Allergy medication in Japanese volunteers: treatment effect of single doses on nocturnal sleep architecture and next day residual effects

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Key words: Antihistamines – Chlorpheniramine – Fexofenadine – Japanese – Residual effects – Sleep

Abstract

Objectives: To evaluate the acute effects of two histamine H1-receptor antagonists on nocturnal sleep architecture and on next day cognitive function and psychomotor performance.

Methods: This was a single-site, randomized, double-blind, 3-way crossover study, comparing the effects of a single dose of chlorpheniramine (8 mg), fexofenadine (120 mg) and placebo in 16 healthy (male and female) Japanese volunteers aged 20–65 years. Volunteers were resident for 3 days and each period was separated by a minimum 5-day washout period. The three treatments were administered at 23.00 h. Overnight sleep was measured from 23.00 h to 07.00 h, using polysomnography. Residual effects were studied at 07.00 h and 9.00 h the next morning, with the latency to sleep (sleep latency test) measured at 06.30 h.

Results: Compared with placebo, chlorpheniramine increased the latencies to sleep onset and rapid eye movement (REM) sleep (p ≤ 0.05 for both), and reduced the duration of REM sleep (p ≤ 0.01), but this was not observed with fexofenadine. As far as residual effects the next morning were concerned there were decrements in performance with chlorpheniramine, but not with fexofenadine. Chlorpheniramine 6 mg impaired divided attention (p < 0.001), vigilance (p < 0.05), working memory (p < 0.0001) and sensorimotor performance (p < 0.01), and the latency to daytime sleep was reduced (p < 0.0001). Six adverse events possibly related to study medication were reported during the study, three of which were related to placebo, two to fexofenadine and one to chlorpheniramine.

Conclusion: These findings suggest that a single nocturnal dose of fexofenadine has advantages over the first-generation antihistamine chlorpheniramine, being free of disruption of night-time sleep and detrimental effects on cognitive performance the next day. It is likely that this advantage will remain with chronic ingestion, but this would need to be confirmed.

Introduction

Chronic idiopathic urticaria (CIU) and allergic rhinitis (AR) affect around 10–25% of the population. Symptoms associated with these disorders are produced by the release of inflammatory mediators from mast cells and other inflammatory cells such as lymphocytes and polymorphonuclear cells. The most important mediator, and a major contributor to symptoms seen in both CIU and AR, is histamine which acts on
histamine $H_3$-receptors throughout the peripheral and the central nervous systems. The so-called first-generation antihistamines were lipophilic and crossed the blood-brain barrier with ease, interacting with central histamine receptors. These antihistamines are one of the main classes of drugs used to alleviate symptoms of allergic disorders. However, first-generation antihistamines are historically associated with side effects such as sedation and reduced psychomotor and cognitive function. Cognitive impairment may be a consequence of increased sedation and reduced alertness. However, impairment of specific cognitive functions such as memory, may not be solely accounted for by the sedative actions of antihistamines, but arise from a direct action on memory processes.

In addition, first-generation antihistamines are associated with non-selective actions. Pathophysiological effects such as urinary retention and cardiac arrhythmias have been shown to be caused by reactivity of monoaminergic and cholinergic systems. In this context, selective, hydrophilic antihistamines, termed second-generation antihistamines have been developed over the years to improve safety and reduce side effects. Second-generation antihistamines do not cross the blood-brain barrier readily, and may selectively antagonize peripheral histamine $H_3$-receptors. These antihistamines include fexofenadine and loratadine and their therapeutic efficacy has been well-documented. For example, fexofenadine has shown therapeutic efficacy in chronic idiopathic urticaria and allergic rhinitis, with few if any deleterious side effects.

Fexofenadine is now available in many countries and was recently licensed for use in Japan, a country which represents 20% of the overall global allergy market. Although the effects of first-generation antihistamines and fexofenadine have been widely studied in Western populations, there are limited data comparing the effects of first- and second-generation antihistamines in Japanese subjects. Where drugs are predominantly metabolized by the liver, genetic polymorphism of cytochrome P (CYP) 450 enzymes may make certain subjects and populations more sensitive to the side effects of the drug. Therefore, it is important to assess the effects of medication in all populations to assess the risk benefit ratio of the treatment in question.

First-generation antihistamines, such as chlorpheniramine, undergo significant hepatic metabolism by the P450 isoenzyme CYP2D6 and it is known that CYP2D6 mutant alleles leading to relatively low CYP2D6 activity are fairly common in the Japanese population. In contrast, fexofenadine undergoes negligible hepatic metabolism and is, therefore, less likely to be influenced by genetic variation.

The aim of this study was to compare the effects of a second-generation antihistamine, fexofenadine, on nocturnal sleep architecture immediately after dosing and on sedation, cognitive function and psychomotor performance the morning after drug administration, in healthy Japanese volunteers. There is a lack of information concerning the effects of both first- and second-generation antihistamines on sleep architecture and this study gave an opportunity to characterize any differential effects that the drugs may have on the sleep process.

**Methods**

**Subjects**

Healthy male and female Japanese volunteers aged 20–55 years, with a body mass index (BMI) greater than or equal to 18 and less than or equal to 30, and no history of physical or mental illness were eligible for enrolment. Volunteers were excluded if they had participated in another study within the last 6 months prior to the study, or were receiving any regular medication, except (where female) oral contraceptives. In addition, those participants with a history of drug allergy, malignant tumours or with significant disease or abnormality were excluded. Pregnant or breastfeeding females and volunteers with a history of drug abuse, including alcohol, or with an irregular sleep/awake cycle were also excluded.

Volunteers underwent a medical examination including a 12 lead electrocardiogram (ECG), haematology, urinalysis, biochemical examination of blood and screening for drugs of abuse. All participants were familiarized with the study procedures before the study began and written informed consent was obtained.

**Subject number**

Eighteen healthy Japanese volunteers were randomized to the study. No formal power calculation was carried out. However, from previous experience with similar clinical trials in Caucasian subjects, 18 volunteers were determined to be sufficient.

**Study design**

This was a single-site, randomized, double-blind, single dose 3-way crossover study. The study was performed over three periods and each study period was separated by at least a 5-day washout period. The treatment sequence was balanced for residual effects using a Latin Square design. The drugs under investigation were placebo, fexofenadine 120mg and chlorpheniramine 6mg.

Period 1 included a habituation night (D-1), to familiarize the subjects with the environment, a baseline
PSG night (D1) and daytime psychometrics (D2) and a treatment night (D2) and treatment psychometrics (D3). All other periods contained a re-habitation night and treatment night only. Each period was separated by at least 5 days in order to ensure adequate washout of the treatment and avoid carryover effects. Plasma half-lives for chlorpheniramine and fexofenadine were estimated at 17.6 ± 4.4 and 13.8 ± 8.9 h respectively with 6 half-lives corresponding to 4.4 and 3.5 days. Thus a 5-day washout period was deemed appropriate for this study.

The study was conducted at the Centre for Clinical Trials and Clinical Research, Kitasato University East Hospital, Japan and the data analysed at the Human Psychopharmacology Research Unit, School of Biomedical and Molecular Sciences, University of Surrey, UK. The study was approved by the institutional review board, Kitasato University East Hospital and carried out in accordance with the Declaration of Helsinki.

Volunteers were not allowed to consume citrus fruits and apples during the 1-week period before study drug administration, or any food or drinks containing St. John's Wort during the 2-week period before study drug administration as these might affect the metabolism of the study drugs\textsuperscript{32,33}. Additionally, consumption of beverages containing caffeine or alcohol and products containing nicotine were prohibited 24 h prior to and during each study period, as these compounds are known to affect various cognitive and psychomotor functions\textsuperscript{33,32}. To ensure compliance with study protocol, a breath alcohol test and test for drugs of abuse were taken on Day 1 for each study period and volunteers were supervised throughout each period. For safety, a urine pregnancy test was required for all female participants.

Baseline measures were obtained on Day 1 of the first study period. Study medication (fexofenadine 120 mg, chlorpheniramine 6 mg or placebo) was administered at 22:55 on Day 1. All treatments were supplied in identical capsules. Volunteers stayed at the Centre overnight and conducted a Sleep Latency Test (SLT) and psychometric tests the following morning. The same procedure was carried out on three separate occasions to receive each of the treatment options, with a washout period of at least 5 days between each treatment.

Assessments

The measure of primary interest was the latency to sleep onset during the morning after night-time dosing with chlorpheniramine 6 mg, fexofenadine 120 mg and placebo. The Sleep Latency Test (SLT) was carried out at 09:30 h in the morning, 10:35 h post-dose. The subjects were asked to lie in the supine position on a bed in a dark room and asked to try to fall asleep. The time taken for three epochs of Stage 2 sleep was measured by electroencephalogram (EEG)\textsuperscript{32}. Of secondary interest was cognitive function and psychomotor performance the morning after night-time dosing. The measures included: Critical Flicker Fusion (CFP) (overall mean, mean ascending, mean descending and interval of uncertainty in Hz); Continuous Tracking Task (CTT) (tracking accuracy in pixels and mean peripheral reaction time in ms); Sternberg Memory Scanning Task (STM) (mean reaction time in ms); Rapid Visual Information Processing task (RVIP) (number of valid responses and valid response time in ms) and Choice Reaction Time (CRT) (recognition reaction time [RRT], motor reaction time [MRT] and total reaction time [TRT] in ms)\textsuperscript{32,33}. These psychometric tests were performed the morning after dosing at 8 h and 10 h post-dose.

Subjective ratings of sedation, mood and co-ordination the morning after night-time dosing, were assessed by Line Analogue Rating Scale (LARS), Milford Epworth Sleepiness Scale (MESS) (mean analogue score in mm) and Leeds Sleep Evaluation Questionnaire LSEQ (analogue score in mm)\textsuperscript{32,33}. LARS was performed at 8 h and 10 h post-dose, while LSEQ and MESS were performed at only one time point, 8 h and 10 h post-dose, respectively. The tests used in this battery have been used in previous studies with Japanese subjects and the subjective rating scales have been translated and validated in Japanese\textsuperscript{35}.

Night-time sleep architecture was assessed using polysomnography (PSG). Variables analysed included: sleep efficiency (%), total sleep time (min), latency to sleep Stages 1, 2, 3, 4 and rapid eye movement (REM) sleep (min), numbers of awakenings, and duration and percentage of wake throughout the night. Total duration and percentage of Stages 1, 2, 3, 4 and REM sleep and total slow wave sleep (Stages 3 and 4 combined). Nocturnal recordings were made on a Viaport 3 system and data transferred, in EDF format, to HPRU for manual scoring. All records were scored according to standard criteria\textsuperscript{36}.

Safety

Physical examinations, including electrocardiogram (ECG) and laboratory tests were performed at screening and at last day of study period three. Adverse events were reported by physicians during the study.

Statistical analysis

For each sleep and psychometric variable the analysis included all randomized subjects who gave rise to some data for all three treatment periods – the Full Analysis
Data Set (FADS). All the LARS and psychometric data were, after subtraction of the appropriate baseline values (with the exception of LARS which is intrinsically adjusted for baseline), subjected to analyses of variance using SAS PROC MIXED with fixed effect factors for subject, treatment and period, and with time of day as a repeated measure, with a compound-symmetric variance–covariance structure, and with a treatment by time interaction additionally in the model. In those cases only for which the interaction term in this model was statistically significant at the 5% probability level, the relevant data, again with the subtraction of baseline values, except for LARS, were subsequently analysed by the separate time points, using the same software, with a model incorporating fixed effect factors for subject, treatment and period. All other data were analysed, without baseline subtraction, using the same software, with a model incorporating fixed effect factors for subject, treatment and period. The model did not correct for small sample size and did not consider sequence and the maximum likelihood estimation option was chosen. Treatment effects were evaluated on a two-sided significance test with a significance level of 0.05. Significance level adjustments for multiple comparisons were not made.

Results

Latency to sleep onset

The latency to sleep onset (min) the morning after night-time dosing was assessed by the Sleep Latency Test (SLT) at 10:35 h post dose at each of the three treatment periods. Chlorpheniramine 6 mg (2.6 min ± 0.69) decreased the latency to sleep onset compared with fexofenadine 120 mg (6.02 min ± 0.77, \( p < 0.0001 \)) and placebo (4.51 min ± 0.69, \( p < 0.0001 \)). Fexofenadine 120 mg increased sleep latency after night-time dosing compared with placebo (\( p < 0.05 \)) (Figure 1A).

Psychomotor performance and cognitive function measures

All measures of cognitive functioning and psychomotor performance, with the exception of the critical flicker fusion (CFF) test and choice reaction time-motor reaction time (CRT–MRT), showed significant differences between treatments. Chlorpheniramine 6 mg impaired cognitive and psychomotor performance compared to placebo and fexofenadine. The mean scores and standard error (SEM) for all treatments on

![Figure 1](image-url)

*Figure 1. Figures to show the effects of placebo (PLC), fexofenadine 120 mg (FEX) and chlorpheniramine 6 mg (CHLOR) on (A) daytime sleep onset latency (min), (B) total reaction time (ms) on the choice reaction test (CRT), (C) mean tracking error (pixels) on the continuous tracking task (CTT) and (D) average correct response time (ms) on the Sternberg memory scanning task (STM). Values are expressed as mean and error bars show standard error (SEM). *\( p < 0.05 \), **\( p < 0.01 \), ***\( p < 0.001 \) and ****\( p < 0.0001 \) when compared to placebo.
all psychomotor and cognitive tests are presented in Table 1.

Chlorpheniramine 6 mg impaired divided attention as demonstrated by impaired performance on the tracking task (CTT). Peripheral reaction time was increased following chlorpheniramine at 8 and 10 h post-dose (560.96 ms ± 21.5 and 620.58 ms ± 44.3, respectively) compared with placebo (544.31 ms ± 23.7 and 518.49 ms ± 17.6, respectively, p < 0.001) and fexofenadine (535.54 ms ± 21.1 and 521.96 ms ± 19.0, respectively, p < 0.001) (Figure 1C). Tracking error was also increased following chlorpheniramine (18.37 ± 1.56 and 22.31 ± 3.04, respectively) compared with placebo (16.91 ± 1.43 and 16.00 ± 1.01, p < 0.001) and fexofenadine (16.08 ± 1.61 and 16.28 ± 1.14, respectively, p < 0.001). There was no significant difference in peripheral reaction time or tracking ability following fexofenadine compared with placebo.

Vigilance, as assessed by the RVIP task, was impaired 8–10 h post chlorpheniramine dosing. There

| Table 1. Mean scores and standard error (SEM) for all psychomotor and cognitive tests with placebo, fexofenadine 120mg (fex 120 mg) and chlorpheniramine 6 mg (chlor 6 mg) |
|----------------|----------------|---------------|-----------------|----------------|
| Test           | Time           | Mean (SEM) for all treatments | p-value | p-value |
|                |                | Placebo       | Fex (120 mg)   | Chlor (6 mg)  |
| CTT-MD (pixels)| 07.00          | 16.91 (1.45)  | 16.03 (1.61)   | 18.37 (1.56)  | < 0.001 |
|                | 09.00          | 16.00 (1.01)  | 16.28 (1.14)   | 22.31 (3.04)  |     |
| CTT-RT (ms)    | 07.00          | 544.31 (22.7) | 535.54 (21.1)  | 500.96 (21.5) | < 0.001 |
|                | 09.00          | 518.49 (17.6) | 521.96 (19.0)  | 620.58 (44.3) |     |
| STM (ms)       | 07.00          | 620.56 (22.8) | 628.72 (25.7)  | 648.72 (25.8) | < 0.001 |
|                | 09.00          | 571.67 (15.0) | 583.11 (17.6)  | 647.67 (22.1) |     |
| CRT-RRT (ms)   | 07.00          | 369.81 (9.7)  | 370.64 (8.4)   | 389.75 (11.3) | < 0.0001 |
|                | 09.00          | 367.26 (9.2)  | 369.85 (9.3)   | 395.20 (14.7) |     |
| CRT-MRT (ms)   | 07.00          | 278.47 (12.7) | 277.82 (14.8)  | 286.46 (14.8) |     |
|                | 09.00          | 275.36 (12.9) | 258.53 (10.8)  | 270.52 (12.0) |     |
| CRT-TRT (ms)   | 07.00          | 648.28 (17.0) | 648.43 (18.3)  | 676.21 (22.3) | < 0.01 |
|                | 09.00          | 642.02 (17.9) | 622.38 (12.3)  | 665.73 (22.5) |     |
| RVIP-number of valid responses | 07.00 | 39.67 (3.45)  | 42.00 (3.47)   | 38.89 (3.90)  | 0.05  |
|                | 09.00          | 43.22 (3.71)  | 43.17 (3.03)   | 36.89 (3.46)  |     |
| RVIP-average valid response time (ms) | 07.00 | 579.05 (14.3) | 593.72 (18.2)  | 610.99 (17.0) | < 0.0001 |
|                | 09.00          | 556.70 (12.7) | 578.02 (20.8)  | 609.51 (18.0) |     |
| CFF-mean threshold frequency (Hz) | 07.00 | 29.4 (50.56)  | 29.55 (0.51)   | 29.45 (0.48)  |     |
|                | 09.00          | 28.92 (0.52)  | 29.10 (0.54)   | 28.73 (0.43)  |     |
| CFF-mean descend frequency (Hz)   | 07.00          | 28.08 (0.71)  | 28.13 (0.66)   | 28.07 (0.58)  |     |
|                | 09.00          | 27.75 (0.68)  | 27.83 (0.69)   | 27.61 (0.67)  |     |
| CFF-mean ascend frequency (Hz)    | 07.00          | 30.82 (0.55)  | 30.97 (0.47)   | 30.83 (0.52)  |     |
|                | 09.00          | 30.10 (0.43)  | 30.40 (0.46)   | 28.86 (0.46)  |     |
| CFF-interval of uncertainty (Hz)  | 07.00          | 2.99 (0.51)   | 3.01 (0.44)    | 2.96 (0.47)   |     |
|                | 09.00          | 2.54 (0.38)   | 2.61 (0.45)    | 2.78 (0.49)   |     |
| LARS-sedation (mm)                | 07.00          | 50.86 (0.79)  | 51.05 (1.08)   | 52.59 (1.50)  | < 0.001 |
|                | 09.00          | 49.18 (1.18)  | 49.39 (1.10)   | 55.81 (2.00)  |     |
| LARS-Mood (mm)                    | 07.00          | 49.30 (0.70)  | 48.95 (0.51)   | 48.56 (0.62)  |     |
|                | 09.00          | 48.02 (0.71)  | 48.30 (0.79)   | 50.14 (1.29)  |     |
| LARS-co-ordination (mm)           | 07.00          | 51.75 (0.88)  | 51.77 (1.05)   | 54.61 (1.64)  | < 0.01 |
|                | 09.00          | 51.17 (0.77)  | 51.74 (0.56)   | 53.76 (1.29)  |     |
| MESS (mm)                         | 07.00          | 48.05 (0.90)  | 47.86 (2.42)   | 37.99 (3.83)  | < 0.001 |
| LSEQ-getting to sleep (mm)        | 07.00          | 20.01 (2.45)  | 17.07 (1.54)   | 21.93 (2.35)  |     |
| LSEQ-quality of sleep (mm)        | 07.00          | 52.39 (3.19)  | 52.60 (2.20)   | 52.90 (3.17)  |     |
| LSEQ-early morning awakenings (mm)| 07.00          | 50.26 (2.48)  | 49.36 (2.53)   | 51.20 (2.97)  |     |
| LSEQ-behaviour following awakening (mm) | 07.00 | 54.28 (1.75)  | 54.64 (1.68)   | 56.29 (2.35)  |     |

p-values show statistical significance for treatment compared with placebo for combined time points unless a significant treatment by time interaction was observed and then separate p-values per time point were reported.

CFF = critical flicker fusion; CTT-MD = continuous tracking task uncertainty; CTT-RT = continuous tracking task reaction time; STM = Stenberg memory scanning task-average correct response time; RVIP = rapid visual information processing task—number of valid responses and average valid response time; CFF-RRT = choice reaction time-recognition reaction time; CTT-MRT = choice reaction time—motor reaction time; CTT-TRT = choice reaction time—total reaction time; LARS = Line Analogue Rating Scales; MESS = Mofford Epworth Sleepiness Scale; and LSEQ = Leeds Sleep Evaluation Questionnaire.
was a reduced number of valid responses following chlorpheniramine (38.89 ± 3.90 and 36.89 ± 3.46) compared with placebo (39.67 ± 3.45 and 43.22 ± 3.71, p ≤ 0.05) and fexofenadine (42.00 ± 3.47 and 43.17 ± 3.63, respectively, p ≤ 0.01). There was also an increased response time to valid responses following chlorpheniramine (610.99 ms ± 17.0 and 609.51 ms ± 18.0, respectively) compared with placebo (579.65 ms ± 14.3 and 556.70 ms ± 12.7, p ≤ 0.0001) and fexofenadine (593.72 ms ± 18.2 and 578.62 ms ± 20.8, respectively, p ≤ 0.01).

There was evidence of increased response time following fexofenadine compared with placebo (p ≤ 0.05). However, the results suggested that there was an improved number of valid responses at 07:00 h following fexofenadine and, therefore, the increased response time observed may relate to speed accuracy trade-off at this time point.

Short-term memory was assessed by the Sternberg Memory Scanning Task. Compared with placebo [620.56 ms ± 22.8 and 571.67 ms ± 15.0, at 8 and 10h post-dose, respectively] and fexofenadine [626.72 ms ± 25.7 and 583.11 ms ± 17.6, respectively] chlorpheniramine 6mg impaired short term working memory on Day 2 (648.72 ms ± 25.8 and 647.67 ms ± 32.1, respectively) (p ≤ 0.0001 and p ≤ 0.001 for comparison with placebo and fexofenadine, respectively). There was no significant effect of fexofenadine compared with placebo (Figure 1D).

There was a significant impairment of recognition reaction time (RRT) and total reaction time (TRT) (Figure 1E) after chlorpheniramine treatment. At 8 and 10h post-dose chlorpheniramine increased RRT (389.75 ms ± 11.3 and 395.20 ms ± 14.7, respectively) compared with placebo (369.81 ms ± 7.97 and 367.26 ms ± 5.27, p ≤ 0.0001) and fexofenadine (370.64 ms ± 8.4 and 363.85 ms ± 8.98, p ≤ 0.001). This in turn led to an increased TRT following chlorpheniramine (676.21 ms ± 22.3 and 665.73 ms ± 22.5) compared with placebo (648.28 ms ± 17.0 and 642.62 ms ± 17.9, respectively, p ≤ 0.01) and fexofenadine (648.45 ms ± 18.3 and 622.38 ms ± 12.5, p ≤ 0.01). There was no impairment in recognition or total reaction time following fexofenadine.

Sleep measures

Sleep architecture immediately after treatment was assessed using polysomnography (PSG). Chlorpheniramine increased the latency to sleep (Sleep Onset Latency, SOL) (28.06 min ± 6.36) compared with placebo (18.78 min ± 5.77, p ≤ 0.05) and fexofenadine (16.05 min ± 5.03, p ≤ 0.01). Latency to REM sleep was also increased following chlorpheniramine (105.56 min ± 10.8) compared with placebo (86.56 min ± 9.53, p ≤ 0.05) and fexofenadine (75.42 min ± 5.81, p ≤ 0.01) (Table 2).

In addition, chlorpheniramine reduced the percentage and duration of REM sleep (17.90% ± 1.02 and 77.47 min ± 5.03) compared with placebo (21.76% ± 1.53 and 93.42 min ± 7.32, p ≤ 0.001 and p ≤ 0.01, respectively) and fexofenadine (21.76% ± 0.88 and 95.67 min ± 4.23, p ≤ 0.001 and p ≤ 0.01, respectively). In contrast, there was no significant change in latency to REM sleep, %REM sleep or REM sleep duration after dosing with fexofenadine compared with placebo (Table 2).

Furthermore, chlorpheniramine increased the percentage of non-REM sleep (82.10% ± 1.02) compared with placebo (76.96% ± 0.90, p ≤ 0.0001) and fexofenadine (78.24% ± 0.88, p ≤ 0.0001). Chlorpheniramine also increased the duration of non-REM sleep (352.44 min ± 5.32) compared with placebo (311.67 min ± 17.7, p ≤ 0.01) but not compared with fexofenadine (342.97 min ± 6.08). Fexofenadine increased non-REM sleep duration compared with placebo (p ≤ 0.05), but there was no significant difference in %NREM sleep (Table 2). The increase in non-REM sleep by chlorpheniramine and fexofenadine was due to an increase in the duration (235.86 min ± 6.65 and 234.19 h ± 7.43, respectively, p ≤ 0.01 for both) and percentage (54.98% ± 1.45 and
Table 2. Sleep variables from overnight polysomnography (PSG). Treatments were placebo, fexofenadine 120 mg (fex 120 mg), and chlorpheniramine 6 mg (chlpr 6 mg)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Fex 120 mg</th>
<th>Chlor 6 mg</th>
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<tbody>
<tr>
<td>PSG sleep onset latency (min)</td>
<td>18.78 (5.77)</td>
<td>16.06 (5.03)</td>
<td>20.35 (6.69)*</td>
</tr>
<tr>
<td>PSG latency to REM sleep (min)</td>
<td>86.56 (9.53)</td>
<td>75.42 (5.81)</td>
<td>105.56 (10.8)*</td>
</tr>
<tr>
<td>PSG REM sleep percentage</td>
<td>21.76 (1.53)</td>
<td>21.76 (0.88)</td>
<td>17.90 (1.02)**</td>
</tr>
<tr>
<td>PSG REM sleep duration (min)</td>
<td>95.42 (7.32)</td>
<td>95.67 (4.23)</td>
<td>77.47 (5.03)**</td>
</tr>
<tr>
<td>PSG Stage 2 sleep percentage</td>
<td>50.74 (1.25)</td>
<td>53.52 (1.67)**</td>
<td>54.98 (1.45)**</td>
</tr>
<tr>
<td>PSG Stage 2 sleep duration (min)</td>
<td>207.14 (3.5)</td>
<td>234.19 (7.43)**</td>
<td>235.86 (6.66)**</td>
</tr>
<tr>
<td>PSG non-REM sleep percentage</td>
<td>76.26 (0.90)</td>
<td>78.14 (0.88)</td>
<td>84.10 (1.02)**</td>
</tr>
<tr>
<td>PSG non-REM sleep duration (min)</td>
<td>311.67 (17.7)</td>
<td>342.97 (6.08)**</td>
<td>352.44 (6.32)**</td>
</tr>
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Values are expressed as mean and standard error of mean (SEM). *p < 0.05, **p < 0.01, ***p < 0.001 and ****p < 0.0001 when compared to placebo.

53.52% ± 1.67, p < 0.001 and p < 0.01, respectively) of Stage 2 sleep compared with placebo (207.14 min ± 13.5 and 50.74% ± 1.25, respectively).

Ten adverse events were reported during the study of which six were classified as possibly related to the study drug. Of the six possibly related adverse events, three were due to placebo (weakness of upper extremities and sleepiness), two were related to fexofenadine (fuzzy feeling in head and sleepiness) and one was related to chlorpheniramine (sleepiness).

Discussion

First-generation antihistamines such as chlorpheniramine are associated with central effects such as sedation and reduced psychomotor and cognitive function while fexofenadine, a second-generation antihistamine, has been shown to be non-sedating and to be free of impairing effects on cognitive or psychomotor performance. Central effects and the clinical safety of antihistamines have been widely studied in Caucasian subjects but there are limited data available on the effects of antihistamines in Japanese subjects. There may be differences in enzyme metabolism of drugs across different populations and it is, therefore, important to evaluate the central effects of drugs in discrete populations. The aim of this study was to investigate the effects of a single dose of the selective H1-receptor antagonist fexofenadine 120 mg compared with the first-generation antihistamine chlorpheniramine 6 mg and placebo in healthy Japanese volunteers.

During the single dose study both drugs were well tolerated with no increase in adverse events recorded compared with placebo.

There was no significant change in sleep onset latency immediately after dosing with fexofenadine (120 mg). Fexofenadine also had little effect on sleep architecture throughout the night only acting to increase the duration and proportion of Stage 2 sleep and consequently, the duration of non-REM sleep. Furthermore, fexofenadine was not associated with hangover effects the following morning and instead there was a significant increase in latency to sleep onset the morning after night time dosing. Similar improvement in next day alertness has been demonstrated with other antihistamines such as terfenadine and desloratadine. These data are in agreement with previous studies in Caucasian subjects, where fexofenadine has been shown to be indistinguishable from placebo in a comprehensive range of objective and subjective tests, suggesting that fexofenadine is a non-sedating antihistamine in more than one population group.

In contrast, acute dosing with chlorpheniramine (6 mg) demonstrated residual effects in Japanese subjects the morning after dosing with decrements in cognitive function, psychomotor performance, and objective and subjective evidence of increased sleepiness. Chlorpheniramine had a sedative effect the morning after night time dosing compared with fexofenadine and placebo. The sleep latency test (SLT) showed that chlorpheniramine 6 mg significantly decreased the latency to sleep onset 10h 30min post-dose. In addition, subjects felt more sedated as assessed subjectively by the Milford Epworth Sleepiness Scale (MESS) and the Line Analogue Rating Scale (LARS) and demonstrated impaired cognitive and psychomotor performance, including reduced attention, vigilance and memory performance. These data support previous findings from studies in Caucasian subjects that have shown chlorpheniramine to impair psychomotor performance, sensorimotor co-ordination, information processing, sensory skills as well as physiological measures and subjective rating scales. Furthermore, administration of chlorpheniramine 10 mg has been shown to decrease sleep latency the morning after dosing and to reduce the ability to perform mental work and similar effects have been observed for both 2 mg and 6 mg doses.
In the current study, chlorpheniramine also disrupted sleep architecture immediately after dosing. There was a decrease in the duration and percentage of REM sleep and an increase in latency to REM sleep. This decrease in REM sleep has been seen with other antihistamines, such as triprolidine and the reduction is thought to be caused by monoaminergic activity rather than an antagonising action on H₁-receptors. There is also the possibility that the effect on REM may be partially explained by an anticholinergic effect causing a reduction in REM sleep by interference of the REM-sleep maintenance. These actions on other receptor systems are characteristic of first generation antihistamines such as chlorpheniramine. In addition, chlorpheniramine significantly increased PSG sleep onset latency compared with placebo. Fexofenadine on the other hand, caused no such change in sleep architecture, including REM sleep, suggesting that fexofenadine has minimal central activity.

Conclusion

In conclusion the study provided both objective and subjective data on the effects of a single dose of fexofenadine and chlorpheniramine on sleep architecture, psychomotor performance, cognitive function and daytime sedation in healthy Japanese volunteers.

Chlorpheniramine caused a significant worsening of next day cognitive functioning and psychomotor performance which agrees with earlier performance data on chlorpheniramine reported with Caucasian subjects. Fexofenadine was statistically indistinguishable from placebo in the above parameters confirming that fexofenadine is a non-sedating antihistamine in these population groups. Furthermore, this study demonstrated that nocturnal dosing with fexofenadine had no deleterious effects on night-time sleep whilst in contrast the traditional H₁-antagonist, chlorpheniramine, disrupted sleep architecture. These findings suggest that nocturnal dosing with fexofenadine has advantages over first-generation antihistamines, being free of disruption of night-time sleep and detrimental effects on cognitive performance the next day. In Japan sedative antihistamines, in particular chlorpheniramine, are prescribed at night as it is believed that this aids sleep and, therefore, improves daytime functioning. It is, therefore, important that the negative effects on sleep architecture and residual impairing effects of chlorpheniramine are not ignored.

It should be noted, however, that the data reported in this study relate to an acute dosing regimen which may differ from repeated dosing. Further research should be conducted to assess whether impairment in sleep architecture and daytime behaviour persist with chronic treatment.

Acknowledgement

Declaration of interest: This study was supported by the Osaka Foundation for the Prevention of Cancer and Cardiovascular Diseases, Osaka, Japan. Publication costs were supported by sanofi-aventis Japan. None of the authors has any conflict of interest to declare with respect to the contents of this manuscript.

The authors would like to thank Mika Sawada and staff at the Clinical Investigation Centre, Kitasato University East Hospital, Japan for conducting the study and to Professor A. N. Nicholson for his kind advice.

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http://www.cmjojournal.com
Paper CMRO-3125_3, Accepted for publication: 09 May 2006
Published Online: 07 June 2006
doi:11.185/3007996G2X1126690