective feeling : drowsiness

Figure 3 shows changes in VAS (Alert-Drowsy) by group. Significant differences among drug groups were observed at 2 hours and 4 hours after administration in ANOVA ($p < 0.05$, $p < 0.01$, respectively). The measured distances in the scale at 2 hours after administration were 43.6 ± 4.8 mm (adjusted mean $\pm$ SE; same below) with the placebo group and 43.4 ± 4.8 mm and 39.7 ± 4.8 mm with the loratadine 10 mg group and 20 mg groups, respectively. All were significantly different from the distance of 59.9 ± 4.9 mm with the chlorpheniramine group ($p < 0.05$, $p < 0.05$, $p < 0.01$, respectively). There was a significant difference between the distance of 37.6 ± 5.0 mm with the placebo group and 58.3 ± 5.1 mm with the chlorpheniramine group at 4 hours after administration ($p < 0.001$) (data not shown).

Table 2 Subject characteristics

Variables		
Number of subjects		20
Sex	Male	9
	Female	11
Age (years)	Mean $\pm$ SD	22.9 ± 3.7
	Min-Max	20-35
Height (cm)	Mean $\pm$ SD	161.6 ± 7.4
	Min-Max	149.5-175.9
Body weight (kg)	Mean $\pm$ SD	54.2 ± 4.7
	Min-Max	46.2-61.7
BMI (kg/m ²)	Mean $\pm$ SD	20.8 ± 1.8
	Min-Max	18.5-23.7
Number of correct figures typed for 15 minutes in the morning	Mean $\pm$ SD	1044.6 ± 157.4
	Min-Max	780-1356

Discussion

It is known that sedation of CNS results from the interaction of antihistamines with central H₁ receptors. McQuade et al. examined seven antihistamines for ability to inhibit *in vivo* binding of ³H-mepyramine to mouse brain membranes¹³⁾. Only loratadine and terfenadine (withdrawn from market) did not inhibit *in vivo* binding of ³H-mepyramine, whereas diphenhydramine, chlorpheniramine, astemizole, mequitazine and cetirizine significantly decreased binding of ³H-mepyramine *in vivo*. They concluded that loratadine and terfenadine are antihistamines which do not cross the blood-brain barrier and therefore possess low sedative liability¹³⁾. Ongini et al. reported that p. o. administration of loratadine at 30 mg/kg did not affect the sleep-wake cycle of cats with chronically implanted electrodes, whereas p. o. administration of terfenadine at 30 mg/kg reduced rapid eye movement (REM) duration and p. o. administration of diphenhydramine at 3 mg/kg in-

Fig. 2 Number of correct figures typed at 2 hours after drug administration in the morning

Number of correct figures typed after drug administration in the morning. Columns shown are mean with standard error ($n=20$ each). ANOVA in mixed effect model was performed using "the number of correct figures in the morning" as the response variable, "the number of correct figures in the morning before drug administration" as covariate, and "drug group", "period" and "sequence" as fixed effect and "subjects" as a random effect. Following that significant difference was observed among the drug groups ($p=0.0086$), paired comparisons using error variance extracted from the mixed effect model between drug groups was performed regardless of multiplicity. There was no significant difference among placebo, loratadine 10 mg and 20 mg groups.

*: $p < 0.05$, **: $p < 0.01$

Fig. 3 VAS (Alert-Drowsy)

Mean of VAS (Alert-Drowsy) at baseline and 2 hours after administration was measured with standard error ($n=20$ each) of subjective sedative effects. ANOVA in a mixed effect model was performed using VAS as an indicator of drowsiness. A significant difference was observed among the drug groups ($p=0.0144$); then paired comparisons using error variance extracted from the mixed effect model were performed between drug groups regardless of multiplicity. There was no significant difference among placebo, loratadine 10 mg and 20 mg groups.

*: $p < 0.05$, **: $p < 0.01$

creased spindle sleep (i. e., the electrophysiological correlate of drowsiness) and suppressed REM sleep in cats¹⁴). These reports suggested that the sedative effect of loratadine was weak due to its lower affinity for brain H₁ receptors and lack of effect on the sleep-wake cycle.

Many clinical pharmacological studies have consistently demonstrated the non-sedative profile of loratadine, using several pharmacological endpoints⁴⁻⁸). In addition, many placebo-controlled clinical studies in patients with seasonal allergic rhinitis or allergic skin diseases have proven that the incidence of sedation of loratadine at the dose of 10 mg is comparable to that with placebo¹⁵). In fact, loratadine was classified as a non-sedating antihistamine by the US Food and Drug Administration (FDA)¹⁵).

In Japan, a placebo-controlled comparative study with loratadine was conducted in patients with allergic rhinitis to assess efficacy and safety of loratadine¹⁰). The incidences of sleepiness caused by loratadine did not differ between loratadine (13.6%) and placebo (12.9%) groups, suggesting that loratadine does not have a sedative effect. However, there have been no clinical pharmacological studies evaluating the sedative effect in Japanese.

Clinical pharmacological studies of other antihistamines have been conducted in Japan to investigate sedative effects, examining driving performance^{16,17}), typing accuracy^{11,18}), and accuracy of adding up figures¹⁹). Of these indices, the results of studies conducted to the present have indicated that data input into a personal computer represents a practical procedure which can be objectively and quantitatively assessed with a high degree of sensitivity^{11,18,20,21}). Although both the "alphabet-typing method" and "figure-typing method" have been used^{11,18,20,21}), the "figure-typing method" has been demonstrated to be highly sensitive even in subjects not familiar with handling a keyboard while the "alphabet-typing method" is highly sensitive only in trained subjects²⁰), and the sensitivity of figure-typing method is higher than that of the conventional performance tests²²). Then, in order to assess the effect of loratadine on psychomotor performance, a double-blind, placebo and *d*-chlorpheniramine maleate controlled, 4-way crossover study was conducted using "figure-typing method" by

operating efficiency in inputting figures into the personal computer as index. When this method is used, even a person who is familiar with a computer fails to input data correctly without concentration.

The primary endpoint in this study was correct input of figures after the drug was administered in the morning. For evaluation of changes in subjective symptoms of subjects, assessment by VAS was set as the secondary endpoint. The number of correct input was significantly high in the placebo, loratadine 10 mg and loratadine 20 mg compared to that in the chlorpheniramine group ($p < 0.05$, $p < 0.05$ and $p < 0.01$, respectively). On the other hand, a significant difference was not detected among placebo, loratadine 10 mg and loratadine 20 mg groups. Concerning the result of VAS (Alert-Drowsy), an index of subjective evaluation of subjective symptoms, although a significant difference was observed between the chlorpheniramine and placebo groups, the difference between the loratadine 10 mg and 20 mg groups, and the placebo group was not significant. As shown above, in the result of VAS as in the case of primary endpoint, no significant difference was consistently observed between the loratadine 10 mg and 20 mg groups, and the placebo group although a significant difference was observed between the chlorpheniramine and placebo groups.

The result of this study shows that loratadine has no sedative effect and that the figure-typing method is highly sensitive and sufficient to detect sedation.

Supported in part by a grant-in-aid for scientific research (c) from the Japan Society for the Promotion of Science (No. 15590469)

References

- 1) Slater JW, Zechnich AD, Haxby DG. Second-generation antihistamines : a comparative review. *Drugs* 1999 ; **57** : 31-47.
- 2) Mattila MJ, Paakkari I. Variations among non-sedating antihistamines : are there real differences? *Eur J Clin Pharmacol* 1999 ; **55** : 85-93.
- 3) Hindmarch I, Shamsi Z. Antihistamines : models to assess sedative properties, assessment of sedation, safety and other side effects. *Clin Exp Allergy* 1999 ; **29**(Suppl 3) : 133-42.
- 4) Roth T, Roehrs T, Koshorek G, Sicklesteel J, Zorick F. Sedative effects of antihistamines. *J Allergy Clin Immunol* 1987 ; **80**(1) : 94-8.
- 5) Salmun LM, Gates D, Scharf M, Greiding L, Ramon F,

- Heithoff K. Loratadine versus Cetirizine : assessment of somnolence and motivation during the workday. *Clin Therapeutics* 2000 ; **22**(5) : 573-82.
- 6) Ramaekers JG, Uiterwijk MMC, O'Hanlon JF. Effects of loratadine and cetirizine on actual driving and psychometric test performance, and EEG during driving. *Eur J Clin Pharmacol* 1992 ; **42** : 363-9.
 - 7) Neves-Pinto RM, Moreira Lima G, da Mota Teixeira R. A double-blind study of the effects of loratadine versus placebo on the performance of pilots. *Am J Rhinol* 1992 ; **6**(1) : 23-7.
 - 8) Vuurman EFP, van Veggel LMA, Uiterwijk MMC, Leutner D, O'Hanlon JF. Seasonal allergic rhinitis and antihistamine effects on children's learning. *Ann Allergy* 1993 ; **71** : 121-6.
 - 9) Kawashima M, Kukita A, Harada S, et al. The efficacy and safety of SCH29851 (Loratadine), a long-acting and selective histamine H₁ receptor antagonist, for chronic urticaria in a phase III, randomized, double-blind, multi-center comparative study-Investigation of the superiority of SCH29851 10 mg once daily to SCH29851 1 mg once daily and to ketotifen fumarate 1 mg twice daily-. *J Clin Therap Med* 2002 ; **18**(7) : 881-905.
 - 10) Okuda M, Ishikawa T, Baba K, et al. The efficacy and safety of loratadine for perennial allergic rhinitis in a phase III, randomized, double-blind, multi-center comparative study. *Practica Otologica Kyoto* 2002 ; **107**(Suppl) : 1-24.
 - 11) Urae A, Okada M, Irie S, et al. Effects of fexofenadine hydrochloride on psychomotor performance-Comparison of impaired performance of a word processor by fexofenadine hydrochloride with that by *d*-chlorpheniramine maleate in healthy volunteers-. *Jpn J Clin Pharmacol Ther* 2000 ; **31**(5) : 649-58 (in Japanese).
 - 12) Tyrer P. *The Role of Bodily Feelings in Anxiety*. Oxford University Press, 1976 : 31.
 - 13) McQuade RD, Richlan K, Duffy RA, Chipkin RE, Barnett A. In vivo binding properties of non-sedating antihistamines to CNS histamine receptors. *Drug Development Res* 1990 ; **20** : 301-6.
 - 14) Ongini E, Marzanatti M, Guzzon V. Comparative effects of loratadine and selected antihistamines on sleep-waking patterns in the cat. *Drug Development Res* 1987 ; **10** : 75-83.
 - 15) Nolen TM. Sedative effects of antihistamines : safety, performance, learning, and quality of life. *Clin Ther* 1997 ; **19**(1) : 39-55.
 - 16) Aso T, Sakai Y. Effects of Terfenadine on actual driving performance. *Jpn J Clin Pharmacol Ther* 1988 ; **19**(4) : 681-8 (in Japanese).
 - 17) Aso T, Okamoto K, Sakai Y. Effects of WAL801CL (Epinastine hydrochloride) on actual driving performance. *Jpn J Clin Pharmacol Ther* 1992 ; **23**(2) : 507-14 (in Japanese).
 - 18) Nakano S. Impaired performance test conducted in Japan. *Prog Med* 1993 ; **13** : 1138-9 (in Japanese).
 - 19) Nakano S, Naruo T, Watanabe K, et al. Chronopharmacological study of a non-sedative H₁-blocking agent (WAL801CL, Epinastine). *Jpn J Clin Pharmacol Ther* 1991 ; **22**(3) : 617-26 (in Japanese).
 - 20) Sunami Y, Umetsuki M, Niu S, et al. Study on impaired performance by drug-Development of figure typing program using a word processor-. *Jpn J Clin Pharmacol Ther* 1997 ; **28**(1) : 447-8 (in Japanese).
 - 21) Niu S, Kotegawa T, Sunami Y, et al. Influence of antihistamines on the figure typing using a word processor-Comparison between epinastine and *d*-chlorpheniramine-. *Jpn J Clin Pharmacol Ther* 1997 ; **28**(1) : 489-90 (in Japanese).
 - 22) Sunami Y, Uemura N, Niu S, Matsuki S, Nakamura K, Nakano S. Study on impaired performance by drug-Comparison of figure typing using a word processor with other performance test-. *Jpn J Clin Pharmacol Ther* 1999 ; **30**(1) : 203-4 (in Japanese).