HUMAN PSYCHOPHARMACOLOGY
Hum Psychopharmacol Clin Exp 2005; **20**: 501–509.
Published online 5 August 2005 in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/hup.713

Effects of fexofenadine and hydroxyzine on brake reaction time during car-driving with cellular phone use

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Antihistamines are a mainstay treatment for allergic rhinitis; however, many older agents cause adverse events, including sedation and central nervous system (CNS) impairment. Research has shown sedating effects of antihistamines on driving; currently, no known study has examined whether cellular phone usage while driving further compounds impairment in individuals administered antihistamines. The aim of this study was to examine this endpoint. In a randomized, double-blind, placebo-controlled, three-way crossover study, healthy volunteers received fexofenadine HCl 120 mg, hydroxyzine HCl 30 mg and placebo. Brake reaction time (BRT) was used to examine driving performance across four conditions: driving only; driving while completing simple calculations; complex calculations; and conversing on a cellular phone. Subjective sedation assessments were also conducted. Brake reaction time with and without cellular phone usage in fexofenadine-treated subjects did not differ significantly from placebo in any condition. In contrast, hydroxyzine-treated subjects were significantly more sedated and had slower BRTs, suggesting slower hazard recognition and brake application, compared with the fexofenadine and placebo groups in all conditions. Importantly, cellular phone operation was an additive factor, increasing BRTs in hydroxyzine-treated volunteers. Fexofenadine did not impair CNS function in subjects involved in a divided attention task of driving and cellular phone operation. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS — antihistamines; cognitive function; fexofenadine; hydroxyzine; car driving; cellular phone

INTRODUCTION

Histamine, a biogenic monoamine, is a chemical mediator that is synthesized and stored in human mast cells and basophils (Marone *et al*., 1995, 2000). Upon its release, histamine induces the characteristic symptoms of allergic rhinitis (AR), such as runny nose, sneezing, nasal congestion and itchy, red, watery eyes. Histamine also plays a major role in neurotransmission and central nervous system (CNS) function, including arousal, maintenance of attention and the sleep–wake cycle (Haas and Panula, 2003; Theunissen *et al*., 2004). In the brain, histamine is produced by histaminergic neurons primarily located in the tuberomammillary nucleus of the posterior hypothalamus. These neurons project to various regions of the brain, with histamine effects exerted through the activation of three histaminergic receptors, H_1, H_2 and H_3 (Haas and Panula, 2003; Theunissen *et al*., 2004); however, the majority of the histamine effects are mediated through H_1-receptor interactions (White, 1990).

Antihistamines, first launched approximately 60 years ago, block histamine action at H_1-receptor sites, thus managing the symptoms of AR. For this reason, antihistamines are considered the mainstay treatment option for AR. However, these first-generation antihistamines have been found to cause several undesirable side effects, including sedation and impairment

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Contract/grant sponsors: Aventis Pharmaceuticals; Ministry of Education, Culture, Sports, Science, and Technology, Japan; Sagawa Traffic Safety Foundation.

Received 1 February 2005
Accepted 14 June 2005

of CNS and psychomotor function, due to their ability to cross the blood–brain barrier and block histaminergic systems in the brain. As a result, newer-generation antihistamines were introduced and were shown to be less sedative, although most still show some level of CNS impairment, particularly at supraclinical dose levels (Simons *et al*., 1996; Kay and Harris, 1999; Roberts and Gispert, 1999; Rosenzweig and Patat, 1999; Kay, 2000; Tagawa *et al*., 2002; Casale *et al*., 2003; Holgate *et al*., 2003; Ridout *et al*., 2003a; Verster *et al*., 2003; Theunissen *et al*., 2004).

Currently, the newer-generation antihistamine fexofenadine is the only antihistamine that has been proven to be non-impairing and non-sedating even at doses higher than those recommended (Hindmarch *et al*., 1999; Mason *et al*., 1999; Hindmarch *et al*., 2002; Tashiro *et al*., 2004; Kamei *et al*., 2003; Ridout and Hindmarch, 2003; Ridout *et al*., 2003a). Furthermore, recent positron emission tomography (PET) studies have shown that fexofenadine does not cross the blood–brain barrier and bind to H_1-receptors, while the newer-generation agent cetirizine was found to occupy H_1-receptors in the brain (Tashiro *et al*., 2002; Tashiro *et al*., 2004), which could, consequently, lead to CNS impairment. Due to this distinction, fexofenadine has occasionally been referred to as a third-generation antihistamine (Hindmarch *et al*., 2002; Ridout *et al*., 2003a; Verster and Volkerts, 2004).

Ironically, first-generation agents have the greatest sedative effects and are the ones most commonly sold over-the-counter (OTC). Impairment of CNS and psychomotor function can lead to impairment in everyday tasks, including driving, and increase a patient's risk of injury (Ridout *et al*., 2003a). In a recent literature review, Verster and Volkerts (2004) found that first-generation antihistamines, including triprolidine, diphenhydramine, dexchlorpheniramine, terfenadine and clemastine, significantly impaired driving performance after one dose and repeated (daily) administration. Furthermore, diphenhydramine is considered one of the top-selling OTC drugs for AR (RedBook, 1998), yet data have shown that it has a greater impact on driving ability than alcohol (Weiler *et al*., 2000). Several newer-generation agents, such as loratadine, cetirizine, acrivastine, ebastine, mizolastine, emedastine and mequitazine also cause impairment, although to a lesser extent than the first-generation compounds (Verster and Volkerts, 2004). However, fexofenadine does not impair the driving performance of volunteers after either one-time or repeated administration, or at supraclinical dose levels up to 360 mg (Vermeeren and O'Hanlon, 1998; Weiler *et al*., 2000; Meeves and Appajosyula, 2003; Potter *et al*., 2003; Ridout *et al*., 2003a; Verster and Volkerts, 2004).

Over the past few years, as the popularity of cellular phone use has increased, several studies have been conducted examining the effect of cellular phone operation on driving. Data have revealed that cellular phone use while driving can effect a speaker's performance on a number of tasks, including the maintenance of constant speed (Alm and Nilsson, 1994; Burns *et al*., 2002), shifts in lateral position (Alm and Nilsson, 1994, 1995) and reaction time (McKnight and McKnight, 1993; Alm and Nilsson, 1994, 1995; Lamble *et al*., 1999; Burns *et al*., 2002; Consiglio *et al*., 2003; Strayer *et al*., 2003; Lesch and Hancock, 2004). Furthermore, accidents are four times more likely to occur if the driver is talking on a cellular phone (Redelmeier and Tibshirani, 1997).

To date, however, there are no known data on the additive effects that cellular phone use may have on driving performance in individuals taking antihistamines. Histamine plays a major role in maintaining vigilance and attention. Therefore, it is reasonable to consider that blockade of histamine-producing receptors due to antihistamine administration, combined with a divided attention task, such as cellular phone use and driving, may decrease an individual's driving performance. Thus, the aim of the current study was to examine whether the sedative properties of an antihistamine will affect driving performance, and whether cellular phone operation while driving would compound the impairing effect.

MATERIALS AND METHODS

Subjects

Eighteen right-handed, male volunteers aged 20–26 years (mean = 23.4, standard deviation [SD] = 1.61) were recruited for participation in the study. All subjects were in good health as determined by physical examination, chest x-ray, visual and hearing testing. No subject had a significant clinical history of physical or mental illness, psychomotor defects or hearing impairment. All subjects possessed a driver's licence for at least 1 year, with an opportunity to drive at least twice a week. No subject was taking any concomitant medications that would interfere with study measures. After explaining the study to the participant, written informed consent was obtained. The study protocol was approved by the ethics committee of Tohoku University Graduate School of Medicine.

Study design

This was a randomized, double-blind, placebo-controlled, three-way crossover study, with each subject acting as their own control. The treatment sequence was balanced for order and carry-over effects using a Latin square design. The drugs under investigation were fexofenadine HCl 120 mg, hydroxyzine HCl 30 mg and placebo. Recommended dosing regimens for fexofenadine vary from country to country and according to indication. This study used 120 mg, the highest indicated dose prescribed in Japan for AR. Hydroxyzine 30 mg was included in the study as a positive control to validate the sensitivity of the psychometric tests to non-specific impairment. Each treatment day was separated by a washout period of at least 6 days. All study treatments were administered between 10–11 am followed by the test sessions accordingly.

The day before the experiment, subjects were familiarized with the test car and trained on the brake reaction time (BRT) task to a performance plateau in order to minimize learning effects. The use of alcohol and nicotine was prohibited 24 h prior to the experiment and on the treatment day. Products containing caffeine, grapefruit juice or any supplement drink that includes active agents, such as amino acids, vitamins and catechin were prohibited on treatment days. Only water was allowed during testing. Food consumption was controlled, including a light breakfast and lunch, at specified meal times.

On the treatment day, subjects were re-familiarized with the BRT task 20–30 min prior to pre-treatment baseline measurement to ensure performance plateau. Study treatments were then administered and testing was conducted at 90 and 240 min post-drug administration. The Stanford sleepiness scale (SSS) and line analogue rating scale (LARS) were used to measure subjective assessments of sedation prior to objective measurements of BRT at each test interval. Subjective testing was conducted first to prevent the effect of elevated arousal levels that can occur with the more attention-demanding and time-consuming (20–25 min) objective measures.

Subjective sedation assessment

Stanford sleepiness scale. The SSS is a seven-level self-report measure examining how alert an individual feels (Hoddes *et al.*, 1973), with proven sensitivity in a number of studies (Okamura *et al*., 2000; Mochizuki *et al*., 2002; Tagawa *et al*., 2002). For example, subjects may indicate feeling active, vital, alert, or wide awake, feeling somewhat foggy, let down, or asleep.

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

Brake reaction time

The BRT test is a measure of cognitive and psychomotor performance, including attention deficit, and is sensitive to psychotropic drug effects (Ridout and Hindmarch, 2001; Ridout *et al*., 2003a; Ridout *et al*., 2003b). Break reaction time is assessed in an automatic car driven on a closed driving course that consists of two straight lanes 1.5 km in length connected by U-shaped turning roads on both ends. A red rear-brake light mounted on the hood simulates the brake light of a vehicle in front of the test car. The brake light is illuminated at random intervals throughout the test. Subjects were required to extinguish the brake light as quickly as possible by depressing the foot brake pedal. The interval between the illumination of the red light and the subject depressing the foot brake was measured in milliseconds using an onboard-microcomputer system (Psion Co., Ltd.).

Subjects were instructed to maintain a cruising speed of 40 km/h. One investigator was seated in the passenger seat of the car to subjectively monitor the driver's state of arousal to ensure that no driver fell asleep and to examine steering ability throughout testing. The investigator was in communication with a second external investigator to indicate the start of the test. For BRT testing with cellular phone usage, subjects were instructed to wear a hands-free headset with a microphone situated at close proximity to the mouth. Brake reaction time measurements were conducted for four test conditions. A total of 25 trials were undertaken per condition from which mean reaction times were calculated. The conditions were randomly presented to eliminate the contribution of an

order effect. Each driving condition took approximately 3–4 min to complete and a 2 min break was provided between conditions.

Condition 1: driving-only. In condition 1, subjects drove without talking on the cellular phone (BRT_{driv}).

Condition 2: driving while completing simple calculations. In condition 2, subjects were asked to answer simple arithmetic questions on the cellular phone while driving, such as 'what does two plus three equal?' (BRT_{calcS}).

Condition 3: driving while completing complex calculations. The third condition entailed answering complex arithmetic questions, such as 'what does 55 minus 37 equal?' (BRT_{calcC}), in order to investigate whether the complexity of the task affects BRT.

The subjects' mean baseline reaction times and accuracy were examined to confirm that the cognitive task of the complex condition was more difficult compared with the simple condition. Analysis was conducted by examining the time interval (ms) from the end of the spoken arithmetic question by the investigator, such as 'what does 1 plus 4 equal?', to the beginning of the subject's answer (e.g. 5).

Condition 4: driving while engaged in conversation. In the final condition, subjects were engaged in a conversation in which the subject was asked to provide 1–2 min answers on six to eight pre-determined topics, such as a favourite movie (BRT_{conv}).

Adverse events

All adverse events occurring during the study were reported.

Statistical analysis

For the statistical analyses, the data for subjective assessments and BRT obtained at the 90 and 240 min time points were combined to provide an overall assessment of study treatment. The SSS and LARS scores were analysed using the Friedman test, a non-parametric analogue of analysis of variance (ANOVA), as the results of both tests did not satisfy the criteria for the assumption of normality or equality of variance (SPSS 12.0 [Japanese version]), with factors for drug treatment and task. Significant findings were followed by post-hoc multiple pairwise treatment comparisons using Bonferroni-correction (two-tailed; $p < 0.05$). The BRT data were analysed using a repeated measures ANOVA model with factors for drug treatment and condition. Analogue of analysis of variance models were also used to examine across the following task conditions for fexofenadine and hydroxyzine separately: (1) placebo + driving; (2) antihistamine + driving; (3) placebo + cellular phone talking; and (4) antihistamine + driving + cellular phone talking. Significant findings were followed by post-hoc Bonferroni correction. The 95% confidence interval (CI) values were also calculated. In order to ensure that there were no significant differences across tasks and conditions at pre-treatment, baseline statistical analyses were conducted and used for comparison to post-treatment results.

RESULTS

For all measurements of subjective sleepiness and BRT, there were no significant differences between drug treatments at baseline, suggesting that an order effect and non-specific factors were controlled.

Subjective sedation assessment

Stanford sleepiness scale. The SSS assessment revealed a significant main effect of treatment ($p = 0.001$). Post-hoc tests revealed that subjects given hydroxyzine were significantly less alert compared with those administered fexofenadine ($p = 0.018$) or placebo ($p < 0.001$). No significant difference in alertness was found in subjects given fexofenadine compared with placebo ($p = 0.10$; Figure 1 [top]).

Line analogue rating scale. The LARS results also showed a significant treatment effect ($p = 0.001$). Post-hoc tests revealed that subjects given hydroxyzine felt significantly more sedated compared with those administered fexofenadine ($p < 0.001$) or placebo ($p = 0.007$). No significant difference in alertness was found for subjects given fexofenadine compared with those given placebo ($p = 0.90$; Figure 1 [bottom]).

Brake reaction time

Assessment of arithmetic task difficulty. Analysis of subject baseline scores revealed significant differences ($p < 0.000001$) in task difficulty. Faster mean reaction times (mean ± standard error of the mean [SEM]: 1307 ± 98.3 ms and 4213 ± 354.3 ms, respectively) and better mean accuracy (98.8 ± 0.575% and

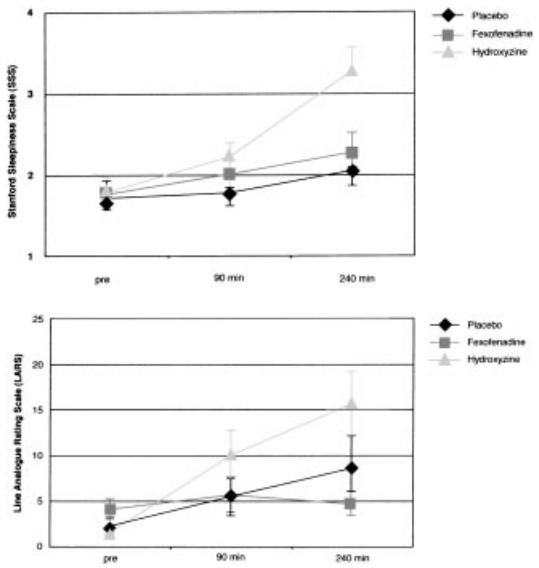

Figure 1. Mean Stanford sleepiness scale (top) and line analogue rating scale (bottom) scores. Standard error of the mean is illustrated by the error bars

$82.4 \pm 2.57\%$, respectively) was found in subjects completing simple compared with complex calculations, respectively.

Assessment of brake reaction time. Results revealed a significant main effect of drug treatment ($F[2, 33] = 7.04$, $p = 0.002$) and condition ($F[3, 32] = 115.9$, $p < 0.001$). Furthermore, a significant treatment by condition interaction ($F[6, 29] = 3.156$, $p < 0.017$) was found. No significant ($p = 0.754$) main effects of time were observed.

Condition 1: driving-only. No significant main effect of treatment ($F[2, 33] = 1.58$, $p = 0.22$) was found in the driving-only condition (BRT_{driv}; Figure 2).

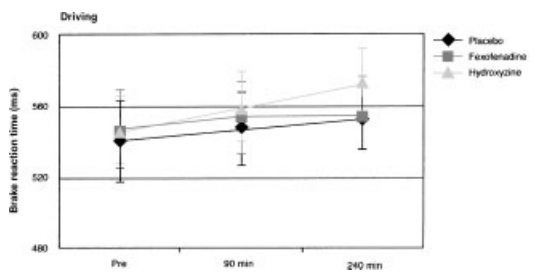

Figure 2. Mean brake reaction time scores for the driving-only condition, with standard error of the mean illustrated by the error bars

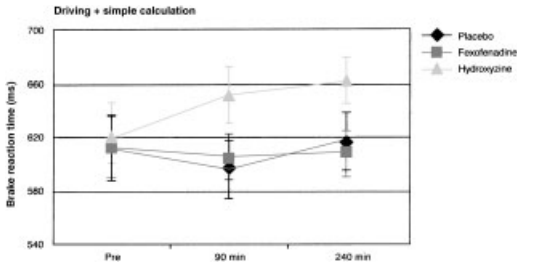

Figure 3. Mean brake reaction time scores for the driving condition in which subjects completed simple arithmetic calculations. Standard error of the mean is illustrated by the error bars

Condition 2: driving while completing simple calculations. A significant main effect of treatment was found ($F[2, 33] = 11.97$, $p < 0.001$). Post-hoc testing revealed that subjects given hydroxyzine had significantly slower BRTs compared with subjects receiving fexofenadine ($p = 0.001$; 95% CI of difference: 18.96, 82.52) and placebo ($p = 0.001$; 95% CI of difference: 18.23, 83.43). No significant difference in BRT was found for subjects given fexofenadine compared with placebo ($p = 1.00$; Figure 3).

Condition 3: driving while completing complex calculations. A significant main effect of treatment was found ($F[1.7, 57.0] = 3.39$, $p = 0.049$). Volunteers administered hydroxyzine had slower BRTs compared with those recorded for fexofenadine ($p = 0.164$; 95% CI of difference: -10.35, 88.42) or placebo ($p = 0.053$; 95% CI of difference: -0.31, 69.27). At threshold level, no significant difference in BRT was found for subjects administered fexofenadine compared with placebo ($p = 1.00$; Figure 4).

Condition 4: driving while engaged in conversation. Significant main effects of treatment were found for

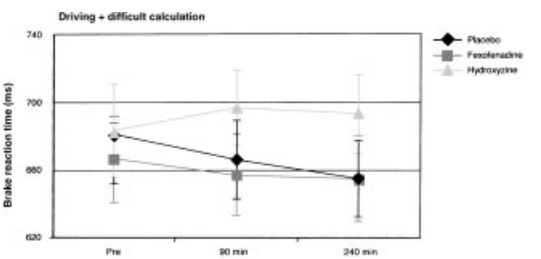

Figure 4. Mean brake reaction time scores for the driving condition in which subjects completed complex mathematical calculations. Standard error of the mean is illustrated by the error bars

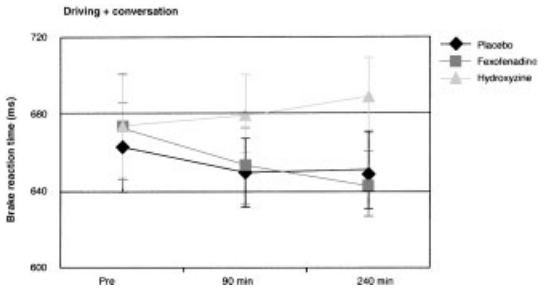

Figure 5. Mean brake reaction time scores for the driving condition in which subjects were engaged in conversation. Standard error of the mean is illustrated by the error bars

BRT_{calcC} ($F[2, 33] = 6.19$, $p = 0.003$). Post-hoc testing revealed that subjects given hydroxyzine had significantly slower BRTs compared with those receiving fexofenadine ($p = 0.028$; 95% CI of difference: 3.20, 70.17) and placebo ($p = 0.015$; 95% CI of difference: 5.58, 63.95). No significant difference in BRT was found for subjects administered fexofenadine compared with those receiving placebo ($p = 1.00$; Figure 5).

Effect of antihistamines and cellular phone talking

Hydroxyzine compared with placebo. A significant main effect of condition was found for BRT_{calcS} ($F[1.9, 65.9] = 43.8$, $p < 0.001$). Post-hoc testing revealed that subjects administered placebo and engaged in a simple cognitive task (BRT_{calcS}) had significantly slower BRTs than driving-only patients given hydroxyzine (BRT_{driv}; $p = 0.002$; 95% CI of difference: 12.5, 67.8), but significantly faster BRTs than hydroxyzine-treated subjects completing simple calculations (BRT_{calcS}; $p = 0.002$; 95% CI of difference: 14.6, 87.1).

A significant main effect was also found for participants completing a complex calculation (BRT_{calcC}; $F[2.2, 75.4] = 70.6$, $p < 0.001$). Multiple comparisons showed that BRT_{calcC} after placebo treatment was significantly slower than BRT_{driv} after hydroxyzine treatment ($p < 0.001$; 95% CI of difference: 62.7, 126.3), but was not significantly different from subjects given hydroxyzine and completing a simple task (BRT_{calcS}; $p = 0.11$). In addition, a significant main effect of condition was found for BRT_{conv} ($F[2.4, 80.8] = 72.7$, $p < 0.001$). Post-hoc testing revealed that BRT_{conv} after placebo administration was significantly slower than BRT_{driv} post-hydroxyzine treatment ($p < 0.001$; 95% CI of difference: 50.0, 118.0), but significantly faster than hydroxyzine-treated subjects engaged in conversation (BRT_{conv}; $p < 0.001$; 95% CI of difference: 2.3, 67.2).

Fexofenadine compared with placebo. Analysis of the fexofenadine group revealed significant main effects of BRT_{calcS} ($F[1.8, 62.4] = 25.8$, $p < 0.001$), BRT_{calcC} ($F[1.8, 62.7] = 54.7$, $p < 0.001$) and BRT_{conv} ($F[1.9, 64.2] = 69.4$, $p < 0.001$). Multiple comparison analysis revealed that BRT_{calcS} after placebo treatment was significantly slower than BRT_{driv} post-fexofenadine administration ($p < 0.001$; 95% CI of difference: 24.1, 80.1), but was not significantly different from fexofenadine-treated participants completing simple calculations (BRT_{calcS}; $p = 0.11$). In addition, post-hoc testing revealed that BRT_{calcC} after placebo treatment was significantly slower than BRT_{driv} after fexofenadine treatment ($p < 0.001$; 95% CI of difference: 65.2, 147.5), but was not significantly different from BRT_{calcC} after fexofenadine treatment ($p = 1.0$). Furthermore, BRT_{conv} after placebo treatment was significantly slower than BRT_{driv} after fexofenadine treatment ($p < 0.001$; 95% CI of difference: 58.5, 133.4), but was not significantly different from subjects engaged in conversation post-fexofenadine administration (BRT_{conv}; $p = 1.0$).

Adverse events

There were no reports of serious adverse events or withdrawals due to adverse events.

DISCUSSION

The current study was undertaken to examine whether the sedative properties of an antihistamine and cellular phone operation affect BRT. In addition, the combined effects of antihistamine administration and cellular phone operation were also investigated. To date, no known study has been conducted to examine the effects of cellular phone use while driving in individuals administered antihistamines. Psychomotor and CNS impairment have been found to affect how an individual functions in everyday tasks, such as driving, potentially increasing a patient's risk of injury (Ridout *et al*., 2003a). Furthermore, drivers using a cellular phone are four times more likely to be involved in an accident (Redelmeier and Tibshirani, 1997). Measurements of driving performance, such as maintenance of a constant speed (Alm and Nilsson, 1994; Burns *et al*., 2002), shifts in lateral position (Alm and Nilsson, 1994, 1995) and reaction time (McKnight and McKnight, 1993; Alm and Nilsson,

1994, 1995; Lamble *et al*., 1999; Burns *et al*., 2002; Consiglio *et al*., 2003; Strayer *et al*., 2003; Lesch and Hancock, 2004) have also been found to be altered in drivers operating a cellular phone. In addition, one known driving simulator study showed that drivers talking on a cellular phone were more impaired than drivers who ingested alcohol, within the legal limits, with a blood alcohol concentration of 80 mg/100 ml (Burns *et al*., 2002).

Subjective sedation assessments and BRT scores revealed no significant differences between subjects administered fexofenadine or placebo in any test condition. These findings are consistent with those of other researchers who have reported the non-sedating and non-impairing effects of fexofenadine on cognition, psychomotor and driving performance (Vermeeren and O'Hanlon, 1998; Hindmarch *et al*., 1999; Weiler *et al*., 2000; Hindmarch *et al*., 2002; Ridout and Hindmarch, 2002; Kamei *et al*., 2003; Ridout and Hindmarch, 2003; Ridout *et al*., 2003a). Thus, the current study provides further evidence that fexofenadine does not impair CNS function even when subjects perform divided attention tasks.

In contrast, hydroxyzine-treated subjects were found to be significantly more sedated and had slower BRTs compared with subjects receiving fexofenadine or placebo in all test conditions. Drivers given prescribed doses of hydroxyzine were slower at recognizing hazards in the road ahead and applying the brake. Driving impairment reported with the positive control hydroxyzine validates the sensitivity of the BRT test and further highlights the dangerous adverse effects of first-generation antihistamines (Casale *et al*., 2003; Holgate *et al*., 2003; Kamei *et al*., 2003). Importantly, cellular phone use was an additive factor, further increasing BRTs in subjects given hydroxyzine.

The danger of cellular phone use while driving has previously been well documented, partly encouraged by the recent social background with increasing cellular phone use and increased car accidents related with telephone use (Redelmeier and Tibshirani, 1997; De Jong, 2003; Stutts *et al*., 2003; Taylor *et al*., 2003; Johnson *et al*., 2004; Lesch and Hancock, 2004; The General Insurance Association of Japan, 2004; White *et al*., 2004). Redelmeier and Tibshirani demonstrated that the risk of a collision when using a cellular phone was four times higher than the risk when no cellular phone was used while driving (Redelmeier and Tibshirani, 1997). Furthermore, White *et al.* reported that nearly half of the drivers questioned in a large survey ($n = 1320$) used a mobile phone while driving (White *et al*., 2004). In a recent Japanese survey conducted by the General Insurance Association of Japan, 6.8% of drivers studied ($n = 600$) always had a cellular phone with them while driving, 65.9% of drivers sometimes or often had a phone with them while driving, and only 27.3% drivers had never spoken on a mobile phone while driving (The General Insurance Association of Japan, 2004).

It would seem that most drivers do not perceive a decrement in driving during cellular phone use, similar to drivers who do not perceive an impairment caused by sedative drugs. With more than 70% of drivers operating a cellular phone while driving (The General Insurance Association of Japan, 2004), the combined effect of sedation by hydroxyzine and cellular phone use could potentially increase the risk of an accident. Additionally, as patients are often overcompliant by, for example, taking more than the recommended dose or taking the next dose earlier, believing that it will increase the effectiveness of the product (National Council on Patient Information and Education, 2002), their risk of an accident increases.

Neuroimaging research has provided biochemical support for psychometric findings. Histamine has been found to play a major role in maintaining vigilance and attention (Haas and Panula, 2003; Theunissen *et al*., 2004), such as during a divided attention task (Baddeley, 1998), with studies showing that subjects involved in attention tasks recruit the prefrontal cortex (Herath *et al*., 2001; Szameitat *et al*., 2002). Positron emission tomography research has shown that sedative antihistamines occupy central H_1-receptors in the brain, including the prefrontal cortex (Yanai *et al*., 1999; Tagawa *et al*., 2001; Tashiro *et al*., 2002; Tashiro *et al*., 2004), while volunteers given fexofenadine maintained rich H_1-receptor activity, suggesting high cortical response (Tashiro *et al*., 2002; Tashiro *et al*., 2004). Consequently, antihistamines that reduce H_1-receptor activity in the prefrontal cortex can potentially impair performance on divided attention tasks, such as driving and speaking on a mobile phone.

In conclusion, the findings of the current study revealed that hydroxyzine-treated subjects were significantly more sedated and had slower BRTs compared with subjects administered fexofenadine or placebo in all test conditions. This suggests that drivers given hydroxyzine may be slower at recognizing dangers in the road ahead and applying the brake to stop the vehicle. Furthermore, cellular phone use increased BRTs in subjects given hydroxyzine, which could potentially increase a patient's risk of having an accident. In contrast, volunteers given fexofenadine were no different from those in the placebo group in terms of their BRTs in a divided attention task of driving and cellular phone operation, providing new

evidence of the non-impairing effects of fexofenadine. Additional research is needed to support the current findings as BRT measurements on a closed driving course may differ from driving on the open road with numerous unpredictable drivers.

ACKNOWLEDGEMENTS

Further support was provided by grants from the Ministry of Education, Culture, Sports, Science, and Technology (Yanai K, Tashiro M) and Sagawa Traffic Safety Foundation (to Tashiro M). We would like to thank Professor Jiro Gyoba and Mr Yasuhiro Kitamura (Tohoku University) for their constant encouragement and support during this study. We would like to thank the staffs of Yamagata Pref. Police for their cooperation with the study.

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