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Comparative study of acute effects of single doses of fexofenadine, olopatadine, *d*-chlorpheniramine and placebo on psychomotor function in healthy volunteers

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Since most classical (first-generation) antihistamines have undesirable sedative effects on the central nervous system (CNS), newer (second-generation) antihistamines have been developed to relieve the sedative effects and to improve the patient's quality of life. However, the psychomotor profiles of second-generation antihistamines are not fully elucidated. In this randomized, double-blind, crossover study, the acute effects of single doses of second-generation antihistamines, fexofenadine (120 mg) and olopatadine (10 mg), on cognitive and psychomotor performance were investigated in comparison with those of placebo and *d*-chlorpheniramine (4 mg), a first-generation antihistamine, using objective and subjective assessments, in 11 healthy Japanese volunteers. In a battery of psychomotor tests, *d*-chlorpheniramine impaired tracking ability in the compensatory tracking task and caused a reduction in behavioural activity as continuously measured by wrist actigraphy. Olopatadine, like *d*-chlorpheniramine, reduced the behavioural activity, while fexofenadine had no effect in any of the tests. No significant changes in the subjects' self-ratings of drowsiness were found with the three antihistamines. These results suggest that *d*-chlorpheniramine and olopatadine, but not fexofenadine, produce sedative effects on psychomotor performance, and that the CNS profile of fexofenadine is different from that of olopatadine.

KEY WORDS — antihistamines; psychomotor performance; sedation; *d*-chlorpheniramine; fexofenadine; olopatadine

INTRODUCTION

Antagonists of histamine H_1 receptors, antihistamines are widely used for the treatment of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria. It is well known that the classical (first-generation) antihistamines such as *d*-chlorpheniramine, diphenhydramine and promethazine, have undesirable side effects including sedation, at therapeutic doses (Simons, 1994; Hindmarch and Shamsi, 1999; Shamsi and Hindmarch, 2000). Sedation induced by antihistamines impairs cognitive and psychomotor functions (Passalacqua *et al.*, 1993). Notably, daytime sedation disturbs the ability to perform daily work such as driving a vehicle and operating machinery, and thus increases the risk of accidents (Brookhuis *et al.*, 1993). Further, excessive sedation reduces the patient's compliance with treatment regimens (Pechadre *et al.*, 1991).

The sedative effect of antihistamines on the central nervous system (CNS) is due to their ability to cross the blood–brain barrier and to block histamine neurotransmission through central H_1 receptors. A number of the newer (second-generation) antihistamines,

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which do not readily cross the blood–brain barrier, have been developed to relieve side effects on the CNS and to improve the quality of life (Nolen, 1997; Tagawa *et al.*, 2001; Tashiro *et al.*, 2002). Some second-generation antihistamines do not impair the function of the CNS at the recommended doses, but have sedative effects at higher than the recommended doses (O'Hanlon and Ramaekers, 1995). Therefore, their sedative effects should be investigated in detail using objective psychometric assessments.

Recently, fexofenadine, a second-generation antihistamine, was approved in Japan for the treatment of allergic disorders at a recommended total daily dose of 120 mg (60 mg twice daily). Fexofenadine is a selective H_1-receptor antagonist, which does not readily penetrate the blood–brain barrier, and thus allows an effective blockade of H_1-receptors in peripheral tissues without any central side effects (Bernstein *et al.*, 1997; Howarth *et al.*, 1999). With regard to its CNS profile, it has been reported that fexofenadine does not produce any disruptive effects on psychomotor or cognitive performance in European healthy volunteers, when administered at doses up to 360 mg (Hindmarch *et al.*, 1999, 2002). However, there is little evidence for the Japanese population. It is known that there is a racial difference in the effects of CNS-active drugs. For example, nitrazepam shows a difference in sedative effect between Japanese and Europeans, although there are no pharmacokinetic differences between the two populations (van Gerven *et al.*, 1998). Therefore, it is possible that the CNS profile in the pharmacodynamics of fexofenadine in Japanese subjects is different from that in European subjects.

Another novel second-generation antihistamine, olopatadine was also approved in Japan for the relief of symptoms of allergic rhinitis, chronic urticaria and itching associated with skin diseases at a recommended total daily dose of 10 mg (5 mg twice daily). Further, an ophthalmic solution of olopatadine was approved in the United States and European Union for the treatment of seasonal allergic conjunctivitis. Olopatadine is a selective H_1-receptor antagonist with a potent antiallergic property. After a single oral administration to healthy volunteers at doses of 5, 10, 20, 40 and 80 mg, olopatadine is absorbed rapidly with the maximum concentration reached within 0.5–2 h (Ohmori *et al.*, 2002). Its elimination half-life ranges from 7 to 9 h (Ohmori *et al.*, 2002). Olopatadine effectively suppresses histamine-induced wheal and flare within 1 h of a single oral administration at 5 mg in healthy volunteers (Morita *et al.*, 2002). Furthermore, olopatadine at doses of between 2.5 and 10 mg administered twice daily for 7 days effectively suppresses histamine- and allergen-induced skin wheal in volunteers with seasonal allergic rhinitis (Hamilton *et al.*, 1994). The inhibitory effects of olopatadine are greater than those of terfenadine at 60 mg twice daily for 7 days (Hamilton *et al.*, 1994). Clinical phase III studies have shown that olopatadine is effective in the treatment of allergic rhinitis and chronic urticaria at 10 mg twice daily for 2 or 4 weeks (Ohmori *et al.*, 2002). These studies have also indicated that it is well tolerated and produced no serious side effects. The major adverse reaction was drowsiness. However, the sedative property of olopatadine is not clear, because its effect on psychomotor or cognitive performance has not been examined to date.

Thus, the present study was designed to investigate the effects of fexofenadine and olopatadine on psychomotor and cognitive function in Japanese healthy volunteers, in comparison with placebo and *d*-chlorpheniramine, a positive control.

MATERIALS AND METHODS

The present study was approved by the institutional review board of the Medical School Hospital of Nagoya University.

Subjects

All subjects gave written informed consent with respect to their participation in the study. Eleven healthy Japanese volunteers (6 female, 5 male) aged between 21 and 29 (mean $\pm$ SE: 24.8 ± 0.8) years were entered into the study. The sample size in the present study is small, since the aim was to search for adequate doses of test drugs. None of the subjects had evidence of previous or current physical and mental illness on the basis of medical history, a clinical examination, a 12-lead electrocardiogram, and standard laboratory tests of plasma and urine. None had a history of alcohol or drug abuse or drug allergy. Subjects received no medication for 2 weeks before and during the study.

Study design and treatments

The study was a randomized, double-blind, placebo-controlled, crossover study with four periods of treatment each separated by a washout period of 6 days. During each period, subjects received a single dose of each of the study drugs: *d*-chlorpheniramine (4 mg: half daily dose), a first-generation antihistamine, fexofenadine (120 mg: daily dose) and olopatadine (10 mg: daily dose), second-generation

antihistamines, and placebo. The study drugs were assigned according to the randomization list. All treatments were supplied in capsules, which were identically matched in size, colour and shape to respect the double-blind nature of the study. The study drugs were administered with about 150 ml of water.

Procedure

The examination was performed over 4 weeks at intervals of 1 week. Subjects attended the examination site on the day before each of the test days, where breath alcohol, health and medication were checked. On the day before the first test, they received sufficient training (at least three times) for the psychometric tests in order to eliminate the effects of learning (Parkin *et al.*, 1997). At each visit, they were instructed to go to bed in a single room at the examination site at 23:00 h.

On each of the test days, the subjects were awakened and gathered in the examination room at 7:00 h, and then breath alcohol was checked. The psychometric tests (described below) before medication (a baseline measurement) were performed at 8:00 h. Thirty minutes after breakfast, study drugs were administered at 9:30 h, and then the tests were carried out at 1, 2, 4, 6 and 8 h after drug administration.

The use of alcohol, nicotine, caffeine and grapefruit were prohibited for 2 days before and during testing. Food consumption was strictly controlled the night before and during testing. Adverse events and concomitant medication were recorded at each visit.

Assessments

Critical flicker fusion. Critical flicker fusion (CFF) was used as a means of measuring overall CNS arousal using the ability to discriminate discrete 'bits' of sensory information (Hindmarch, 1982). The test device was composed of four light-emitting diodes arranged in a 1 cm square. The diodes were held in foveal fixation 1 m from the subject. The lights flicked on and off at a constantly increasing or decreasing rate. Subjects were required to discriminate flicker from fusion, and vice versa. Individual thresholds were determined as the mean of each threshold in four ascending (flicker to fusion) and four descending (fusion to flicker) measurements.

Choice reaction time. The choice reaction time (CRT) was used as a sensitive measure of drug-induced changes in sensorimotor performance (Hindmarch, 1980). The test device was composed of a central starting button, six red buttons aligned in the shape of a fan, which were equally separated from the starting button, and six green lights located behind each red light. Subjects placed the index finger of their preferred hand on the starting button and then were required to extinguish one of six equidistant red lights, illuminated at random, by touching the corresponding response button in front of the light as quickly as possible. The green light was used as a potential stimulus of the red light lighting. The time between the red light lighting and touching the response button was taken as the CRT. The mean reaction time for 48 stimulus presentations was recorded.

Compensatory tracking test. The compensatory tracking test (CTT) was used as a means to assess divided attention (Hindmarch *et al.*, 1983). Subjects were required to keep a cursor in alignment with a moving target on a visual display unit screen using a mouse. The evaluation measure of this tracking task was the mean difference between the centres of the target and cursor in pixels, sampled 5 times per second, during the 9 min test period. Lower scores are indicative of more accurate tracking.

In addition, a peripheral awareness task is included in which the subject responds to a stimulus presented in the periphery of vision, while simultaneously attending to the tracking task described above. The mean reaction time to these stimuli over the trial period was taken as the response measure for this component of the divided attention task.

Rapid visual information processing. Rapid visual information processing (RVIP) was used as a means to assess attention performance (Wesnes and Warburton, 1983). Subjects were required to monitor a series of single digits (0–9) appearing on the screen at a rate of 100 digits every minute and respond to consecutive sequences of three odd or even digits by using a mouse button during the 9 min test period. The RVIP task was performed just before and 2 h after administration of study drugs. The evaluation measures are the mean reaction time and number of correct and wrong responses.

Line analogue rating scale. The line analogue rating scale (LARS) was employed as a measure of the subjective effects of psychoactive drugs (Hindmarch and Gudgeon, 1980). Subjects were required to mark the point, which represented their feeling, on the 100 mm line analogue scales. The mean score of rating of drowsiness was taken as a measurement of sedation (Hindmarch *et al.*, 2002).

Wrist actigraphy. Actigraphy has been shown to be capable of measuring reductions in behavioural

activity (sedation) caused by psychoactive drugs (Stanley, 1997; Stanley and Hindmarch, 1997). On each test day, a watch-type wrist actigraph (WA: Actiwatch, Cambridge Neurotechnology Ltd, UK) was placed on the wrist of subjects to detect three-dimensional movements, and the behavioural activity of subjects was measured from 1 h pre-dose to 8 h post-dose. WA contains a piezoelectric transducer that detects motion in all three axes and generates a signal voltage. In zero crossing mode, each crossing of the reference voltage during an epoch is counted, which gives a measure of the frequency but not the intensity (amplitude) of the movements. Mean behavioural activity over the whole recording period was automatically calculated for % sleep-like behaviour using the ACTION3 software and its validated sleep/wake algorithm (Ambulatory Monitoring Inc, USA).

Analysis

The data were analysed using the one-way ANOVA or two-factor factional ANOVA, followed by Scheffe's test, on the changes from baseline measurements. A *p*-value of less than 0.05 defined statistical significance.

RESULTS

All 11 subjects completed the four periods of the study. As shown in Table 1, there was no difference in baseline data for each parameter among the treatment groups used in this study.

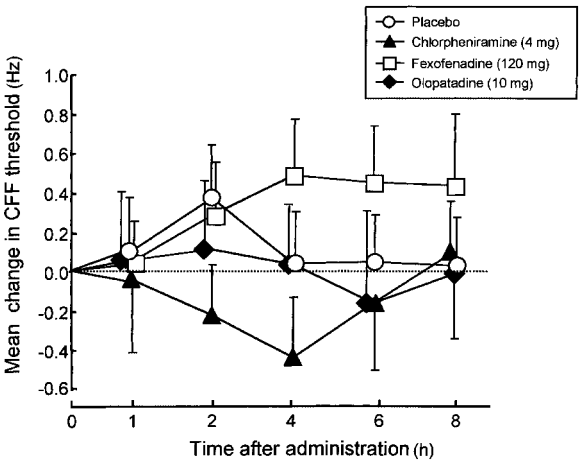

Figure 1. The effects of antihistamines on critical flicker fusion (CFF) thresholds. Each value represents the mean change from baseline, and is the mean ± SEM of 11 subjects

For CFF (Figure 1) and CRT (Figure 2) tests, a two-factor factional ANOVA indicated that the main effect of group was not significant.

The effects of antihistamines on the tracking task in the CTT are shown in Figure 3. A two-factor factional ANOVA showed a significant main effect of group [$F(3, 219) = 4.3535$, $p < 0.01$], although the effects of time and interaction between group and time were not significant [$F(4, 219) = 2.2507$ and $F(12, 219) = 0.5578$, respectively]. *Post-hoc* pair-wise comparisons confirmed that *d*-chlorpheniramine

Table 1. Baseline data for the psychomotor performance

Assessment	Placebo	Chlorpheniramine (4 mg)	Fexofenadine (120 mg)	Olopatadine (10 mg)
CFF (Hz)	27.9 ± 0.8	28.0 ± 0.5	27.4 ± 0.5	27.9 ± 0.6
CRT (ms)	594.8 ± 13.5	596.4 ± 11.4	592.0 ± 14.5	589.9 ± 11.1
CTT Tracking task (pixels)	16.9 ± 1.4	15.1 ± 1.1	15.1 ± 0.8	15.9 ± 1.1
CTT Peripheral awareness task (ms)	499.5 ± 37.2	524.2 ± 33.2	510.9 ± 23.9	513.9 ± 31.3
RVIP Number of correct responses	73.0 ± 4.6	75.8 ± 4.4	76.8 ± 4.9	77.9 ± 4.6
RVIP Number of wrong responses	1.5 ± 0.4	2.0 ± 0.6	3.1 ± 0.9	2.4 ± 0.8
RVIP Reaction time (ms)	515.1 ± 13.3	508.1 ± 8.9	521.3 ± 17.7	522.1 ± 16.9
LARS (mm)	53.5 ± 2.6	56.3 ± 2.9	51.5 ± 2.6	51.9 ± 4.8
WA Sleep-like behaviour (%)	27.3 ± 6.8	21.1 ± 6.2	22.6 ± 5.0	21.8 ± 6.3

Values are the mean ± SE.
CFF, critical flicker fusion; CRT, choice reaction time; CTT, compensatory tracking test; RVIP, rapid visual information processing; LARS, line analogue rating scale; WA, wrist actigraphy.

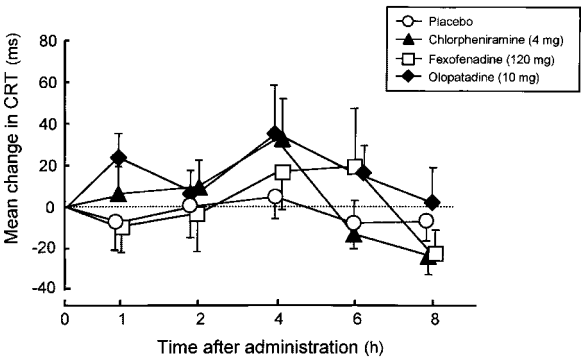

Figure 2. The effects of antihistamines on choice reaction time (CRT). Each value represents the mean change from baseline, and is the mean ± SEM of 11 subjects

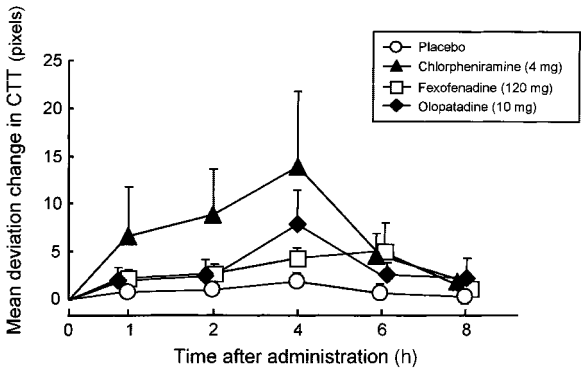

Figure 3. The effects of antihistamines on tracking ability in the compensatory tracking task (CTT). Each value represents the mean change from baseline, and is the mean ± SEM of 11 subjects

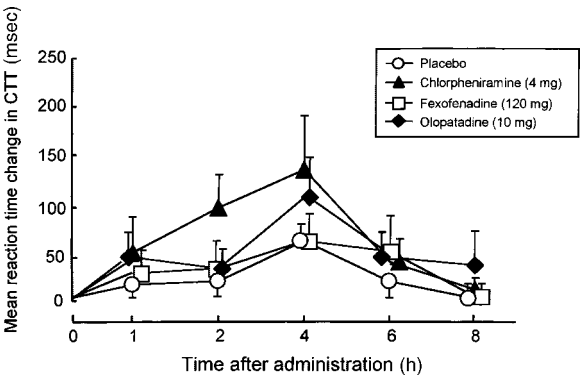

Figure 4. The effects of antihistamines on reaction time in the compensatory tracking task (CTT). Each value represents the mean change from baseline, and is the mean ± SEM of 11 subjects

significantly increased the deviation from the target point compared with the placebo ($p < 0.01$), which indicated that *d*-chlorpheniramine reduced the tracking ability in the CTT. However, there was no significant main effect of group on the peripheral awareness task in the CTT (Figure 4).

For RVIP (Figure 5), a one-way ANOVA of correct responses or reaction time showed that there was no significant main effect of group. An analysis of wrong responses indicated a significant main effect of group [$F(3, 43) = 3.3063$, $p < 0.05$]. However, *post-hoc* pairwise comparisons among the *d*-chlorpheniramine, fexofenadine or olopatadine group and placebo group failed to reach a level of significance.

A two-factor factional ANOVA on the sedation score of LARS revealed that there was no significant main effect of group (Figure 6).

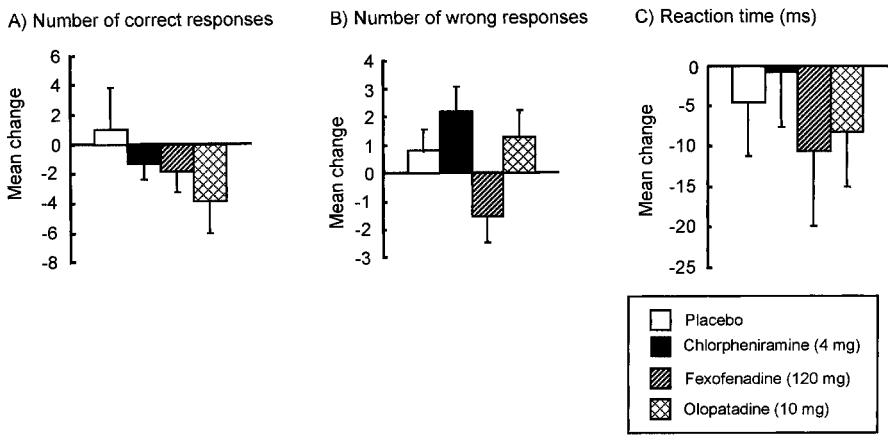

Figure 5. The effects of antihistamines on correct response (A), wrong response (B) and reaction time (C) in the rapid visual information processing task. Each value represents the mean change from baseline, and is the mean ± SEM of 11 subjects

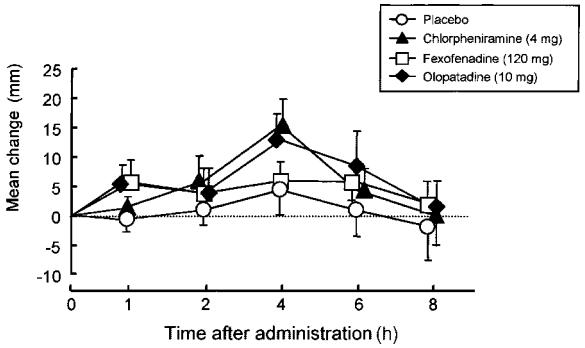

Figure 6. The effects of antihistamines on line analogue rating scale of drowsiness. Each value represents the mean change from baseline, and is the mean ± SEM of 11 subjects

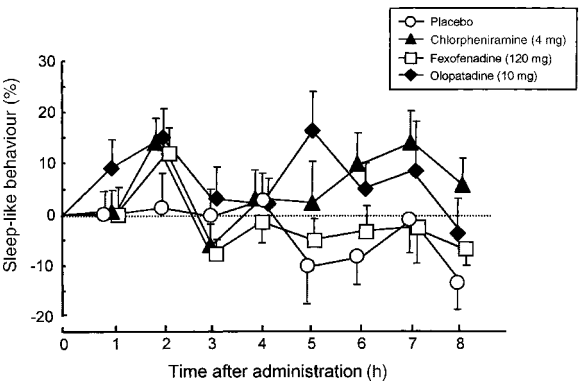

Figure 7. The effects of antihistamines on sleep-like activity measured by wrist actigraphy. Each value represents the mean change from baseline, and is the mean ± SEM of 11 subjects

An analysis of percentage sleep measured by WA showed a highly significant effect of group [$F(3, 351) = 6.4208$, $p < 0.001$] and a significant effect of time [$F(7, 351) = 2.4706$, $p < 0.05$], although the effect of interaction between group and time was not significant [$F(21, 351) = 0.8117$] (Figure 7). *Post-hoc* pair-wise comparisons revealed that *d*-chlorpheniramine and olopatadine caused a significant reduction in behavioural activity when compared with the placebo ($p < 0.05$ and $p < 0.01$, respectively). There was also a significant difference between fexofenadine and olopatadine groups ($p < 0.01$).

There were no serious adverse events and no subject withdrew due to drug intolerance or any drug-related adverse event.

DISCUSSION

In the present study, the acute effects were evaluated of fexofenadine and olopatadine, second-generation antihistamines, on the cognitive and psychomotor function in comparison with placebo and *d*-chlorpheniramine, a first-generation antihistamine, by using various psychometric tasks.

The psychometric tests used in this study have been shown to be valid and reliable measures in the evaluation of cognitive and psychomotor function impaired by sedative antihistamines and other psychoactive substances (Hindmarch *et al.*, 1999, 2002; Stanley and Hindmarch, 1997). The various psychometric tests have been categorized according to their most relevant feature. Namely, Shamsi and Hindmarch (2000) have proposed that CFF, CRT, CTT, RVIP, WA and LARS are useful as a means of measuring arousal, psychomotor-speed, sensorimotor coordination, attention, physiological and subjective ratings, respectively.

A single oral administration of *d*-chlorpheniramine at a half daily dose (4 mg) impaired tracking ability in the CTT and caused a reduction in behavioural activity as measured by WA. But it failed to affect the performance in the other objective assessments including CFF, CRT and RVIP, and the score of LARS used as a subjective assessment of sedation. Recently, it has been reported that changes in pupil diameters induced by serotonin reuptake inhibitors affect the CFF thresholds (Schmitt *et al.*, 2002). Thus, it is possible that psychoactive drugs, which affect the pupil diameters, modify the outcome of CFF measurements. However, *d*-chlorpheniramine (4 mg) and second-generation antihistamines such as terfenadine (60 mg) and astemizole (10 mg) do not change the pupil size and CFF thresholds (Kulshrestha *et al.*, 1978; Nicholson *et al.*, 1982). Several investigators have also observed the ability of *d*-chlorpheniramine to impair psychomotor performance in studies conducted with a randomized, double-blind, placebo-controlled crossover design. For instance, Clarke and Nicholson (1978) have reported that *d*-chlorpheniramine (4 mg) impairs tracking ability in the visuo-motor coordination task, which is similar to the CTT used in the present study. Unchern *et al.* (1986) have observed that *d*-chlorpheniramine impairs performance in tests for psychomotor coordination function, but not in tests for alertness and cognitive functions. On the other hand, Kulshrestha *et al.* (1978) have reported that *d*-chlorpheniramine (4 mg) fails to affect the threshold in the CFF and reaction time task, which is similar to the CRT used in this study, the results being consistent with our results.

It has been reported that the sedative effects of *d*-chlorpheniramine at 4 mg, which is the therapeutic dose, are weaker than those of other first-generation

antihistamines such as diphenhydramine in objective tests (Witek *et al.*, 1995), although they were more apparent after repeated doses for 4 days (Hindmarch and Parrott, 1978). In contrast to *d*-chlorpheniramine, a highly sedative first-generation antihistamine, promethazine at 25 or 30 mg, which is the therapeutic dose range, has been demonstrated to cause an impairment of performance in most of the tests used in this study (Hindmarch *et al.*, 1999, 2002). These findings taken together with our results, show that *d*-chlorpheniramine does not have a highly sedative effect for a first-generation antihistamine.

A second-generation antihistamine olopatadine at a daily dose of 10 mg, as well as *d*-chlorpheniramine, showed a decrease in behavioural activity as measured by WA, although it failed to affect other assessments. It has been shown that reduced behavioural activity indicated by WA is associated with sedation (Stanley, 1997; Stanley and Hindmarch, 1997). WA provides a continuous measurement of psychomotor function, which is different from other measurements. Promethazine, as well as other psychoactive drugs, lowers motor activity as assessed by WA (Hindmarch *et al.*, 1999). Thus, WA is capable of accurately measuring daytime sedation and is a useful measure of the effects of psychoactive drugs on behavioural activity. Since *d*-chlorpheniramine and olopatadine failed to affect the subjects' self-ratings of sleep in the present study, it is suggested that the assessment of sedation by WA is more sensitive than subjective assessment.

In contrast to *d*-chlorpheniramine and olopatadine, fexofenadine at a daily dose of 120 mg had no significant effect in any test, which was consistent with the findings in our previous study (Hindmarch *et al.*, 1999, 2002). Fexofenadine does not have any disruptive effects on psychomotor or cognitive performance in healthy European volunteers, when administered at doses of up to 360 mg, in a double-blind, placebo-controlled study with objective psychometric assessments (Hindmarch *et al.*, 2002). Recently, a study using positron emission tomography techniques has demonstrated that in healthy Japanese volunteers, *d*-chlorpheniramine administered orally even at a dose as low as 2 mg occupies 50% of histamine H_1 receptors in the cerebral cortex (Tagawa *et al.*, 2001), whereas fexofenadine at 120 mg does not (Tashiro *et al.*, 2002). These findings suggest that the degree of the sedative effect induced by antihistamines is related to the ability to penetrate the brain–blood barrier, and that the absence of effects on psychomotor performance by fexofenadine is due to its lower penetration of the CNS. Experiments with LLC-PK1 cells, a polarized epithelial cell line lacking *p*-glycoprotein, and with *p*-glycoprotein knock-out mice have shown that fexofenadine is effectively transported by *p*-glycoprotein (Cvetkovic *et al.*, 1999). Thus, fexofenadine's lower penetration of the human brain may be due to the *p*-glycoprotein in the brain–blood barrier, although further study is required to clarify the possible role of *p*-glycoprotein in the fexofenadine disposition. Another possibility regarding the profile of fexofenadine is that it has a mild stimulative effect on the CNS. It has been reported that fexofenadine enhances driving performance when administered at 120 mg twice daily for 4 days (Vermeeren and O'Hanlon, 1998). A similar observation has been reported with ebastine, another non-sedative second-generation antihistamine (O'Hanlon and Ramaekers, 1995). These findings suggest that some antihistamines have the effect of increasing arousal, which may contribute to their non-sedative property, although their pharmacological actions are not clear.

In conclusion, fexofenadine did not cause any psychomotor dysfunction in Japanese or European volunteers even when administered at its regular daily dose. This finding is in contrast to the sedative effect of *d*-chlorpheniramine, a first-generation antihistamine. Further, it is suggested that fexofenadine is more useful than olopatadine in patients who engage in activities requiring mental alertness, since the present results show a difference between the two antihistamines in continuous behavioural activity. However, further comparative studies should be carried out using more subjects to determine the clinical profile of antihistamines in the relationship between their efficacy (antihistaminic activity) and sedative side effects on the CNS.

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