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# 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

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Twenty-seven healthy male volunteers participated in a double-blind, five-way crossover designed comparison of the new, selective $H_1$-receptor antagonist cetirizine (10 mg q.d.) and terfenadine (60 mg b.i.d. and 120 mg q.d.) versus the older $H_1$-receptor antagonist triprolidine (5 mg b.i.d.) and placebo.

Medication was administered during four consecutive days. Subjects were tested on the 1st and 4th treatment day. On each test day subjects drove an instrumented vehicle over a 100 km highway circuit while attempting to maintain a constant speed (90 km/hr) and a steady lateral position within the right traffic lane. Thereafter they performed three computerized memory tasks. On the 4th treatment day, sleep latency was measured before and after the driving test. On both days, triprolidine significantly impaired performance in the driving and psychometric tests. Triprolidine also significantly reduced sleep latency in comparison to placebo on the 4th treatment day. Terfenadine 60 mg b.i.d. impaired psychometric performance after subchronic treatment.

It was concluded that cetirizine, like terfenadine, belongs to the newer class of antihistamines and can be safely used by patients who continue their daily activities.

KEY WORDS—Cetirizine, terfenadine, driving performance, psychometric performance, daytime sleepiness.

## INTRODUCTION

Antihistamines are widely prescribed for treatment of various allergy symptoms. Until the mid seventies sedation was the most common side-effect of antihistaminic treatment. Therefore, a newer class of $H_1$ receptor antagonists has been developed with an improved balance between central nervous system (CNS) and peripheral effects. It is now well established that for instance terfenadine, loratidine and astemizole fall into this new class of antihistamines. Cetirizine, a new $H_1$ receptor antagonist introduced in 1987, is said to be one of the second generation antihistamines. The objective of this study was to investigate this claim by comparing the effects of cetirizine in three qualitatively different tests with a well established member of the new class of antihistamines, i.e. terfenadine, and with triprolidine, a classical antihistamine.

This study was carefully designed by choosing relevant tests. This means, we have selected tests which are sensitive, realistic, comparable and complementary. First, we incorporated the standardized on the road driving test (O'Hanlon *et al.*, 1982). Over the years this on-the-road test has been applied in studies of the effects of hypnotics, antidepressants and anxiolytics and shown to be sensitive to drug induced impairment (Laar van *et al.*, 1992; Louwerens *et al.*, 1986; Volkerts *et al.*, 1983, 1988, 1989). A major advantage of the test is its realistic character, an aspect which is difficult to simulate in the laboratory. However, this does not implicate that the on-the-road test can replace a laboratory test. The driving test measures not all aspects relevant to safe driving behavior, such as reaction time. Therefore, the second test in this study comprised three choice reaction time (RT) tasks. All three tasks placed high demands on memory functioning which is important because animal studies indicate that histamine can play a role in memory processes (Pollard and Schwartz, 1987; Schwartz *et al.*, 1986). Since the results of these studies also indicate that histamine may have a waking effect, a third test was used to measure daytime sleepiness using elec-

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trophysiological measures such as the electroencephalogram (EEG). This test has been developed by Carskadon *et al.* (1986) and is, unlike performance measures, less sensitive to motivational factors, does not require practice and baseline values remain stable from one day to the next. Because of practical reasons the number of subsequent tests per day was reduced from the recommended five to two.

A reliable test design is necessary if relevant conclusions are to be drawn from the test results. We therefore ensured that: (1) the sample size ($N$ = 27) was sufficient enough to yield the statistical power to detect significant differences (2) dose levels encompassed the recommended therapeutic range (3) a positive control agent of the same class of drugs under study was used and (4) measurements were done in an acute and subchronic phase. Moreover, we found it important to give a clear definition and operationalization of the concepts used in this study: (1) Sedation is an objectively measured impairment of psychomotor or cognitive functions, determined by task parameters such as tracking or reaction time (2) Sleepiness and drowsiness refer to a mental state in terms of reduced alertness. Both can be subjectively assessed using Visual Analogue Scales (VAS). Sleepiness, however, also can be objectively measured by using electrophysiological registrations such as in the Multiple Sleep Latency Test.

It was hypothesized that in contrast to triprolidine, neither cetirizine nor terfenadine would impair performance or induce daytime sleepiness.

### *Drug profile*

Cetirizine is the major metabolite of hydroxyzine and its high polarity and protein-binding capability result in poor penetration of the blood-brain barrier (Simons *et al.*, 1987; Snyder and Snowman, 1987). After being rapidly absorbed, cetirizine reaches peak plasma concentrations within 1 hour after single oral doses. Cetirizine has a biphasic elimination pattern with an elimination half-life of approximately 9 hours (hrs.) (Wood *et al.*, 1987). In several controlled studies no impairing effects on (CNS) functioning were found after treatment with cetirizine (Gengo *et al.*, 1987, 1990; Seidel *et al.*, 1987; Simons *et al.*, 1990).

Terfenadine is rapidly absorbed and peak plasma levels occur within 1–2 hrs. after single oral doses. Initially, the plasma elimination half-life was reported as being approximately 25 hours. However, based upon measurements of $^{14}$C-labeled terfenadine, its elimination half-life has been reported to be only 4·5 hrs. The two major metabolites of terfenadine accounted for 54 per cent of this $^{14}$C activity (Garteiz *et al.*, 1982). Since it has been shown that the first major metabolite is active in animals and that the pharmacodynamics in adults are consistent with the shorter half-life value, this metabolite seems to be responsible for a large proportion of the clinical efficacy of terfenadine (Simons, 1990). As reviewed by McTavish *et al.* (1990) the incidence of objectively measured impairment of CNS functioning in several controlled studies due to terfenadine was comparable with that of placebo.

Triprolidine reaches peak plasma concentrations approximately 2 hrs. after single oral doses and has an elimination half-life of approximately 2 hrs. (Drouin, 1985). After treatment with triprolidine, impairing effects on CNS functioning were found in several studies (Peck *et al.*, 1975; Betts *et al.*, 1984; Nicholson *et al.*, 1982, 1983). Tolerance to the impairing effects of triprolidine begins to occur within 24 hrs after repeated administration (Bey *et al.*, 1977).

## MATERIALS AND METHODS

### *Subjects*

Twenty-seven males with a mean weight of 76·2 kg, and varying in age from 24 to 41 years (mean 29·9 yrs.), were selected as volunteers. They had held a drivers licence for at least five years and drove more than 10,000 km per year. The subjects were physically and mentally healthy, were no excessive smokers and used alcohol moderately. Subjects were treated in accordance with the Declaration of Helsinki as modified in Venice (1983). They gave their written consent, after receiving a written and oral description of the test procedures and possible effects of the drugs. They were paid for their participation.

### *Design*

The study was conducted according to a double blind 5-way cross-over design. Each subject received drug treatment or placebo at fixed times a day, six hrs. apart, in a random order at weekly intervals. Cetirizine 10 mg (CET) and terfenadine 120 mg (T120) were administered once a day (q.d.) in the morning followed by placebo in the after-

noon, whereas terfenadine 60 mg (T60), triprolidine 5 mg (TRI) and placebo (P) were administered twice a day (b.i.d.). Each drug dose or placebo was administered during four consecutive days. The use of concomitant medication and illicit drugs was not allowed. The use of alcohol was forbidden on the day preceding the tests and on the test days. Caffeine-containing beverages were prohibited on both test days.

A saliva alcohol test, urine samples, blood samples and a histamine skin prick test were used to monitor compliance. The time schedule of the procedure during each treatment condition is given in Table 1.

Table 1. Time schedule

| DAY 1 | | DAY 4 | |
|---|---|---|---|
| 09:00 | Controlled Intake Alcohol Screening | 14:00 | Controlled Intake & Alcohol Screening & EEG Preparations |
| 09:15 | Skin Prick Test | 14:15 | Skin Prick Test |
| 09:30 | Warming Up Psychometric Test | 15:10 | Warming Up Psychometric Test |
| | | 15:20 | Sleep Test |
| 10:00 | Driving Test | 16:00 | Driving Test |
| 11:30 | Psychometric Test | 17:30 | Psychometric Test |
| | | 18:05 | Sleep Test |
| 12:05 | Skin Prick Test & Blood Sample | 18:30 | Skin Prick Test & Blood Sample |

During the week prior to the initial treatment, all subjects underwent a complete rehearsal of the driving test, to familiarize them with the procedure, the test vehicle and the test circuit. They further performed 5 training sessions of the psychometric testbattery. In addition, on each test day a short (5 min.) warm-up trial of this test was given.

*Driving test*

The driving test was conducted over 100 km circuit of a primary highway during normal traffic. The highway consists of two traffic lanes in each direction. Structural modifications to the test vehicle included redundant controls for use, if necessary, by a licensed driving instructor. An electro-optical 'lane tracker' was mounted on the roof of the car to measure the vehicle's lateral position relative to the painted stripe road delineation. The lane-tracker was oriented so that its lens required an image of the road surface directly behind the vehicle. Speed was measured from a pulse generator triggered by magnetic induction at a rate proportional to the revolutions of the drive wheels. The analog signals from lateral position and speed sensors were A/D converted and sampled on-line at 2 Hz by a Compaq computer system installed in the test vehicle. The subjects were instructed to maintain a constant speed (90 km/hr) and a steady lateral position within the right traffic lane.

The standard deviation of lateral position (SDLP in cm) and standard deviation of speed (SD Speed in km/hr) over the total 100 km test were the primary performance measures of the test. Time on task was approximately 75 minutes (min.).

Three questionnaires were used to assess the subject's experience during performance of the driving test. On the first, the subject indicated the perceived quality of his driving performance using a visual analogue scale (20 cm) which varied from 'I drove exceptionally poorly' to 'I drove exceptionally well' around a midpoint of 'I drove normally'. On the second, he indicated his level of mental activation on a 27 cm, equal interval scale developed by Bartenwerfer (1969). On the third, the subject described the level of effort he had to invest in the task on a 15 cm equal interval scale.

*Psychometric test*

The psychometric testbattery comprised three computerized laboratory choice RT tasks. These tasks were programmed with the aid of ERTS 2·0 (Experimental Run time System, Beringer, 1988). The tasks were performed in a sound attenuated room in which lightning conditions were kept constant.

The first task was a letter-matching task (Figure 1). The subject had to decide if two letters, displayed simultaneously belonged to the same category, i.e. vowels or consonants. Time on task was $\pm 10$ min.

The second was a memory scanning task (Figure 2). In this task the subject first had to memorize a short list of successively presented digits containing up to five digits. He was then presented with a probe digit and had to decide whether or not this digit had been part of the original list. Time-on-task was $\pm 13$ min.

In the third task the subject had to decide whether a presented character was a letter or a digit (Figure 3). Time on task was $\pm 10$ min.

In all three tasks a feedback message was given with regard to the correctness of the response and time between successive presentations was

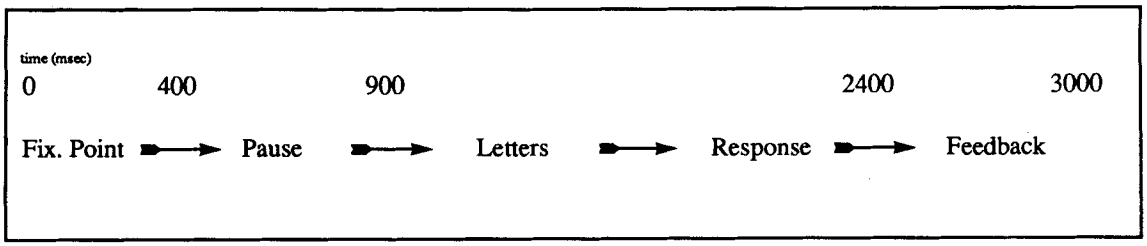


Figure 1. Task 1: Letter Matching

3000 msec. Mean Reaction Time in msec.was the primary parameter of this test.

*Sleep Latency Test*

On the 4th treatment day, two Sleep Latency Tests were given. This test is a standard measure of sleepiness developed by the Association of Sleep Disorders Center's Task Force on Daytime Sleepiness (Carskadon *et al.*, 1986). Using the OXFORD system (Medilog MR-90), 5 channels of EEG and 2 channels of EOG were recorded on a portable cassette recorder. EEG electrodes were positioned on the scalp according to the international 10–20 system. EEG recordings were taken from referential leads: left and right central and occipital, referred to the contralateral mastoid (C3-A2, C4-A1, O1-A2, O2-A1) and a F0-Cz lead.

Sleep Latency (in min), the primary parameter of the Sleep Latency Test, was measured as the time the subject took to enter at least 16 seconds of sleep stage 1 (Rechtschaffen and Kales, 1986). A sleep inducing environment without competing stimuli was required so tests were conducted in a quiet, darkened room with a comfortable temperature. The test lasted 20 minutes.

*Blood sampling and analysis*

On the 1st and 4th treatment day of each treatment condition, blood samples were collected within 15 minutes following the last test, i.e. 3 hrs. after treatment on the 1st treatment day. On the 4th treatment day this was 4·5 hrs. after terfenadine 60 mg b.i.d. and triprolidine 5 mg b.i.d. and 10·5 hrs. after terfenadine 120 mg q.d. and cetirizine 10 mg q.d. Plasma samples were analyzed for cetirizine using Gas Chromatography (GC). Determination of the first major metabolite of terfenadine was carried out using High Performance Liquid Chromatography (HPLC). No determination of triprolidine was carried out due to the absence of an appropriate method. The purpose of analyzing plasma samples was to verify the subject's self-administration of the appropriate experimental drug and to determine possible correlations between plasma concentrations and corresponding performance measures.

*Statistical analysis*

Statistical analysis were done employing the SPSS $PC^+$ and the SPSS-X statistical program. Descriptive statistics were calculated for every parameter in each test. Main effects and interactions were tested for significance ($p \leq 0{\cdot}05$) by multivariate

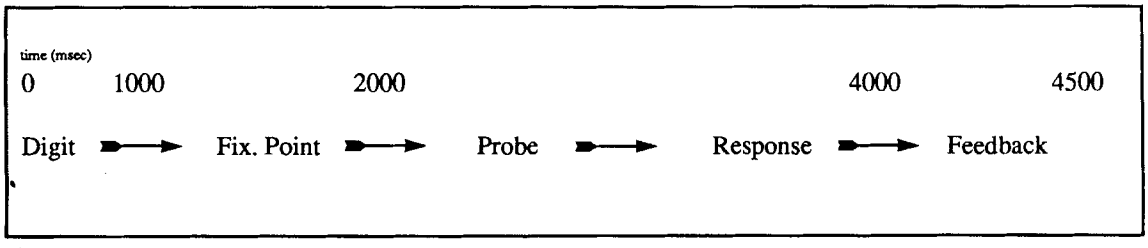


Figure 2. Task 2: Memory Scanning

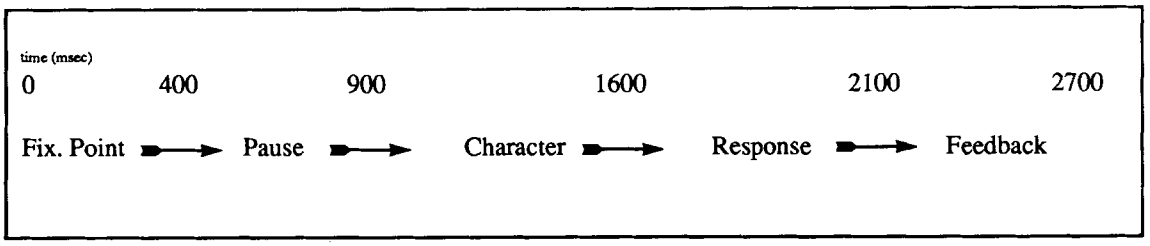


Figure 3. Task 3: Letter/digit Differentiation

analysis of variance of repeated measures data. Univariate mean paired (drug versus placebo) comparisons were made, independent of the outcome of the overall F-test. This procedure is legitimate if the specific comparisons are built into the design or suggested by the theoretical basis for the experiment (Winer, 1971, p. 384).

Relationships between plasma drug concentrations and performance measures were determined using Pearson's product-moment coefficient of correlation.

## RESULTS

### *Driving test*

*Lateral position parameter.* The group means (±SE) of SDLP for each treatment condition are

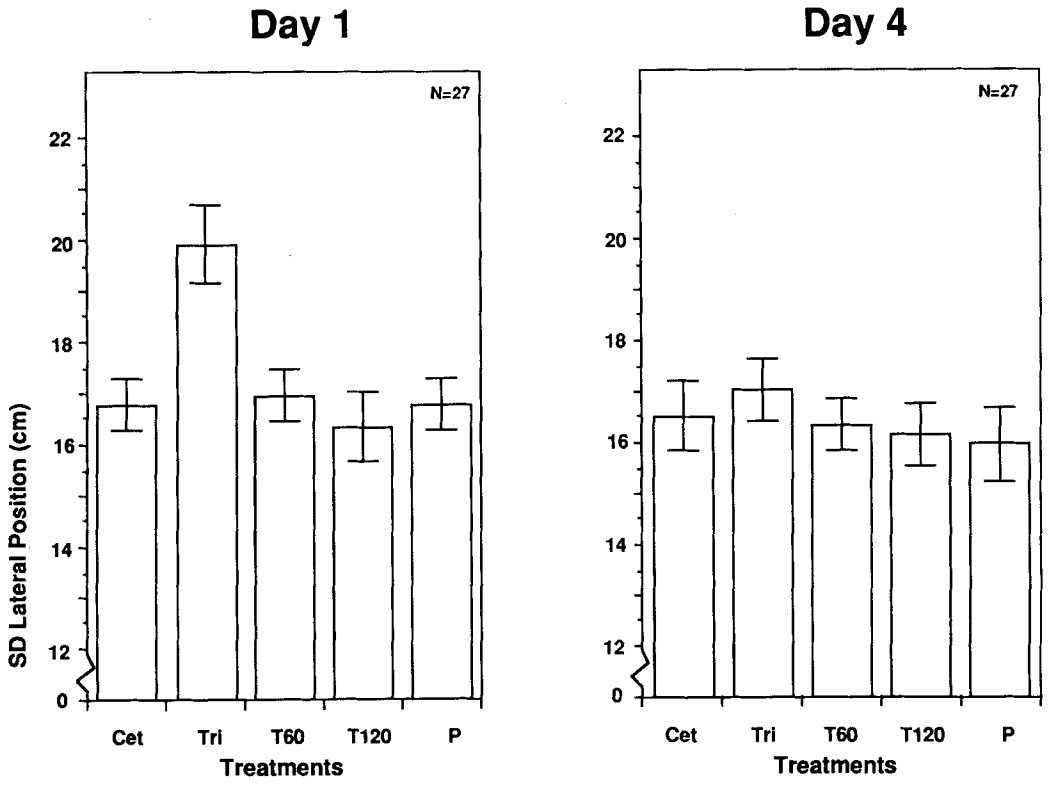


Figure 4. Mean (±SE) of SDLP (cm) in treatment conditions CET, TRI, T60, T120 and P on test 1 and 2

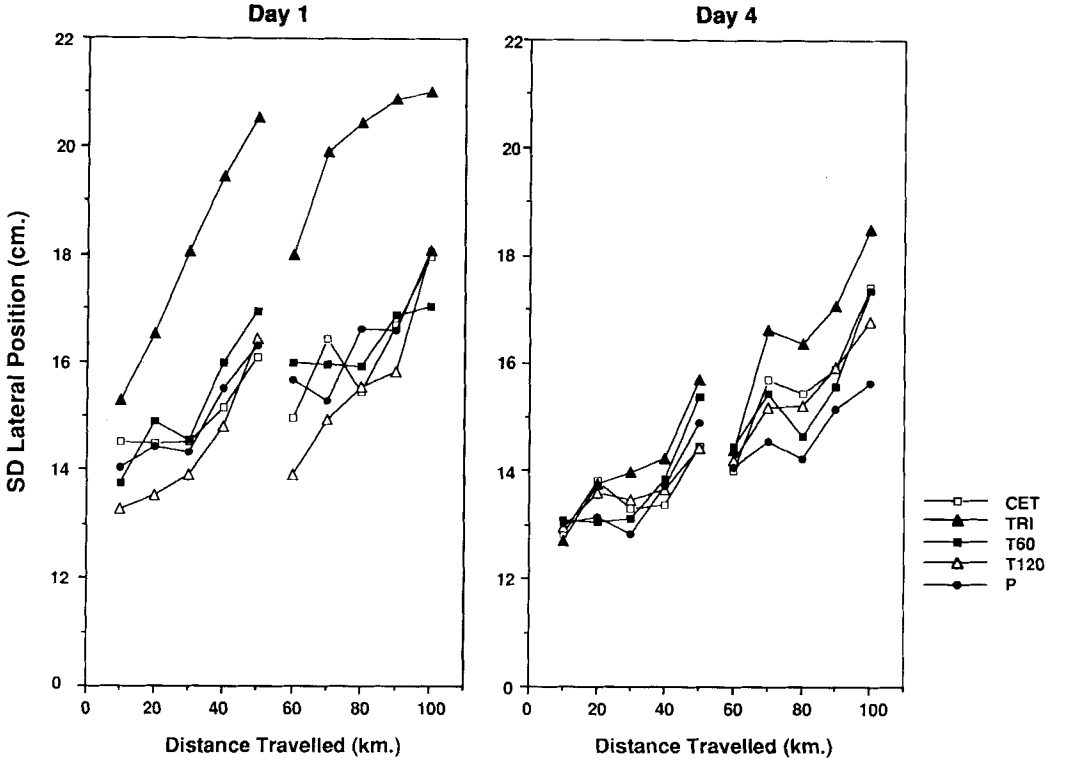


Figure 5. Mean SDLP on test day 1 and 2 in treatment conditions CET, TRI, T60, T120 and P as functions of distance travelled. Breaks in functions indicate the turn around point

shown in Figure 4. It is clear from this figure that TRI increased the SDLP on the 1st treatment day. On the 4th treatment day, however, this effect diminished. The effects of all other treatments on the 1st and 4th day were not substantial.

On the 1st treatment day, the multivariate effect of treatment conditions was significant ($F_{4,23} = 16{\cdot}86$; $p < 0{\cdot}001$). Univariate analysis revealed that the overall effect was mainly produced by the positive control TRI ($F_{1,26} = 28{\cdot}66$; $p < 0{\cdot}001$). On the 4th treatment day, no significant multivariate effect was found ($p = 0{\cdot}15$). However, the univariate analysis still indicated that the SDLP after treatment with TRI remained significantly ($F_{1,26} = 6{\cdot}55$; $p < 0{\cdot}02$) higher than after *P*, although the effect was smaller in comparison to the 1st treatment day.

In Figure 5 the group mean values of successive 10 km segments are shown.

It is evident from this figure that, both on day 1 and 4, mean SDLP was always the highest in the TRI condition, and as in the other conditions, this variable tended to increase as a function of distance travelled. This trend was interrupted at the mid-test turn-around point (50 km) but resumed during the second half of the test.

*Speed parameter.* The statistical analysis of the SD Speed data revealed a significant ($F_{4,23} = 4{\cdot}14$; $p < 0{\cdot}01$) overall-effect on the 1st treatment day. This effect was primarily produced by the increased SD Speed in the TRI condition ($F_{1,26} = 6{\cdot}19$; $p < 0{\cdot}02$). No significant effects were found on the 4th treatment day.

*Subjective assessments.* Of one subject no questionnaire was obtained on the 1st treatment day. On this day subjects reported a significant ($F_{1,25} = 9{\cdot}63$; $p < 0{\cdot}005$) higher level of invested effort, and a significant ($F_{1,25} = 16{\cdot}93$; $p < 0{\cdot}001$) reduced quality of driving performance after treatment with TRI. On the 4th treatment day, ratings on all three scales were not significantly different from *P*.

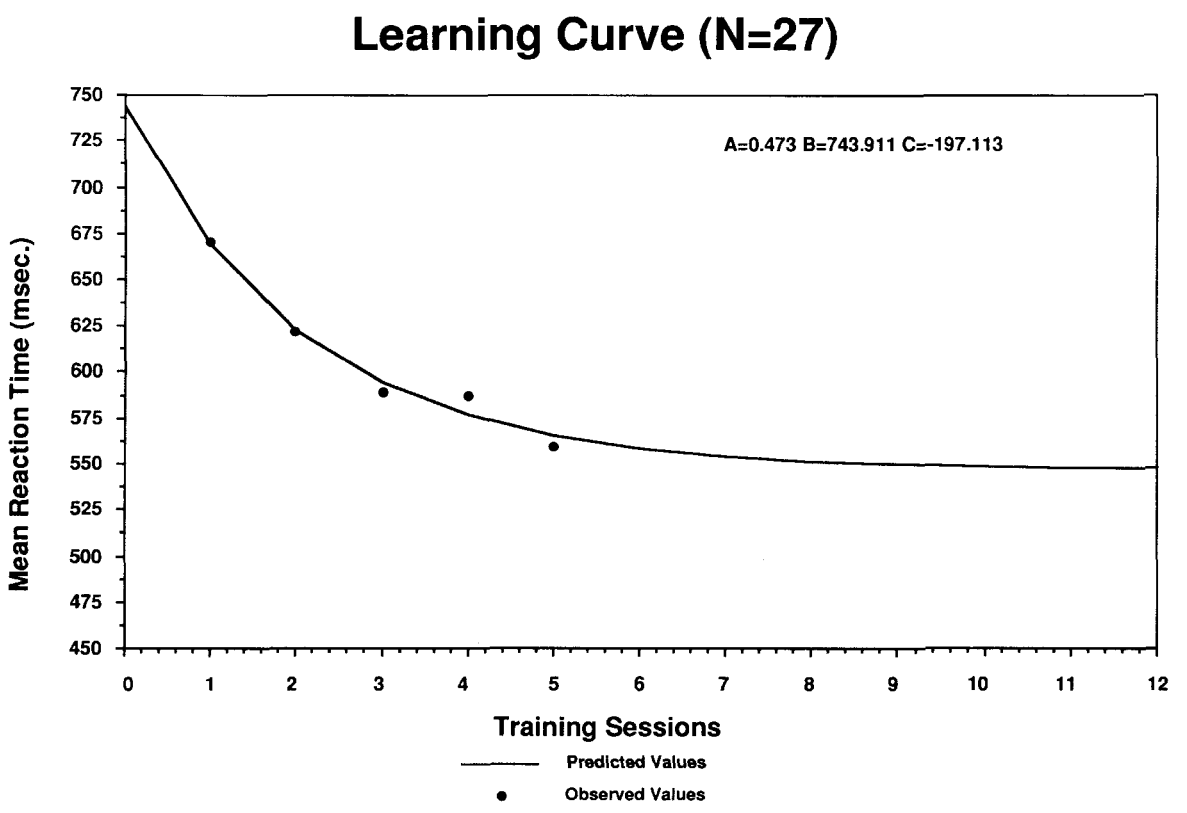


Figure 6. Learning-curve: Mean observed and predicted [$f(x) = B + C(1 - e^{-Ax})$] RT from 27 subjects in 5 successive training sessions

*Psychometric test*

*Effect of training.* The results (averaged over the three tasks) of the training are shown in Figure 6. It is evident from the figure that the predicted values fit the observed mean RT over the five training sessions and performance reached a plateau level.

*Reaction time.* As a consequence of technical computer problems data loss of two subjects occurred. Statistical analysis was therefore done with a reduced subject sample ($N = 25$).

On the 1st treatment day the multivariate effect of treatment conditions was significant in task 2 and 3 ($F_{4,21} = 4{\cdot}66$; $p < 0{\cdot}008$ and $F_{4,21} = 4{\cdot}19$; $p < 0{\cdot}01$, respectively). Univariate tests showed that these effects were mainly produced by a prolonged mean RT in the TRI condition ($F_{1,24} = 16{\cdot}19$; $p < 0{\cdot}001$ and $F_{1,24} = 9{\cdot}61$; $p < 0{\cdot}005$, respectively). The effects of the other treatments were not significant ($F < 1$). In task 1, the multivariate effect of treatment conditions was not significant ($p = 0{\cdot}32$). However, on the univariate level the impairing effect of TRI approached significance ($p < 0{\cdot}08$). Again, the effects of the other treatments were not significant ($F < 1$).

On the 4th treatment day the multivariate effect of treatment conditions was neither significant in task 1 ($F < 1$) nor in task 3 ($p = 0{\cdot}18$). However, in the latter task, separate univariate tests revealed a significant impairing effect of T60 ($F_{1,24} = 4{\cdot}81$; $p < 0{\cdot}04$) and a marginally significant impairing effect of TRI ($F_{1,24} = 3{\cdot}79$; $p < 0{\cdot}06$). In task 2, the multivariate effect of treatment conditions approached significance ($p < 0{\cdot}07$). The univariate analysis revealed significant performance impairment in the TRI ($F_{1,24} = 4{\cdot}73$; $p < 0{\cdot}04$) and in the T60 ($F_{1,24} = 7{\cdot}88$; $p < 0{\cdot}01$) condition.

The effect of memory load on mean RT in task 2 is shown in Figure 7. As expected, mean RT increased nearly linearly as a function of memory

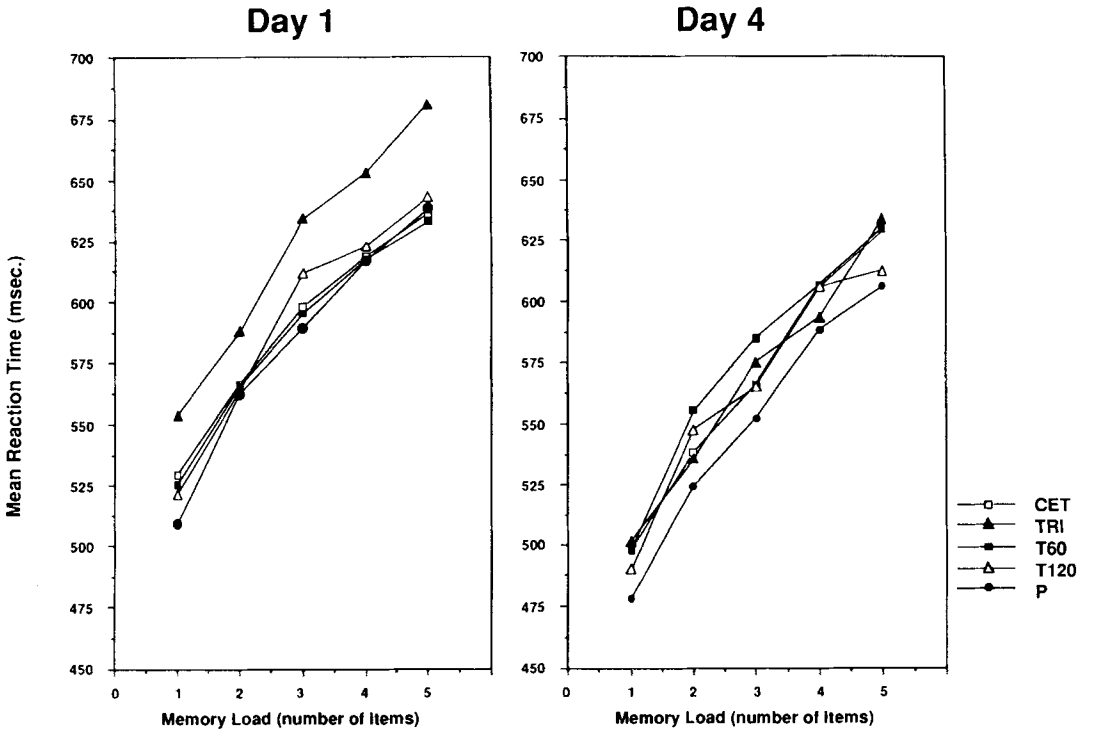


Figure 7. Mean RT as a function of memory load in task 2 in treatment conditions CET, TRI, T60, T120 and P on test day 1 and 2

load. The significant effect of triprolidine on mean RT (when all five memory loads are taken together) on the 1st treatment day is evident from this figure. This effect diminished on the fourth treatment day. Also note the clearly increased mean RT on memory load 2 and 3 and 4 after treatment with T60.

*Sleep Latency Tests*

Data loss occurred because the tapes of two subjects were unreadable. Therefore, the analysis was done with a reduced sample set ($N = 25$).

In Figure 8 the mean Sleep Latency in both tests is shown. The analysis of the Sleep Latency data revealed no multivariate effect in the first test. Univariate analysis indicated that Sleep Latency in the TRI condition was significantly shorter in comparison to P ($F_{1,24} = 4{\cdot}28$; $p < 0{\cdot}05$). In the second test a multivariate effect was found ($F_{4,22} = 2{\cdot}82$; $p < 0{\cdot}05$). However, univariate analysis did not reveal any separate effects.

The analysis revealed no significant interaction between treatment conditions and time of testing ($F_{4,21} = 0{\cdot}77$; $p = 0{\cdot}56$). Therefore, to increase the power of the statistical test, the analysis was applied on the averaged (both time of testing) data. The results showed a significant effect of treatment conditions ($F_{4,21} = 3{\cdot}10$; $p < 0{\cdot}04$). The univariate result showed that TRI was mainly responsible for this effect ($F_{1,24} = 4{\cdot}7$; $p < 0{\cdot}04$); i.e. Sleep Latency after treatment with TRI was significantly shorter.

*Relationships between Plasma Drug Concentrations on both Test Days and Test Parameters*

Mean (SE) plasma concentrations of cetirizine and terfenadine are given in Table 2.

In the CET and 120 condition blood samples were collected 3·5 hrs. after intake on the 1st treatment day and 10·5 hrs. after intake on the 4th treatment day. In these conditions, therefore plasma concentrations on the 1st treatment day were higher than those on the 4th treatment day.

Correlational analysis revealed significant relationships between the plasma drug concentrations on the 1st and 4th treatment day in the CET ($r = 0{\cdot}66$; $p < 0{\cdot}001$) and T60 ($r = 0{\cdot}50$; $p < 0{\cdot}008$)

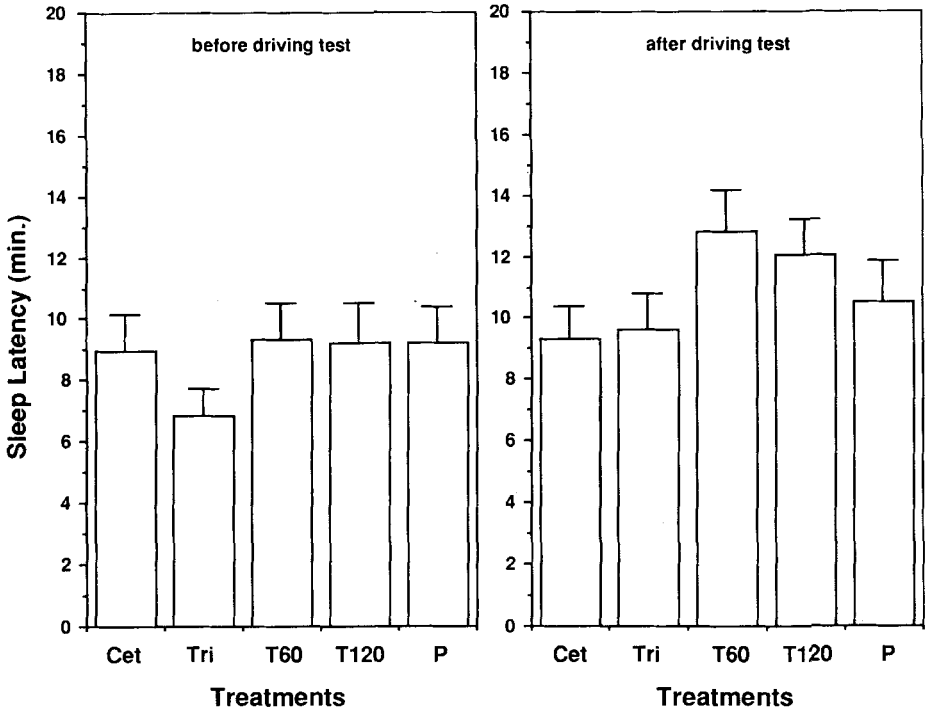


Figure 8. Mean Sleep Latency (+ SE) in treatment conditions CET, TRI, T60, T120 and P before and after the driving test

Table 2. Mean (S.E.) plasma concentrations (ng/ml) of cetirizine and terfenadine

| | DAY 1 | DAY 4 |
|---|---|---|
| CET | 198.71 (39.28) | 114.63 (35.39) |
| T60 | 118.69 (35.73) | 138.04 (47.16) |
| T120 | 234.68 (58.83) | 72.09 (34.60) |

condition. This correlation was not significant in the T120 condition ($r = 0{\cdot}34$; $p < 0{\cdot}08$). On the 4th treatment day a significant relationship between plasma drug concentrations of T60 and T120 was found ($r = 0{\cdot}63$; $p < 0{\cdot}001$). On the individual level, therefore, plasma concentrations on both test days were strongly related and were predictable from each other in the CET and T60 condition. On the 4th day this was also the case for both doses of terfenadine.

Differences between each subject's values of all parameters in P and those measured in every drug condition were calculated. None of the correlations between $\Delta$ SDLP and the drug plasma concentrations reached significance. On both test days, significant ($p \leq 0{\cdot}05$) correlation coefficients were found between drug plasma concentrations in the conditions T60, T120 and $\Delta$ RT's. These correlations ranged from 0·42 to 0·53, and therefore explain just a small proportion (0·16 to 0·25) of the variance.

## DISCUSSION

The purpose of this study was to measure in an objective way the potential of two so-called 'non-sedative' antihistamines, terfenadine and cetirizine to produce impairment in highway driving performance and memory functioning and to induce daytime sleepiness.

The major results of this study were the following: First, both terfenadine and cetirizine show no impairing effects on highway driving. Second, neither of these antihistamines induces daytime sleepiness. Third, terfenadine has the potential to impair memory functions and/or mechanisms related to memory functioning.

Results of studies on the possible effect of terfenadine on actual driving performance and skills

related to driving (O'Hanlon, 1988; Moskowitz *et al.*, 1988; Asoh *et al.*, 1989) are in line with the first major result from this study. To our knowledge, this is the first investigation on the effect of cetirizine 10 mg on highway driving performance. The results however confirm those found in simulator studies and other investigations measuring driving performance in the laboratory or on a closed circuit (Betts *et al.*, 1984; Gengo *et al.*, 1990).

Three studies measuring the effect of the novel antihistamines on daytime sleepiness confirm the results found in the Sleep Latency Test (Roehrs *et al.*, 1984; Nicholson and Stone, 1986; Seidel and Cohen, 1987). In the first two studies diphenhydramine and triprolidine, classical $H_1$ antagonists, decreased sleep latency, whereas terfenadine did not differ from placebo. In the third study, the effect of cetirizine 5, 10 and 20 mg and hydroxyzine 25 mg were compared with placebo. In contrast to hydroxyzine, none of the doses of cetirizine induced daytime sleepiness. It was a surprise to find significant effects of terfenadine on RT after subchronic treatment. This was not because no impairment was found after the 120 mg dose, since subjects performed the psychometric test 9·5 hrs. after intake of terfenadine 120 mg and drug serum plasma concentrations were clearly lower in this condition in comparison to the terfenadine 60 mg condition. Until now, however, several studies have failed to find any significant effects of terfenadine on laboratory test performance. A possible explanation is that in almost none of these studies RT tasks were used to measure memory functioning. More specific, test batteries mostly comprised CFF tests, tracking, arithmetic tasks and visio-motor coordination tests (see White and Rumbold, (1988) and McTavish *et al.* (1990) for a review). In the few RT studies, subjects had to react to simple stimuli (light, sound) or stop a clock (Kulshrestha *et al.*, 1978; Goetz *et al.*, 1989; Moser *et al.*, 1978; Luscombe *et al.*, 1983; Cohen *et al.*, 1987). Moreover, time-on-task never exceeded 5 min. To our knowledge only one study reported RT effects related to memory. In this study (Gaillard *et al.*, 1988) significant effects were found in a RT task, lasting 24 minutes, after single doses of loratadine 10 mg, clemastine 1 mg ($p < 0{\cdot}01$ for both), and terfenadine 60 mg ($p < 0{\cdot}05$). Further, significant effects ($p < 0{\cdot}03$) were found on the error scores of a continuous memory task for both loratadine 10 mg and terfenadine 60 mg.

Although an extrapolation to CNS functioning in man is always hazardous, results from animal studies also indicate that histamine could play a role in memory processes. Morphological studies f.i. show that histamine neurons constitute long and highly divergent systems projecting in a diffuse manner to many cerebral areas including limbic structures such as the hippocampal formation, a structure who's function is closely related to memory processes (Pollard and Schwartz, 1987). Moreover, in a study of De Almeida and Izqueirdo (1986), retention of learned behavior in rats was facilitated by histamine.

Therefore, it is not unlikely that terfenadine has the potential to impair memory functions and/or mechanisms related to memory functioning in relevant tests with sufficient time-on-task. Moreover, since terfenadine only increased RT and did not affect the other task parameters in this study, one can interpret this result as a specific effect of terfenadine on memory functioning. This is in contrast to triprolidine which showed impairing effects on parameters of each tests, indicating a general lowering of CNS functioning.

Finally, we would like to emphasize that the impairing effects of triprolidine 5 mg b.i.d., even in this low dose, proved the sensitivity of the parameters of all tests to the sedative effects of this active (reference) drug control within the study. Moreover, since the smaller effects found on the 4th day in comparison to the first, the results of these tests also replicate the already reported tolerance to the sedative properties of triprolidine (Bey *et al.*, 1977).

In conclusion, based upon these results, we can state that cetirizine, like terfenadine, belongs to the newer class of antihistamines and can be safely used by patients who continue their daily activities. However, effects of prolonged treatment with the newer antihistamines on more specific cognitive processes and mechanisms underlying these processes should be elucidated.

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