CME Review article

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Antihistamines and driving ability: evidence from on-the-road driving studies during normal traffic

Joris C. Verster, PhD, and Edmund R. Volkerts, PhD

Background: All antihistamines are capable of crossing the blood-brain barrier and thus may cause sedation. Most antihistamine users are ambulatory patients and therefore presumably drive a car.

Objective: To summarize the effects of antihistamine drugs on driving ability.

Data Sources and Study Selection: A literature search (MEDLINE and cross-references) was performed using the keywords *driving* and *antihistamine*. Sixteen studies using the on-the-road driving test during normal traffic were included in the review. Studies were double-blind and placebo-controlled and included a positive control.

Results: First-generation antihistamines (diphenhydramine, triprolidine, terfenadine, dexchlorpheniramine, clemastine) significantly impair driving performance after both one-time and repeated (daily) administration. Second-generation antihistamines (cetirizine, loratadine, ebastine, mizolastine, acrivastine, emedastine, mequitazine) may also impair driving performance, but the magnitude and extent of impairment depend on the administered dose, sex, and time between testing and treatment administration. Tolerance develops after 4 to 5 days of administration, but impairment is not absent. Third-generation antihistamines (fexofenadine and levocetirizine) have been shown to produce no driving impairment after both one-time and repeated administration.

Conclusions: First- and second-generation antihistamines may significantly impair driving performance. In the context of driving safety but also taking into account the cardiotoxic properties of some of the second-generation antihistamines, we advise treating patients with third-generation antihistamines such as fexofenadine and levocetirizine.

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INTRODUCTION

Allergic diseases that may require treatment with antihistamines (H_1-receptor antagonists) affect 10% to 25% of the population.[1] Although their therapeutic site of action is peripheral, all antihistamines are capable of crossing the blood-brain barrier. In the brain, antihistamines block histamine H_1-receptors. Histamine is associated with arousal and attention. First-generation antihistamines have a wide pharmacologic profile: they easily cross the blood-brain barrier and bind nonselectively to H_1-receptors, but they also interact with adrenergic, serotonergic, and cholinergic neurons. A variety of adverse effects may accompany their use, including sedation, reduced alertness, and anticholinergic effects (eg, blurred vision). These unwanted effects may affect performance of daily activities such as driving a car. Second-generation antihistamines are composed of relatively large and less lipophilic molecules that cross the blood-brain barrier less easily and act more selectively at the H_1-receptors. Hence, they produce less sedation and anticholinergic effects when compared with first-generation antihistamines. Recently, fexofenadine, desloratadine, and levocetirizine were introduced as third-generation antihistamines, claiming to be devoid of unwanted central nervous system effects. Since the majority of antihistamine users are ambulatory patients, it is important to acknowledge the possible effects of antihistamines on driving ability and to take the differences among antihistamines into account when prescribing these compounds.

METHODS

In The Netherlands, a driving test method was developed during the 1980s.[2,3] The on-the-road driving test has been applied in many studies to determine the effects of psychoactive drugs on driving ability, including antihistamine drugs in different dosages and treatment regimens. The major advantage of the on-the-road driving test is that it is conducted during normal traffic, which greatly enhances the ecologic validity relative to closed-road studies and driving simulators in the laboratory (performed in artificial environments). In

Utrecht Institute for Pharmaceutical Sciences, Department of Psychopharmacology, University of Utrecht, Utrecht, The Netherlands.

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this context, it has been shown in a direct comparison that the on-the-road driving test is more sensitive to drug-induced impairment than a driving simulator.[4] A recent comparison showed that results from laboratory tests poorly predicted actual driving performance. Despite the facts that these standardized tests were known to measure driving-related skills and have proven their reliability and validity, a predictive validity of only 33% was found.[5]

In the standardized driving test, subjects are instructed to drive a car over a 100-km circuit while maintaining a constant speed (90 or 95 km/h) and a steady lateral position within the right (slower) traffic lane. Primary parameter of the test is the SD of lateral position (SDLP, cm), indexing the weaving of the car. The meaning of SDLP is illustrated in Figure 1.

Driving performance in recorded by a camera, mounted on the roof of the car (Fig 2). For safety reasons, a licensed driving instructor provided with a brake and clutch system accompanies the subjects.

To calibrate SDLP measurements in 1987, driving performance was determined for different blood alcohol concentrations (BACs).[6] The study was performed on a closed highway, because the Dutch law prohibits driving while intoxicated with alcohol levels at or above 0.05%. Significant SDLP increments, relative to placebo, were found for BACs of 0.05% (SDLP +2.6 cm), 0.08% (SDLP +4.1 cm), and 0.10% (SDLP +5.3 cm). Since these levels are the most common international legal limits for driving a car, these data are often used to illustrate driving impairment observed in other psychoactive substances.

The present review will discuss the effects of antihistamines on driving ability. A literature search using MEDLINE (keywords *driving* and *antihistamine*) and cross-references found 16 on-the-road driving studies. All studies were placebo controlled and double-blind, and most of them included a positive control.

RESULTS

First-Generation Antihistamines

Results from on-the-road studies with first-generation antihistamines[7–17] are summarized in Tables 1 and 2.

Triprolidine. In 20 healthy men, triprolidine (10 mg, slow-release formulation) significantly impaired driving performance 1 and 3 hours after single-dose administration,[7] comparable with impairment observed with BACs greater than 0.05%. Three subjects were unable to complete their driving tests.

In a second study[8] in 24 healthy volunteers, triprolidine (5 mg, twice daily) significantly impaired driving performance 2 and 4 hours after one-time and repeated administration. Due to drowsiness 6 subjects were unable to complete their driving tests 2 hours after one-time administration.

In 15 healthy men, triprolidine (10 mg) produced significant driving impairment 2 hours after one-time administration (ΔSDLP of 2.9 cm), comparable with a BAC higher than 0.05%.[9] Two driving tests were stopped before completion due to excessive weaving. On day 4, driving performance was no longer impaired 2 hours after treatment administration.

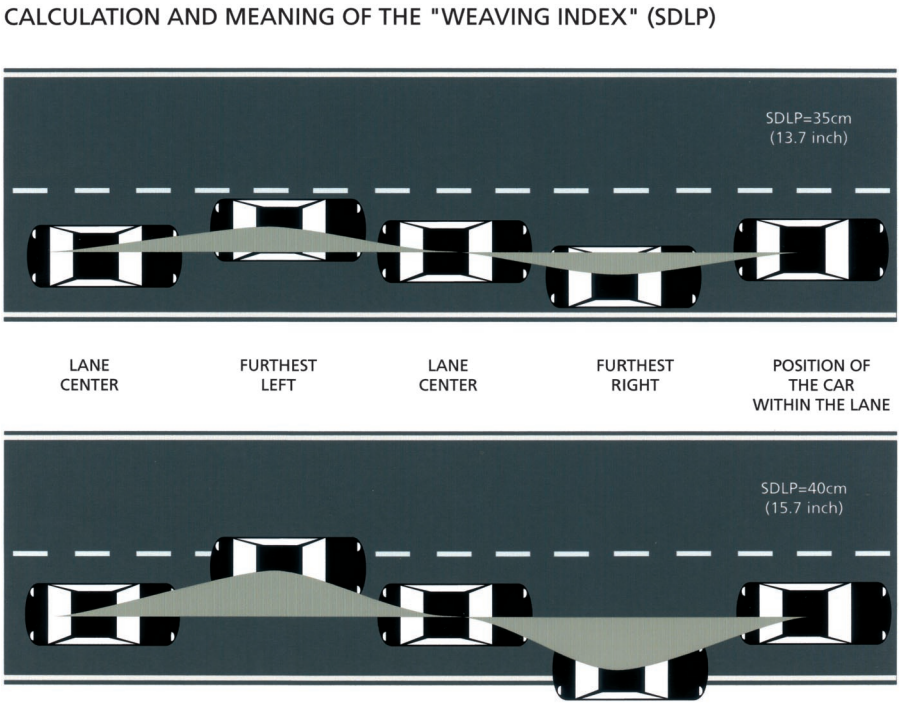

Figure 1. SD of lateral position (SDLP). SDLP values express the weaving of the car and represent the amount of vehicle control. Drug treatment may cause highly elevated SDLP values, resulting in excursions out of lane, into the road shoulder and/or the adjacent traffic lane. Hence, high SDLP values represent unsafe driving behavior.

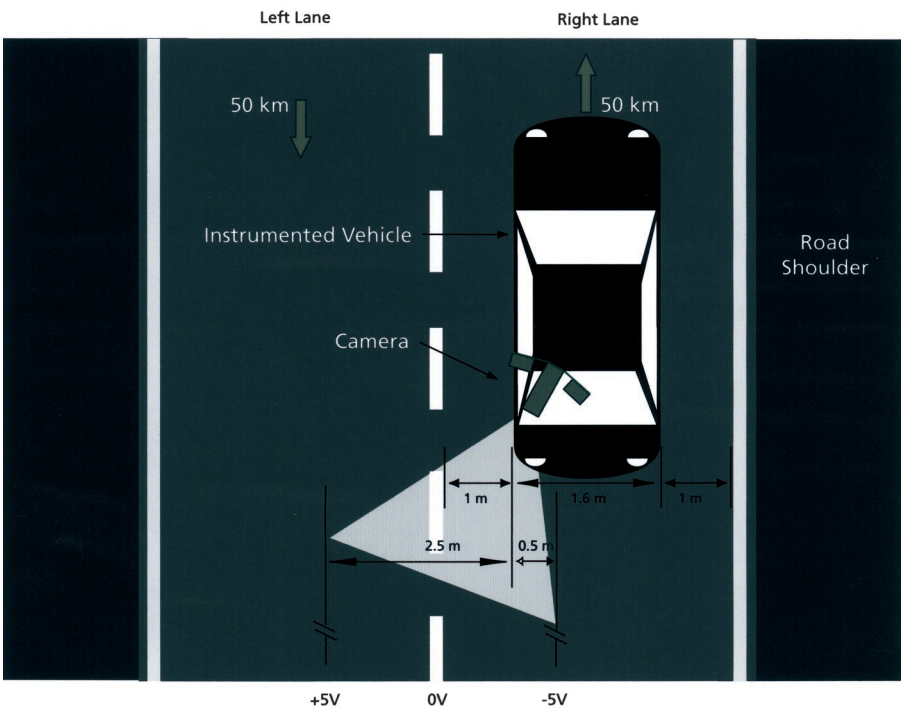

Figure 2. Schematic representation of the on-the-road driving test. The camera records the car's lateral position relative to the left traffic lane delineation. The speed is measured by the revolutions of the wheels. Data are continuously recorded (2 Hz) and edited off-line to remove disturbances by extraneous events such as traffic jam or overtaking maneuvers.

In 27 healthy men, triprolidine (5 mg twice daily) produced significant driving impairment 1 hour after one-time administration.[10] SDLP increment was comparable with that observed with a BAC of 0.08%. Speed variability was significantly increased as well, pointing also to reduced vehicle control after triprolidine administration. After repeated administration (day 4, 2 hours after intake), tolerance to the impairing effects of triprolidine was observed, but impairment was still significant and 1 subject was unable to complete his driving test.[18]

In another study,[11] triprolidine (10 mg, sustained-release formulation) was administrated for 5 subsequent days. In addition to the standardized driving test, a car-following test was performed. In the latter test, subjects were instructed to maintain a constant headway behind a lead vehicle traveling at variable speed. SDLP after triprolidine did not differ significantly from placebo after one-time and repeated administration. However, reaction speed in the car-following test was significantly slower when compared with placebo. Taken together, the results from these 5 studies show that driving a car is unsafe when the driver has been treated with triprolidine.

Diphenhydramine. Significant performance impairment after administration of diphenhydramine has been shown in driving simulators[19–22] and a variety of psychometric tests in a laboratory setting.[23–26] Direct evidence on driving ability comes from 2 on-the-road studies.[12,13]

Eighteen healthy women participated in a study[12] examining the effects of diphenhydramine (50 mg) in the standardized on-the-road driving test and a car-following test, performed 1.5 and 3.25 hours after one-time administration. Performance on both tests was significantly impaired at both testing times (ΔSDLP >5 cm, comparable with that observed with a BAC of 0.10%). Speed variability was significantly increased relative to placebo as well. Four subjects were unable to complete their driving tests. In the car-following test, reaction speed was significantly increased by diphenhydramine at both test occasions.

In a recent study,[13] diphenhydramine (50 mg) was administered to 48 healthy men and women over 4 days. Diphenhydramine produces significant driving impairment 1.5 hours after one-time administration. In fact, 43.8% of the drivers drove worse than the SDLP increment observed with a BAC of 0.05%. Driving ability was also significantly impaired on day 4, although weaving of the car was less pronounced than after immediate administration. Nevertheless, 31.1% drove worse than observed with a BAC of 0.05%. Results from laboratory tests performed by the same subjects 3 hours after administration were in line with the observed driving impairment: diphenhydramine produced significant impairment on all tests after immediate administration. On day 4 performance was also worse than after placebo but did not reach significance.[24] In conclusion, driving is unsafe for persons treated with diphenhydramine.

Clemastine. In one study,[14] 4 hours after one-time administration clemastine (2 mg) significantly impaired performance in 24 healthy volunteers. Due to drowsiness resulting

Table 1. First-Generation Antihistamines and Driving Performance

Reference	N	Subjects	Dose	Day 1 (one-time)	Day 4 (repeated)
Triprolidine					
7	20	Men	10 mg SR	*	—
8	24	Mixed	5 mg BID	*	*
9	15	Men	10 mg	*	NS
10	27	Men	5 mg BID	*	*
11	15	Men	10 mg SR	NS	NS†
Diphenhydramine					
12	18	Women	50 mg	*	—
13	48	Mixed	50 mg	*	*
Clemastine					
14	24	Mixed	2 mg	*	—
15	25	Mixed	2 mg BID	*	*
Terfenadine					
16	10	Patients	60 mg BID	NS	—
7	20	Men	60 mg	NS	—
7	16	Men	60 mg	NS	NS
8	24	Mixed	120 mg BID	NS	*
10	27	Men	60 mg BID	NS	NS
10	27	Men	120 mg	NS	NS
12	18	Women	60,120,180 mg	NS	NS
Dexchlorpheniramine					
17	18	Mixed	6 mg	*	—
17	15	Mixed	6 mg	*	NS

Abbreviations: SR, sustained-release formulation; BID, twice a day; †, day 5; * , significantly different from placebo; NS, not significantly different from placebo; —, not tested.

Table 2. First-Generation Antihistamines

1. Driving is significantly impaired after single-dose administration.
2. Some tolerance develops after repeated daily administration, but driving may remain impaired and sedative and anticholinergic effects are still present.
3. Terfenadine should not be prescribed because of the drug's cardiotoxicity

Thus, patients should be advised not to drive a car when treated with first-generation antihistamines. Safer alternative treatment options are available and should be used whenever possible.

in unsafe driving, 1 subject was unable to complete the driving test. After 4 days of administration, driving performance was not significantly impaired.

A higher dose of clemastine (2 mg, twice daily) significantly impaired driving performance after both one-time and repeated administration in 25 healthy volunteers.[15] On each test day, 1 subject was unable to complete the driving test. Coadministration with alcohol (on day 5) did not produce significantly worse driving performance when compared with administration of alcohol alone. Both studies show that driving is unsafe during treatment with clemastine.

Terfenadine. Ten patients who consulted their physician because they experienced adverse effects (predominantly sedation) during terfenadine treatment performed the standardized driving test after single-dose administration of terfenadine (60 mg, twice daily) and placebo as well as a 24-km within-city driving test.[16] In the latter test, a professional driving examiner scored driving performance subjectively. The results from both tests showed no significant performance differences between terfenadine and placebo.

In 20 healthy men, driving performance was also not significantly impaired 1 and 3 hours after one-time administration of terfenadine (60 mg).[7] All men completed their driving tests. In another study,[7] terfenadine (60 mg, twice daily) also produced no significant driving impairment after repeated administration in 16 healthy men. However, combined administration of terfenadine and alcohol (BAC $<0.05\%$) produced significant driving impairment but equal to that observed when alcohol was administered alone.

In 24 healthy volunteers driving ability was tested 2 and 4 hours after one-time and repeated administration of terfenadine (120 mg, twice daily).[8] After immediate administration, driving performance was not significantly impaired on any test occasion. However, on day 4 (2 hours after administration) 3 subjects were unable to complete their driving tests due to drowsiness, and driving was significantly impaired.

No significant impairment was found in studies performed after one-time and repeated administration of terfenadine (60 mg twice daily and 120 mg daily) in men[10] and in a population of healthy women after administration of terfenadine (60, 120, and 180 mg).[12] In contrast to the male subjects, 2 driving tests in women were stopped before completion due to excessive weaving. Women produced no significant impairment on a car-following test.[12]

Table 3. Second-Generation Antihistamines and Driving Performance

Reference	N	Subjects	Dose	Day 1 (one-time)	Day 4 (repeated)
Loratadine					
7	20	Men	10, 20 mg	NS	—
7	16	Men	10 mg	NS	NS
8	24	Mixed	20 mg	NS	NS
29	16	Mixed	10 mg	NS	NS
Cetirizine					
10	27	Men	10 mg	NS	NS
29	16	Mixed	10 mg	*	NS
30	19	Mixed	10 mg	NS	NS
17	18	Mixed	10 mg	NS	—
17	15	Mixed	10 mg	NS	NS
Ebastine					
11	15	Men	10, 20, 30 mg	NS	NS†
Mizolastine					
14	24	Mixed	5 mg	NS	NS
14	24	Mixed	10, 20, 40 mg	*‡	NS
Acrivastine (+ pseudoephedrine)					
9	14	Men	8 mg TID	NS	NS
12	18	Women	8, 16, 24 mg	*	—
9	15	Men	8 (+60) mg TID	NS	NS§
9	15	Men	12 (+90) mg BID	NS	NS
12	18	Women	8 (+60) mg	NS	—
Emedastine					
30	19	Mixed	2, 4 mg BID	*	*
Mequitazine					
17	18	Mixed	5, 10, 15 mg	NS	—
17	15	Mixed	10 mg	*	NS¶

Abbreviations: BID, twice a day; TID, 3 times a day; * , significantly different from placebo; † , day 5; ‡ , this effect was significant *(P* < .05) also for the 10-mg dose if no Bonferroni correction was performed to compensate for multiple comparisons; § , a significant driving improvement was observed; ¶ , day 8; NS, not significantly different from placebo; —, not tested.

In 24 healthy women, a combination of chlorpheniramine (8 and 12 mg, sustained-release formulation, administered at bedtime) and terfenadine (60 mg, administered the following morning) did not significantly impair driving performance as determined by the standardized test and a car-following test.[27] Due to its cardiotoxic potential,[28] terfenadine has been replaced by its metabolite, fexofenadine.

Dexchlorpheniramine. Dexchlorpheniramine (6 mg) significantly impaired driving performance after immediate administration in 18 healthy volunteers.[17] A second study in 15 other healthy volunteers confirmed these findings[17]: again, driving performance was significantly impaired after one-time administration of dexchlorpheniramine, 6 mg (ΔSDLP of approximately 2 cm). After 8 days of treatment, SDLP did not differ significantly from placebo.

Second-Generation Antihistamines

Results from on-the-road studies with second-generation antihistamines[7–12,14,17,29,30] are summarized in Tables 3 and 4.

Loratadine. In one study,[7] driving performance after immediate administration of loratadine (10 and 20 mg) was not significantly impaired in 20 healthy men. All subjects completed their tests. In 16 other healthy men, one-time and repeated administration of loratadine (10 mg) did not significantly impair driving performance either.[7] These findings were replicated in similar studies in healthy men and women.[8,29] Combined administration of loratadine (10 mg) and alcohol (BAC <0.05%) produced significant driving impairment but were equal to when alcohol was administered alone.[7,29] Taking the results from these studies together, it must be concluded that driving while treated with loratadine is safe.

Cetirizine. In 27 healthy men, cetirizine (10 mg) produced no significant driving impairment 1 to 2 hours after one-time

Table 4. Second-Generation Antihistamines

1. Driving is significantly impaired after single-dose administration, especially with higher dosages.
2. Tolerance develops after repeated daily administration, but driving may remain impaired (5%–10% of the participants fail to complete their driving test due to drowsiness and sedation).
3. Ebastine and mizolastine should not be prescribed because of their cardiotoxicity.

Thus, patients should be warned to be cautious when driving a car during treatment with second-generation antihistamines, especially after single-dose administration or when taking a dosage higher than recommended.

and repeated administration.[10] In contrast, another study[29] reported significant driving impairment 3 to 4 hours after one-time administration of 10 mg of cetirizine in 16 healthy volunteers. However, ΔSDLP was less that that observed with a BAC of 0.05% and not significant on day 4. Recent studies[17,30] in healthy volunteers confirmed that cetirizine (10 mg) does not significantly impair driving performance.

Combined administration of cetirizine (10 mg) and alcohol (BAC <0.05%) also produced significant driving impairment. The impairing effects of alcohol and cetirizine were additive.[29,30] Taking into account that cetirizine intake is recommended at bedtime, it can be concluded that driving the following day is relatively safe.

Ebastine. Driving performance was tested 3 to 4 hours after administration in the standardized driving test followed by a car-following test.[11] Ebastine (10, 20, and 30 mg) produced no significantly impaired driving performance after both one-time and repeated administration. However, a significant dose-related SDLP increment was found, showing improvement relative to placebo for the 10-mg dose and impairment for the 30-mg dose of ebastine. Unfortunately, ebastine is potentially cardiotoxic. Hence, its use should be discouraged.

Mizolastine. In 24 healthy volunteers, mizolastine produced significant driving impairment 4 hours after one-time administration of high dosages (20 and 40 mg) but not with low dosages (5 and 10 mg).[14] Without applying a multiple-comparisons adjustment in their statistics, SDLP differences between mizolastine, 10 mg, and placebo would have reached statistical significance ($P < .05$). Driving impairment was dose-related and equaled that observed with a BAC of 0.08% after the 40-mg dose of mizolastine. Two driving tests were stopped before completion in the 10-mg condition (the recommended dose) due to drowsiness. Two other driving tests were stopped in the 20-mg condition for the same reason. After 4 days of treatment, no significant effects were observed on driving ability. Since mizolastine is potentially cardiotoxic, its use should be discouraged.

Acrivastine. Both the recommended dose of acrivastine (8 mg, 3 times daily) and combinations of acrivastine with pseudoephedrine (8 mg/60 mg 3 times daily or 12 mg/90 mg twice daily) did not significantly impair driving performance after both one-time and repeated administration in 15 healthy men.[9] Instead, on day 4 driving *improvement* was observed for the combination of acrivastine and pseudoephedrine, which was significant for the 8-mg/60-mg dose (an SDLP decrease of 2.0 cm), but not for the 12-mg/90-mg dose (an SDLP decrease of 1.5 cm). Nevertheless, 1 driving test was stopped in the acrivastine/pseudoephedrine (8 mg/60 mg) condition (on day 1) due to driving out of lane for a considerable period. Another driving test was stopped on day 4 in the acrivastine (8 mg) condition due to drowsiness and excessive weaving.

A single-dose study[12] in women reported no significant driving impairment 1.5 hours or 3.25 hours after one-time administration of acrivastine/pseudoephedrine (8 mg/60 mg) on the standardized driving test and a car-following test. When administered alone, acrivastine (8, 16, and 24 mg) produced dose-related and significant driving impairment in women.[12] Car following was significantly impaired for the 16-mg and 24-mg doses of acrivastine, but not for the 8-mg dose.

Patients using acrivastine should be cautioned when driving a car. However, when administered in combination with pseudoephedrine, the effects on driving performance seem less profound.

Emedastine. After both one-time and repeated administration of emedastine (2 mg twice daily and 4 mg twice daily) driving performance was seriously impaired.[30] SDLP increment after administration of both doses of emedastine was comparable with that observed with BACs above 0.08%. Five test-driving tests were stopped before completion in the 2-mg condition, whereas 7 driving tests were stopped in the 4-mg condition. On day 5, emedastine was administered in combination with alcohol (BAC <0.05%). The impairing effects of alcohol were additive to those of emedastine. Six driving tests were not completed in this condition. Thus, patients must be warned not to drive a car while treated with emedastine.

Mequitazine. Driving performance was not significantly impaired after one-time administration of mequitazine (5, 10, or 15 mg). However, a significant dose-response relationship was observed.[17] In contrast, in a repeated-dose study with mequitazine (10 mg daily for 8 days),[17] the same authors reported that mequitazine (10 mg, the recommended dose) impaired driving ability significantly after one-time administration (comparable with BAC of 0.05%). On day 8, driving performance did not differ significantly from placebo.

Third-Generation Antihistamines

Since second-generation antihistamines are not free from sedation and may impair performance of daily activities such as driving a car, 3 new antihistamine drugs were recently introduced. These drugs were developed from compounds that are already used in allergic treatment: desloratadine (from loratadine), fexofenadine (from terfenadine), and levocetirizine (from cetirizine). Relative to their mother compounds, they show improved clinical efficacy and fewer adverse effects.

Fexofenadine. In 25 healthy volunteers, immediate (day 1) and repeated (day 4) administration of fexofenadine (120, 240, 60 twice daily, and 120 mg twice daily) had no significant effects on driving ability.[15] In contrast, on day 4 fexofenadine (120 mg twice daily) *improved* driving performance relative to placebo ($P < .05$, but not significant after Bonferroni correction for multiple comparisons). The clinical relevance of this small improvement is limited and may be regarded as a measurement artifact. Although the authors suggest that the "activating effect of fexofenadine may also be beneficial in drivers whose performance would otherwise be deficient due to fatigue," this has not been observed in other studies.[31,32] On day 5, fexofenadine administrations were combined with a low dose of alcohol (BAC <0.05%).

Despite the alcohol-induced impairment combined with fexofenadine, driving was improved relative to placebo, especially in the 120-mg twice daily dosage regimen ($P < .05$, but not significant after Bonferroni correction for multiple comparisons). These results suggest that it is safe to drive a car when treated with fexofenadine.

Levocetirizine. Levocetirizine, the *R*-enantiomer of cetirizine, was recently studied in 48 healthy volunteers. Driving ability after both immediate (day 1) and subchronic (day 4) administration of levocetirizine (5 mg) matched that of placebo; mean differences in SDLP relative to placebo were only 0.3 cm on day 1 and 0.5 cm on day 4.[13] All driving tests were completed, and individual SDLP differences were small. Results from a laboratory test battery evaluating memory functioning, cognition, and psychomotor performance were in line with the driving test results.[33] That is, levocetirizine produced no significant impairment in any test. These results suggest that it is safe to drive a car when treated with levocetirizine.

CONCENTRATION EFFECTS

In general, performance impairment becomes more pronounced with increasing drug dosages. However, the relationship between blood serum concentrations and actual driving impairment (ΔSDLP) is unclear, and correlations between the 2 are often not significant. For example, nonsignificant correlations ($r = 0.02$) have been reported for combined data on carebastine and triprolidine.[11] Also, correlations for cetirizine and terfenadine did not reach significance.[10] These findings illustrate that there is no linear relationship between blood concentration and performance impairment. Individual and sex differences in sensitivity to drug effects presumably play a more important role.

Time of testing after administration of a single dose is important to take into account when judging adverse drug effects. Most studies conducted the driving tests at peak plasma concentrations (1-4 hours after intake). However, if bedtime administration is recommended (which is the case for cetirizine), the time between intake and actual driving in real life will be much longer. Hence, the drug's adverse effects on driving performance may be much less pronounced when used as recommended.

SEX EFFECTS

There is general consensus than women are more sensitive to the sedative effects of drugs than men. Most studies on antihistamines and driving were not conducted in a mixed-sex population. With the exception of the levocetirizine study,[13,33] including 24 men and 24 women (they reported no sex differences for levocetirizine and diphenhydramine), the number of included subjects in studies with mixed-sex populations is too low to provide hard evidence on possible sex differences with sufficient statistical power. Nevertheless, results from these studies suggest that there are no significant sex differences for clemastine,[14,15] mizolastine,[14] and fexofenadine.[15] However, other studies reported significant differences in sensitivity between men and women. For example, one-time administration of acrivastine (8 mg) significantly impaired driving in women[12] but not in men.[9]

In a recent study,[30] after immediate administration of emedastine (2 mg twice daily and 4 mg twice daily) and cetirizine (10 mg), driving impairment in men was only significantly different from placebo in the emedastine (4 mg) condition, whereas in women driving performance was significantly impaired after doses of both emedastine and cetirizine. After repeated administration, the overall sex-by-treatment interaction did not reach significance, but again, in women driving performance was worse in all conditions, in contrast to men who drove worse only in the emedastine (4 mg) condition ($P < .05$, but not significant after Bonferroni correction for multiple comparisons). The observed performance effects (ΔSDLP) were not correlated to body weight.

INDIVIDUAL DIFFERENCES

Statistical significance as reported by the studies summarized in this review is based on group averages. However, interindividual variability in sensitivity to drug-induced performance impairment is evident in most studies. That is, although drug effects were mild to moderate in most individuals, some subjects using first- or second-generation antihistamines were unable to complete their driving tests due to drowsiness and sleepiness, which resulted in very unsafe driving.

It may be hazardous to extrapolate the number of study participants who were unable to complete their driving tests after using an antihistamine drug (usually 5% to 10% of the participating subjects) to the general population of approximately 4.7 million registered antihistamine users of 26 million adults reporting allergic symptoms in the United States.[34] However, if one makes such a comparison, it would suggest that at least 200,000 to 400,000 drivers using antihistamine drugs have a seriously increased risk of becoming involved in a traffic accident. At present, epidemiologic evidence to confirm this hypothesis is absent.

DISCUSSION

The choice between different antihistamines depends on the risk-benefit ratio between clinical efficacy and unwanted adverse effects. Since the newer antihistamines all possess sufficient clinical efficacy, the choice between different antiallergic compounds should therefore be based on the safety profile. In this context, there is not much support to advocate the use of first-generation antihistamines, since these drugs are known to produce a variety of unwanted central nervous system effects. Second-generation antihistamines do so to a lesser extent and especially at higher dosages. In addition, antihistamines may possess cardiotoxic properties (eg, terfenadine, mizolastine, ebastine, and astemizole) that greatly limit their use.

An overview of the results from on-the-road driving studies with antihistamines is presented in Table 5. Antihistamine drugs are classified according to the extent that they impair driving ability (SDLP increment comparable with that ob-

Table 5. Driving Impairment after Immediate Administration of Antihistamine Drugs Compared with Impairment Observed after Consuming Alcohol

	First generation	Second generation	Third generation
0.05% < BAC < 0.10%	Triprolidine Clemastine Diphenhydramine	Emedastine	
BAC < 0.05%		Terfenadine Loratadine Ebastine Acrivastine Mizolastine Cetirizine	
BAC = 0.00%			Levocetirizine Fexofenadine

Abbreviation: BAC, blood alcohol concentration.

served with most common legal limits for driving while intoxicated with alcohol; ie, a BAC of 0.05% and 0.10%).

First-generation antihistamines generally produce driving impairment comparable with that observed with BACs above 0.05%. Hence, driving with these drugs must be regarded as unsafe. Impairment was most pronounced after one-time administration; but after 4 to 5 days of administration, significant impairment had been shown for triprolidine,[8,10] clemastine,[15] and diphenhydramine.[13] However, the effects on driving performance after 4 to 5 days of administration are much less pronounced than after immediate administration, and some studies failed to find significant impairment after repeated administration of first-generation antihistamines such as triprolidine,[9,11] terfenadine,[7,10,12] and dexchlorpheniramine.[17] Nevertheless, after 4 to 5 days of treatment some subjects were unable to complete their driving tests, illustrating that sedative effects are not absent after repeated administration. Because of the marked sedation produced by some first-generation antihistamines, it is not surprising that diphenhydramine is one of the most popular over-the-counter drugs to aid sleep onset.

Driving impairment with second-generation antihistamines is less pronounced but still present. Driving performance showed significant impairment especially with dosages higher than those recommended. With the recent introduction of fexofenadine and levocetirizine, it seems that a third generation of antihistamines has emerged, without impairing effects on driving ability.

The overview presented in Table 5 enables physicians to understand driving impairment of antihistamine drugs relative to those observed with alcohol. However, in real life patients may actually *not* experience their driving impairment or the presence of sedation. This was illustrated, for example, in the study by Verster et al.[13] Subjects drove significantly worse after repeated administration of diphenhydramine (50 mg), although they reported that their driving performance did not differ from their test drives in the placebo condition. Since patients may not recognize their impairment, physicians should specifically inform them about the sedative effects that are present but may remain unnoticed. Preferably, however, physicians should avoid prescribing potentially sedative antihistamines, since generally nonsedative compounds such as levocetirizine can be used instead.

The combined administration of antihistamines with decongestants seems to improve driving performance. Performance improvement by coadministration of antihistamines with pseudoephedrine has been reported in laboratory settings as well.[35,36] Improvement is most profound after some days of administration, since pseudoephedrine concentrations accumulate over time. For example, statistically significant driving improvement was reported after 4 days of treatment for the acrivastine/pseudoephedrine combination, whereas after one-time administration no difference with placebo was found.[9] It seems that the mild stimulating effects of pseudoephedrine counteract the mild sedative effects of acrivastine. However, the clinical relevance of the SDLP improvement (<2 cm) for driving safety is questionable.

Of greater concern is coadministration with other psychoactive drugs such as hypnotics, antidepressants, and anxiolytics. A substantial number of patients use more than 1 drug at a time. Hence, it is important to know whether the effects of these drugs counteract, are additive, or interact with one another. The research on these matters is indeed limited to coadministration of antihistamines and alcohol (an additive effect) and the decongestant pseudoephedrine (a counteracting effect). That is, no on-the-road driving studies have been performed that examined the effects of concomitant medications with antihistamines. In contrast, a great number of studies have shown that benzodiazepine drugs and tricyclic antidepressants (eg, amitriptyline), when administered alone, may seriously impair driving performance.[37,38] Ten hours after bedtime administration, significant driving impairment greater than that observed with BACs of 0.10% was found for flurazepam (15 and 30 mg) and loprazolam (2 mg). Driving performance worse than that observed with BACs of 0.05% was reported for lorazepam (2 mg), nitrazepam (10 mg), oxazepam (50 mg), and flunitrazepam (2 mg). Although less pronounced than in the morning tests, driving performance

was also significantly impaired in the afternoon, ie, 17 hours after bedtime administration.

It is reasonable to assume that the impairing effects produced by these drugs will be at least additive to those produced by coadministered antihistamine drugs. Unfortunately, there is a general lack of scientific evidence on the interaction between coadministered drugs on driving ability. Hence, future studies are necessary to determine whether coadministered psychoactive drugs interact with antihistamine effects. Until this evidence becomes available, selective serotonin reuptake inhibitors and nonbenzodiazepine drugs are recommended as first-choice treatment regarding driving safety. For example, the nonbenzodiazepine hypnotic zaleplon[37,39] and antidepressants such as fluoxetine, paroxetine, and venlafaxine[38,40] have been shown not to impair driving ability.

CONCLUSION

Future studies should be performed in the intended patient population, to confirm whether the observed driving test results fully apply to them as well. Several authors have addressed the impact of allergic symptoms itself on performance measures.[41,42] It is therefore unfortunate to conclude that over the last 20 years only 1 small driving study (N = 10) used actual patients.[16] In addition, future studies should include a sufficient number of men and women to enable statistically powerful and meaningful comparisons between both sexes. Up to now, fexofenadine and levocetirizine are the only truly nonsedative antihistamines that seem to be safe in patients who want to drive a car.

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Requests for reprints should be addressed to:
Joris C. Verster, PhD
Utrecht Institute for Pharmaceutical Sciences
Department of Psychopharmacology
University of Utrecht
PO BOX 80082
3508 TB Utrecht, The Netherlands
E-mail: j.c.verster@pharm.uu.nl

CME Review Examination

1–5, Verster JC, Volkerts ER. 2004;92:294–304.

Self-Assessment Exam Questions

1. Which second-generation antihistamine drug shows the most profound driving impairment after immediate administration?
   a. emedastine
   b. ebastine
   c. terfenadine
   d. cetirizine
   e. loratadine
2. A secondary parameter sometimes considered in the on-the-road driving test is speed variability (SD speed). In contrast to lateral position variability (SDLP),
   a. speed variability is no measure of vehicle control
   b. speed variability is a robust measure that is not easily affected by drug treatment
   c. the relationship between speed variability and driving safety is unclear
   d. all answers (a, b, and c) are correct

e. none of the answers is correct

3. Results from on-the-road driving tests have greater ecologic validity than those obtained in driving simulators or laboratory tests, because:
   a. laboratory settings and simulators are artificial environments, whereas the on-the-road driving test is conducted in real traffic
   b. the relationship between laboratory tests and actual driving is sometimes unclear
   c. laboratory tests and simulators generally do not measure all aspects involved in driving simultaneously
   d. all answers (a, b, and c) are correct
   e. none of the answers is correct
4. After 4 to 5 days of administration, no significant driving impairment was reported for which first-generation antihistamine drug?
   a. emedastine
   b. triprolidine
   c. diphenhydramine
   d. terfenadine
   e. dexchlorpheniramine
5. In the context of driving safety, when prescribing an antihistamine drug the following should be taken into account:

(1) First- and second-generation antihistamine drugs pass the blood-brain barrier and thus may become active in the central nervous system, leading to impaired driving ability. Third-generation antihistamines do not pass the blood-brain barrier and thus do not affect driving ability.

(2) Although average group effects on driving ability may not differ significantly from placebo for some second-generation antihistamines, approximately 5% to 10% of individual drivers show serious driving impairment while using these drugs.

(3) Thus far, fexofenadine and levocetirizine are the safest antihistamine drugs for those who want to drive a car.
   a. statements (1) and (3) are true
   b. only statement (1) is true
   c. only statement (3) is true
   d. statements (2) and (3) are true
   e. statements (1) and (2) are true.

Answers found on page 355.