

# Fexofenadine's effects, alone and with alcohol, on actual driving and psychomotor performance

Annemiek Vermeeren, MS, and James F. O'Hanlon, PhD

Maastricht, The Netherlands

**Background:** Fexofenadine is the hydrochloride salt of terfenadine's active metabolite.

**Objective:** Fexofenadine's effects on performance were assessed in this study for the purpose of determining its safety of use by patients who engage in potentially dangerous activities, especially car driving.

**Methods:** Fexofenadine was administered in daily doses of 120 or 240 mg, each in single and divided units given over 5 days. Two milligrams of clemastine given twice daily and placebo were given in similar series. Twenty-four healthy volunteers (12 men, 12 women; age range, 21 to 45 years) participated in a double-blind six-way crossover study. Psychomotor tests (critical tracking, choice reaction time, and sustained attention) and a standardized actual driving test were undertaken between 1.5 to 4 hours after administration of the morning dose on days 1, 4, and 5 of each series. On day 5, subjects were challenged with a moderate alcohol dose before testing.

**Results:** Fexofenadine did not impair driving performance. On the contrary, driving performance was consistently better during twice daily treatment with 120 mg fexofenadine than during treatment with placebo, significantly so on day 4. Both of the 240 mg/day regimens significantly attenuated alcohol's adverse effect on driving on day 5. Effects in psychomotor tests were not significant, with the exception of the critical tracking test in which the first single doses of fexofenadine, 120 and 240 mg, had significantly impairing effects. **Conclusion:** It was concluded that fexofenadine has no effect on performance after being taken in the recommended dosage of 60 mg twice daily. (*J Allergy Clin Immunol* 1998;101:306-11.)

**Key words:** Fexofenadine, clemastine, antihistamines, alcohol interactions, healthy volunteers, car driving, psychomotor performance

Fexofenadine was recently approved by the Food and Drug Administration in the dosage of 60 mg twice daily for the indication of seasonal allergic rhinitis. Its structure is identical to terfenadine's active metabolite, except that fexofenadine is the hydrochloride salt. Fexofenadine is a selective H<sub>1</sub>-receptor antagonist, and it is not known to possess any other clinically relevant pharmacologic activity after normal doses.<sup>1</sup> After oral adminis-

## Abbreviations used

|       |                                        |
|-------|----------------------------------------|
| BAC:  | Blood alcohol concentration            |
| CNS:  | Central nervous system                 |
| SDLP: | Standard deviation of lateral position |

tration, it is rapidly absorbed, with the time of maximum concentration occurring within 1 to 2 hours.<sup>2</sup> Elimination half-life ranges from 13 to 16 hours. Single oral doses of 40 mg and above achieve more than 80% maximum inhibition of both wheal and flare. The pharmacologic effect starts 1 to 2 hours after dose administration and is sustained over a period of 24 hours.<sup>3</sup> Fexofenadine has been administered to human volunteers in repeated doses of up to 690 mg twice daily for 28.5 days. It was well tolerated and produced no serious side effects. Clinical trials demonstrated effective treatment of modest to severe symptoms of ragweed or fall seasonal allergic rhinitis with dosages between 60 and 240 mg twice daily.<sup>4,5</sup> Unlike terfenadine, fexofenadine is devoid of quinidine-like effects on myocardial conductivity. The most commonly reported side effect of fexofenadine in clinical trials was headache. The incidence of fatigue, drowsiness, and nausea were comparable with that found in patients receiving placebo. It was therefore expected that fexofenadine would have little or no behaviorally impairing side effects after normal doses and would therefore be safe for use by patients who drive.

This study was designed to test whether fexofenadine impairs psychomotor performance, especially during car driving, in a standardized test. To provide information on the safety margins or the severity of any effects with increasing dose levels, fexofenadine was administered in 1× and 2× the normal daily dose. The effects were compared with those of placebo and a normal therapeutic dose of clemastine (i.e., 2 mg twice daily), which was shown previously to possess moderately impairing properties.<sup>6</sup> A secondary purpose was to assess possible pharmacokinetic or dynamic interactions between fexofenadine and alcohol that could affect driving because many patients using antihistamines occasionally drink and drive.

## METHODS

### Subjects

Twenty-five healthy male and female volunteers (age range, 22 to 44 years) were recruited through newspaper advertise-

From the Institute for Human Psychopharmacology, Maastricht University, Maastricht.

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Reprint requests: Annemiek Vermeeren, MS, Department of Biological Psychology, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands.

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ments and paid for participating in this experiment. Subjects were screened by a medical history questionnaire and a physical examination. The latter included a 12-lead electrocardiogram evaluation, blood chemistry and hematology assessments, and urinary tests for human chorionic gonadotropin and drugs of abuse. Exclusion criteria included pregnancy; any history or current evidence of severe physical or mental disorder, alcohol, or drug abuse; serious gastrointestinal, hepatic, renal, cardiovascular, or neurologic disorders; allergies requiring possible treatment with systemic antihistamines; consumption of more than 10 beverages containing caffeine per day, more than 20 cigarettes per day, or more than 28 glasses of alcohol-containing beverages per week; and participation in any other clinical trial within the previous 4 months. All subjects possessed a valid drivers licence and reported having driven between 5000 and 35,000 km per year (mean, 10,000 km/year) during the preceding 3 years. They agreed not to use any drugs of abuse or oral medication (except oral contraceptives, aspirin, and acetaminophen) for 1 week before and during treatments. They restricted alcohol consumption to a maximum of two glasses of wine or beer with a meal during treatment periods, and on test days their consumption of caffeine-containing beverages was limited to one cup of tea at breakfast. Smoking was prohibited for at least 30 minutes before and during testing. Subjects were instructed to sleep normally on nights before testing.

One subject dropped out after the first treatment period for reasons unrelated to treatment. A total of 24 subjects (12 men, 12 women) completed the study. Their mean  $\pm$  SD age was  $31.5 \pm 8.5$  years. Height and weight of the men were  $180.5 \pm 5.7$  cm and  $75.1 \pm 10.4$  kg, and height and weight of the women were  $167.8 \pm 7.0$  cm and  $65.5 \pm 8.2$  kg. Men reported consuming  $9.5 \pm 5.8$  alcoholic beverages per week, and women reported consuming  $6.0 \pm 6.0$ . Nine subjects were smokers of 2 to 20 cigarettes per day.

The study was conducted in accordance with the Declaration of Helsinki (Hong Kong Modification 1989). Subjects were informed of the study's goal, procedures, and possible adverse effects in writing, and they indicated their informed consent in writing. The study was approved by the standing Ethics Review Committee of Maastricht University.

### Study design and drug/alcohol administration

The study was conducted according to a double-blind, placebo and active drug-controlled, 6-way cross-over design. Subjects were treated with 120 mg fexofenadine once daily in the morning, 60 mg twice daily, 240 mg once daily in the morning, and 120 mg twice daily; 2 mg clemastine twice daily; and placebo twice daily. Treatment periods lasted 5 days, starting on the evening before the first day and ending the morning of the fifth day. Study medication was supplied in identical appearing gelatin capsules. Quarters of the subjects ingested their medication at 8:15, 9:30, 10:45, and 12:00 AM and PM. Treatment orders were randomly assigned from those residing in four replications of a  $6 \times 6$  Williams Square. Washout periods were at least 6 days.

Subjects were treated with an alcohol challenge on the fifth day of each period. The alcohol dosing regimen was developed to achieve and sustain a blood alcohol concentration (BAC) just under the local legal limit for drivers (i.e., 0.05%). This normally required the administration of seven constant 5.6 gm doses at 15-minute intervals from the time of drug or placebo ingestion until the beginning of laboratory performance testing; a larger (10 gm) dose before the longest (45 minute) laboratory test; and two more adjustable doses occurring 30 minutes and

immediately before the driving test. Pure alcohol (99.8%) was mixed with orange juice. BAC was estimated from concentrations in expired alveolar air before the second and subsequent doses by using a Lion Alcolmeter SD-400 (Lion Laboratories Inc). Adjustable doses were set for achieving the desired BAC during the driving test. Adjustments started earlier in some individual cases when BAC was increasing too rapidly or too slowly to achieve that objective.

### Procedure

Subjects were individually trained to perform the psychomotor tests and rehearsed the driving test before the first treatment period. Psychomotor and driving tests were undertaken on days 1, 4, and 5 of each treatment period. Subjects fasted between 3 hours before and 1 hour after ingestion of the morning dose. Thereafter they were given a light meal. Critical tracking, choice reaction time, and sustained attention tests were performed from 1½ to 2½ hours after dosing, and the driving test was performed 3 to 4 hours after dosing.

The critical tracking test measures the ability to control an unstable error signal in a first-order compensatory tracking task.<sup>7</sup> Error is displayed as a horizontal deviation of a cursor from the midpoint on a horizontal, linear scale. Compensatory joystick movements null the error by returning the cursor to the midpoint. The frequency of cursor deviations (i.e., cursor instability [ $\lambda$ ]), increases as a stochastic, linear function of time, and thus the required velocity of corrections increases. The frequency at which the subject loses control is the critical tracking frequency ( $\lambda_c$ , in rad/seconds). The test includes five trials of which the lowest and the highest scores were removed. The average of the remaining scores is taken as the final score.

Average choice reaction time (in milliseconds) of correct responses was measured in the presence of distracting cues. The task is to react to the appearance of the words *left* and *right* by pressing corresponding buttons. Half of the words are displayed at compatible and half at incompatible (left or right) sides of a screen.

The sustained attention test is a variant of the classic Mackworth "Clock Test."<sup>8</sup> The subject is seated in front of a computer screen displaying a circular arrangement of 60 grey dots, which simulate the second marks on a clock. The luminance of each dot briefly increases in clockwise rotation at a rate of two dots per second. Occasionally, the rotation proceeds with a "double jump" by skipping one of the dots in the normal sequence. The dependent variable is the number of correct detections. Test duration is 45 minutes, and 10 signals occur within each successive 15-minute period.

The driving test was originally developed during the 1970s for driver fatigue research in the United States. It was standardized for drug screening purposes in 1982, and has been used in more than 50 separate studies for measuring drug effects on driving performance.<sup>9,10</sup> The subject drives a specially instrumented car over a 100 km (61 mile) primary highway circuit. He or she is accompanied by a licensed driving instructor who has access to dual controls. The subject's task is to maintain a constant speed of 95 km/hour (58 miles/hour) and a steady lateral position between the delineated boundaries of the slower traffic lane. The vehicle's speed and lateral position relative to the left lane line delineation are continuously recorded. These signals are digitally sampled at 4 Hz and edited, off-line, to remove parts where data are disturbed by extraneous events (e.g., passing maneuvers). The remainder is then reduced by successive 5 km segments of the ride. Means and standard deviations of both variables are calculated for the entire test, the latter parameters

**TABLE I.** Failures to complete driving tests by treatment and day of treatment

|              |               | Day 1 | Day 4 | Day 5<br>(with alcohol) |
|--------------|---------------|-------|-------|-------------------------|
|              |               | I/S   | I/S   | I/S                     |
| Placebo      | b.i.d.        | —     | 1/1   | —                       |
| Fexofenadine | 120 mg q.a.m. | 1/0   | 2/0   | 1/0                     |
|              | 60 mg b.i.d.  | 1/0   | —     | 1/1                     |
|              | 240 mg q.a.m. | —     | —     | 2/0                     |
|              | 120 mg b.i.d. | —     | —     | —                       |
| Clemastine   | 2 mg b.i.d.   | 0/1   | 1/0   | 4/0                     |

I, Rides terminated by decision of the driving instructor; S, rides terminated by decision of the subject; *b.i.d.*, twice daily; *q.a.m.*, once daily in the morning.

by taking the square-root of variances pooled over all segments. Standard deviation of lateral position (SDLP) is the primary outcome variable. SDLP is an index of road tracking error or allowed "weaving." It is a very reliable characteristic of individual driving performance: the test-retest reliability coefficient for unmedicated young and middle-aged drivers is  $r = 0.85$ . It has also proven sensitive to many sedating agents, including alcohol, in blood concentrations as low as 0.035%.<sup>11, 12</sup>

### Statistical analysis

Psychomotor and driving performance parameters were analyzed separately for days 1, 4, and 5 by using univariate repeated measures analysis of variance. Statistical tests were conducted using the SAS (SAS Institute, Inc.), (6.09) General Linear Models procedure, with sequential (Type I) sums of squares. Main effects included in the model were Subjects, Gender, Period, Treatment, Treatment by Period, and Treatment by Gender interactions. Drug-placebo differences were tested with the least squares means procedure.

## RESULTS

### Alcohol doses and BACs

Mean  $\pm$  SD cumulative alcohol doses (grams per kilograms) and BACs (percent) at the beginning of the driving tests were practically the same in every condition:  $0.80 \pm 0.08$ ,  $0.81 \pm 0.10$ ,  $0.82 \pm 0.09$ ,  $0.79 \pm 0.09$ ,  $0.80 \pm 0.09$ , and  $0.79 \pm 0.09$  gm/kg; and  $0.045\% \pm 0.007\%$ ,  $0.045\% \pm 0.007\%$ ,  $0.047\% \pm 0.005\%$ ,  $0.049\% \pm 0.007\%$ ,  $0.045\% \pm 0.007\%$ , and  $0.048\% \pm 0.005\%$  for placebo, clemastine, 120 mg fexofenadine once daily in the morning, 60 mg fexofenadine twice daily, 240 mg fexofenadine once daily in the morning, and 120 mg fexofenadine twice daily, respectively.

### Driving performance

Seventeen driving tests (3.9% of a total of 432) were terminated before scheduled completion because the subject (in three tests) or driving instructor (in 14 tests) judged that it would be unsafe to continue (Table I).

Calculation of SDLP values for subjects whose rides were terminated before scheduled completion were adjusted according to a planned last-value-carried-forward procedure. That is, the data collected during the last 5 km segment before stopping were inserted for each of

the unfinished segments. Mean ( $\pm$  SEM) SDLP scores on days 1, 4, and 5 of each treatment series are presented in Fig. 1. Significant overall effects of Treatment were found on both day 1 and 4 ( $F[5,85] = 6.05$ ,  $p = 0.0001$ ;  $F[5,85] = 3.93$ ,  $p = 0.003$ , respectively). Mean drug-placebo comparisons showed that clemastine significantly impaired driving performance on both days ( $p = 0.0006$  and  $0.0309$ , respectively). On day 1, no fexofenadine dose had effects on driving performance that differed significantly from those found with placebo. Yet on day 4, mean SDLP for subjects given 120 mg fexofenadine twice daily was nearly significantly ( $p = 0.0504$ ) lower (i.e., better) than that found for subjects given placebo. Though mean SDLP changes in the other fexofenadine conditions on day 4 were in the same direction, none was significant.

Comparison of SDLP scores on days 4 and 5 indicated that alcohol significantly impaired driving performance ( $F[1,212] = 52.82$ ,  $p = 0.0001$ ). Analysis of SDLP scores on day 5 also showed a significant Treatment effect ( $F[5,85] = 2.94$ ,  $p = 0.017$ ). Mean drug-placebo comparisons revealed that this effect was not attributable to clemastine, but rather to the higher daily doses of fexofenadine. The combined effect of alcohol and 120 mg fexofenadine twice daily was significantly ( $p = 0.0376$ ) less impairing than that of alcohol alone, and the similar effect of 240 mg fexofenadine given once daily in the morning closely approached significance ( $p = 0.0606$ ). The effects of both lower fexofenadine doses and clemastine in combination with alcohol were not significantly different from those of alcohol alone. There were no significant Gender effects or Gender by Treatment interactions, indicating that there were no differences in driving performance between men and women in general or in any particular treatment condition.

### Critical tracking

Analyses showed a significant effect of Treatment on critical tracking frequency ( $\lambda_c$ ) on day 1, but not on day 4 ( $F[5,85] = 2.55$ ,  $p = 0.0337$ ;  $F[5,85] = 1.36$ , not significant). The effect on day 1 was attributable to significant impairment of tracking performance by clemastine and also by 120 mg fexofenadine once daily in the morning and 240 mg fexofenadine once daily in the morning (means  $\pm$  SEM =  $3.82 \pm 0.17$ ,  $3.82 \pm 0.16$ , and  $3.81 \pm 0.17$ ;  $p = 0.0367$ ,  $0.0304$ , and  $0.0219$ , respectively) as compared with placebo (mean  $\pm$  SEM =  $4.00 \pm 0.17$ ). The effects of 60 mg fexofenadine twice daily and 120 mg fexofenadine twice daily were not significantly different from those of placebo (means  $\pm$  SEM =  $3.94 \pm 0.16$  and  $4.01 \pm 0.16$ ). Tracking performance was significantly impaired by alcohol ( $F[1,212] = 18.20$ ,  $p = 0.0001$ ). Analysis of  $\lambda_c$  scores on day 5 showed a significant Treatment effect ( $F[5,85] = 3.52$ ,  $p = 0.0061$ ). Both 240 mg fexofenadine once daily in the morning and 2 mg clemastine twice daily in combination with alcohol had significantly more impairing effects on tracking than alcohol alone (means  $\pm$  SEM =  $3.66 \pm 0.19$ ,  $3.63 \pm$

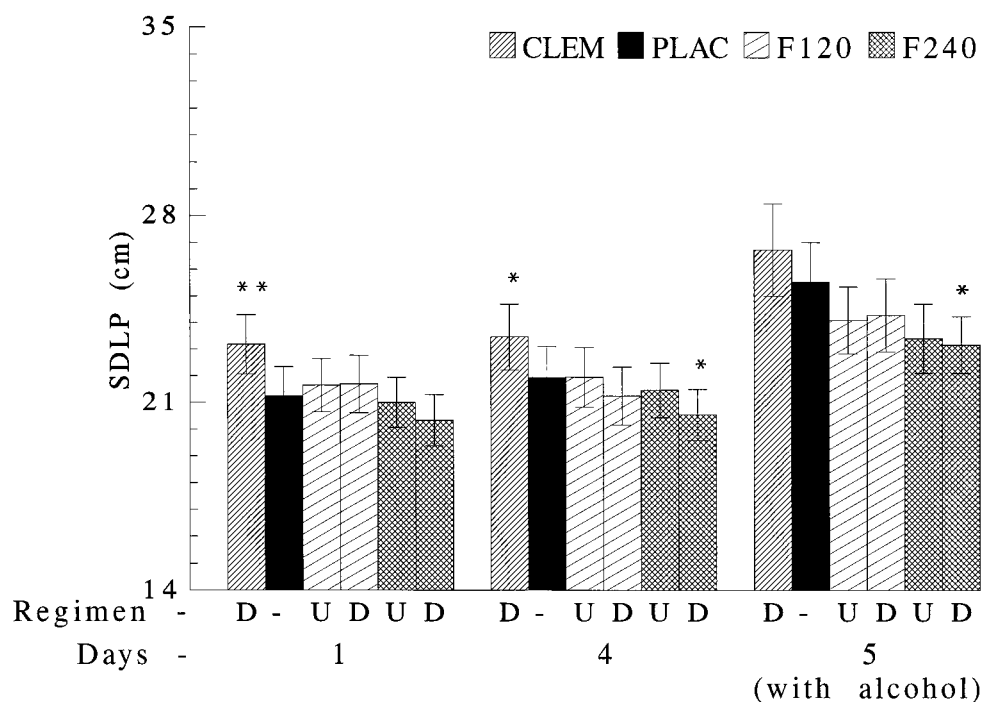


**FIG. 1.** Mean ( $\pm$  SEM) SDLP per treatment and days within treatment. CLEM, 2 mg clemastine twice daily; PLAC, placebo; F120, fexofenadine in a daily dose of 120 mg; and F240, fexofenadine in a daily dose of 240 mg; U, unitary dosing regimen; and D, divided dosing regimen. Asterisks over bars indicate level of significance for drug-placebo differences. \* $p < 0.05$ . \*\* $p < 0.01$ .

0.18, and  $3.83 \pm 0.19$ ;  $p = 0.0349$  and  $0.0145$ , respectively). The effects of 60 mg fexofenadine twice daily, 120 mg once daily in the morning, and 120 mg twice daily in combination with alcohol (means  $\pm$  SEM =  $3.78 \pm 0.18$ ,  $3.72 \pm 0.17$ , and  $3.90 \pm 0.18$ , respectively) were not significantly different from those of alcohol alone. Significant Gender effects on days 1, 4, and 5 ( $F[1,85] = 15.06, 27.89, 41.50$ ;  $p \leq 0.0002$ ) indicated that tracking performance of men was better than that of women.

### Choice reaction time

Analyses showed no significant effects of Treatment on choice reaction time on days 1, 4, and 5, yet alcohol significantly ( $F[1,212] = 27.81$ ;  $p = 0.0001$ ) prolonged mean reaction times. Significant Gender effects on days 1, 4, and 5 ( $F[1,85] = 7.24, 4.52, 5.29$ ;  $p \leq 0.0086, 0.0364$ , and  $0.0239$ , respectively) indicated that men were generally faster.

### Sustained attention

Analyses showed that the Treatment effect on number of correct detections in the sustained attention test only approached significance on day 1 and was not significant on day 4 ( $F[5,85] = 1.95, p = 0.0942$ ;  $F[5,85] = 1.02$ , not significant). Mean drug-placebo comparisons revealed a tendency towards impaired performance on the first day of clemastine treatment as compared with placebo (means  $\pm$  SEM =  $19.9 \pm 1.5$  and  $22.1 \pm 1.2$ ;  $p = 0.0749$ ), which was no longer present on day 4. Fexofe-

nadine had no effects on sustained attention. Alcohol, however, significantly impaired sustained attention ( $F[1,179] = 51.13, p = 0.0001$ ). Analysis of correct detections on day 5 showed a significant Treatment effect ( $F[5,80] = 3.59, p = 0.0056$ ). Mean drug-placebo comparisons showed that this effect was mainly caused by a significantly impairing effect of clemastine in combination with alcohol as compared with alcohol alone (means  $\pm$  SEM =  $15.3 \pm 1.7$  and  $18.3 \pm 1.7$ ;  $p = 0.0201$ ). The effects of alcohol in combination with fexofenadine in this test did not differ significantly from those of alcohol alone (means  $\pm$  SEM =  $19.2 \pm 1.4, 17.4 \pm 1.7, 20.0 \pm 1.4$ , and  $18.3 \pm 1.7$  for 60 mg fexofenadine twice daily, 120 mg once daily in the morning, 120 mg twice daily, and 240 mg once daily in the morning, respectively). Significant Gender effects on days 4 and 5 ( $F[1,85] = 5.78, p = 0.0184$ ;  $F[1,80] = 6.94, p = 0.0101$ ) indicated that women generally detected more signals than men.

### DISCUSSION

Fexofenadine, given over five days in separate dosing regimens (60 mg twice daily, 120 mg once daily in the morning, 120 mg twice daily, and 240 mg once daily in the morning), did not by itself impair driving performance and did not add to the impairment produced by alcohol in a blood concentration of approximately 0.04%. On the contrary, the higher divided dose, by itself, significantly improved driving performance on day

4, and both of the 240 mg/day regimens significantly or almost significantly reduced alcohol's effect on driving performance on day 5. Neither of the 120 mg/day regimens had significant effects on driving. However, both of the lower doses attenuated the alcohol effect to approximately the same extent (about half as much as the higher doses), giving the impression that fexofenadine's capacity to antagonize that effect is dose-related. The active control, 2 mg clemastine twice daily, significantly impaired driving performance on days 1 and 4 to confirm the test's sensitivity to the sedative effects of antihistamines. The combination of clemastine plus alcohol impaired driving performance to a greater degree than placebo plus alcohol, but the difference was not significant.

Fexofenadine did not affect performance significantly in any laboratory test, except critical tracking. In this test after the first 120 and 240 mg doses on day 1, and again after 240 mg in combination with alcohol, the drug reduced the critical tracking frequency,  $\lambda_c$ . Clemastine in combination with alcohol did the same. The question is therefore how two drugs having similar effects on  $\lambda_c$  could have opposite effects on road tracking performance as measured by SDLP. One answer may be implicit in the fundamental engineering model of compensatory manual tracking performance.<sup>13, 14</sup> That model, and all that have evolved from it, use mathematical expressions to describe the relationship between the system's deviance from a desired norm (i.e., error) and the operator's controlling response. These models contain at least two parameters, termed delay and gain, which represent human operating characteristics. In neuropsychologic terms, delay represents the time elapsing between the sensory transduction of an error signal and the beginning of a compensatory motor response. It is the continuous analog of discrete reaction time. An individual's delay can lengthen under the influence of any factor that slows neurotransmission, resulting in a decrease in the maximum error frequency an operator can control, which was estimated by  $\lambda_c$  in this study. Gain in the engineering model is simply the observed ratio of the motor output to the given error input, but within a biologic system that ratio must be related to the number of neural units recruited in expediting the motor response. The more there are, the stronger the motor reaction. Differences in gain determine individual response style. People operating with high gain react very vigorously to the perceived error, which, after the delay, enables them to rapidly restore the controlled system to the desired state when error develops slowly but at the cost of overshooting the mark, particularly when error develops rapidly. Those with low gain react sluggishly. They allow slowly developing errors to accumulate further before correction but do not overreact to faster ones. Gain may vary within an individual with his or her level of CNS activation.

It is possible to explain clemastine's and fexofenadine's effects according to this model. Clemastine is known to be sedating and is likely to increase delay by

slowing neurotransmission. The findings that it impairs road tracking (i.e., increases SDLP) and laboratory tracking (i.e., decreases  $\lambda_c$ ) appear to confirm this hypothesis. In contrast, fexofenadine either improved road tracking (i.e., diminished SDLP), impaired laboratory tracking (i.e., reduced  $\lambda_c$ ), or did both simultaneously. These effects are theoretically those of an agent that increases gain (i.e., better low frequency error compensation in road tracking with a greater tendency to overreact to high frequency error in laboratory tracking). Pharmacologically, these effects are what one might expect from a mild stimulant that raises brain activation as a whole and the excitability of neurons within the motor cortex in particular. Yet the profile displayed by fexofenadine is different from those of the classic psychostimulants such as amphetamines, caffeine, and nicotine. The latter enhance signal detection performance in vigilance tests,<sup>15</sup> whereas in this study fexofenadine did not.

The present indication that fexofenadine might possess mildly activating properties is supported by occasional findings in studies with its metabolic precursor, terfenadine. Significant signs of activation were found on subjective alertness, psychomotor performance, and vehicle handling in closed-course driving tests while subjects were receiving terfenadine therapy.<sup>16, 17, 18</sup> Congruent but nonsignificant effects have also been demonstrated on event-related electroencephalographic potentials and SDLP measured according to the same procedures as used in this study.<sup>19, 20, 21, 22</sup> Signs of performance-improving effects have also been reported for a very similar piperidine antihistamine, ebastine.<sup>9, 23, 24</sup>

Almost the entire terfenadine dose is normally transformed during first-pass metabolism into fexofenadine and azacyclonol, an inactive compound, at a ratio of 2:1.<sup>25</sup> Thus fexofenadine was probably responsible for the effects formerly attributable to its parent. Moreover, assuming equal absorption, one should expect greater effects from the same oral doses of fexofenadine than terfenadine, because fexofenadine forms no inactive metabolites.

Pharmacologic mechanisms whereby antihistamines could affect behavior in the manner fexofenadine appeared to in this study have been previously proposed.<sup>26</sup> One that should theoretically enhance arousal-dependent performance is the inhibition of the enzyme responsible for histamine's extraneuronal catabolism, histamine N-methyltransferase. It is unknown whether fexofenadine possesses that or any other property capable of increasing CNS arousal, but before initiating a search for the mechanism it would be well to inquire whether the drug penetrates the brain after being given in doses equivalent to those in this study. It would appear that it does from the results of an attempt to measure terfenadine's passage through the blood-brain barrier in mice.<sup>27</sup> Separate groups of three to six animals were given single doses of terfenadine (2 to 100 mg/kg), and 1 hour later they were given intraperitoneal tritiated mepyramine. Inhibition of radioligand binding at corti-

cal H1 receptors was measured for determining the extent to which terfenadine or its active metabolite occupied those sites. Two and three milligram per kilogram doses of terfenadine resulted in about 16% and 24% mean receptor occupancy, respectively. Occupancy increased exponentially with higher doses until almost complete inhibition of radioligand binding occurred above 75 mg/kg. The two lowest doses were the equivalent of 140 and 210 mg in a 70 kg human. Even though the former occupied much lower percentages of cortical H1 receptors than did equivalent doses of lipophilic antihistamines (e.g., triprolidine and d-chlorpheniramine, 70%), it is clear that all drugs had more or less crossed the blood-brain barrier. The implication of these results was subsequently noted by Manning and Gengo<sup>28</sup>: chronic daily dosing with terfenadine, and presumably other second generation antihistamines, might eventually result in brain concentrations capable of affecting behavior.

In conclusion, fexofenadine in doses up to 240 mg/day should be safe for use by patients who drive. Doses up to 120 mg/day apparently have no effect on driving performance. Doses of 240 mg/day given consecutively for 4 to 5 days may affect driving performance in a manner that appears beneficial. We attribute this to some activating effect of the drug within the CNS. That effect may also be beneficial in drivers whose performance would otherwise be deficient because of fatigue. Further studies are required to confirm our explanation and to elucidate fexofenadine's mechanism of action.

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## REFERENCES

1. Fexofenadine hydrochloride (MDL 16,455A). Investigational drug brochure. Edition no. 3. Kansas City (MO): Hoechst Marion Roussel, Inc.; 1995.
2. Lippert C, Ling J, Brown P, Burmaster S, Eller M, Cheng L, et al. Mass balance and pharmacokinetics of MDL 16,455A in healthy male volunteers. *Pharm Res* 1995;12:390.
3. Day JH, Briscoe MP, Welsh A, Smith J, Mason J. Onset of action, efficacy and safety of a single dose of 60 mg and 120 mg fexofenadine HCl for ragweed (RW) allergy using controlled antigen exposure in an environmental exposure unit (EEU) [abstract]. *J Allergy Clin Immunol* 1996;97:434.
4. Bernstein D, Schoenwetter W, Nathan R, Storms W, Mason J. Fexofenadine: a new non-sedating antihistamine is effective in the treatment of seasonal allergic rhinitis [abstract]. *J Allergy Clin Immunol* 1996;97:435.
5. Tinkelman D, Falliers C, Bronsky E, Kaiser H, Mason J. Efficacy and safety of fexofenadine HCl in fall seasonal allergic rhinitis [abstract]. *J Allergy Clin Immunol* 1996;97:435.
6. Vuurman EFPM, Uiterwijk MMC, Rosenzweig P, O'Hanlon JF. Effects of mizolastine and clemastine on actual driving and psychomotor performance in healthy volunteers. *Eur J Clin Pharmacol* 1994;47:253-9.
7. Jex HR, McDonnell JD, Phatak AV. Critical tracking task for manual control research. *IEEE Transactions on Human Factors in Electronics* 1966;HFE-7:138-45.
8. Mackworth NH. Researches on the measurement of human performance. HMSO Medical Research Council Special report no. 268. London: Her Majesty's Stationary Office; 1950.
9. O'Hanlon JF, Ramaekers JG. Antihistamine effects on actual driving performance in a standard test: a summary of Dutch experience, 1989-94. *Allergy* 1995;50:234-42.
10. O'Hanlon JF, Vermeeren A, Uiterwijk MMC, van Veggel LMA, Swijman HF. Anxiolytics' effects on the actual driving performance of patients and healthy volunteers in a standardized test. *Neuropsychobiology* 1995;31:81-8.
11. Ramaekers JG, Uiterwijk MMC, O'Hanlon JF. Effects of loratadine and cetirizine on actual driving and psychometric test performance, and EEG during driving. *Eur J Clin Pharmacol* 1992;42:363-9.
12. Vuurman EFPM, Muntjewerff ND, Uiterwijk MMC, Van Veggel LMA, Crevoisier C, Haglund L, et al. Effects of mefloquine, alone and with alcohol, on psychomotor and driving performance. *Eur J Clin Pharmacol* 1996;50:475-82.
13. McRuer DT, Krendel ES. The human operator as a servo system element. *J Franklin Inst* 1959;267:381-403, 511-36.
14. McRuer DT, Jex HR. A review of quasi-linear pilot models. *IEEE Transaction on Human Factors in Electronics* 1967;8:231-6.
15. Koelega HS. Stimulant drugs and vigilance performance: a review. *Psychopharmacology* 1993;111:1-16.
16. Clarke CH, Nicholson AN. Performance studies with antihistamines. *Br J Clin Pharmacol* 1978;6:31-6.
17. Moskowitz H, Burns M. Effects of antihistamines on behavioral skills in driving. *J Respir Dis* 1988;8(Suppl):S1-24.
18. Betts T, Kenwood C, Dalby G, Hull B, Wild J. A comparison of the effects of two non-sedating anti-histamines (terfenadine and cetirizine) on tests of CNS function including driving. *J Psychopharmacol* 1989;3/4:101-3.
19. Simons FER, Fraser TG, Reggin JD, Simons KJ. Comparison of the central nervous system effects produced by six H1-receptor antagonists. *Clin Exp Allergy* 1996;26:1092-7.
20. Riedel WJ, Schoenmakers EAJM, O'Hanlon JF. Sedation and performance impairment with antihistamines. In: Kaline MA, editor. *Management of allergy in the 1990s*. Toronto, Canada: Hans Huber Publishers; 1989. p. 38-49.
21. Volkerts ER, van Willigenburg APP, van Laar MW, Maes RAA. Does cetirizine belong to the new generation of antihistamines? An investigation into its acute and subchronic effects on highway driving, psychometric test performance and daytime sleepiness. *Hum Psychopharmacol* 1992;7:227-38.
22. Ramaekers JG, O'Hanlon JF. Acrivastine, terfenadine and diphenhydramine effects on driving performance as a function of dose and time after dosing. *Eur J Clin Pharmacol* 1994;47:261-6.
23. Mattila MJ, Kuitunen T, Pletan Y. Lack of pharmacodynamic and pharmacokinetic interactions of the antihistamine ebastine with ethanol in healthy subjects. *Eur J Clin Pharmacol* 1992;43:179-84.
24. Brookhuis KA, de Vries G, de Waard D. Acute and subchronic effects of the H1-histamine receptor antagonist ebastine in 10, 20 and 30 mg dose and triprolidine 10 mg on car driving performance. *Br J Clin Pharmacol* 1993;36:67-70.
25. Ling KH, Leeson GA, Burmaster SD, Hook RH, Reith MK, Cheng LK. Metabolism of terfenadine associated with CYP3A(4) activity in human hepatic microsomes. *Drug Metab Dispos* 1995;23:631-6.
26. Simons FER. H1-receptor antagonists: comparative tolerability and safety. *Drug Safety* 1994;10:350-80.
27. Rose C, Quache TT, Llorens C, Schwartz JC. Relationship between occupation of cerebral H1-receptors and sedative properties of antihistamines. Assessment in the case of terfenadine. *Arzneimittelforschung* 1982;32:1171-3.
28. Manning C, Gengo FM. Effects of drugs on human functioning: antihistamines. In: Streufert S, Gengo FM, editors. *Effects of drugs on human functioning*. Basel: Karger; 1993. p. 52-69.