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Acute and subchronic effects of the H_1-histamine receptor antagonist ebastine in 10, 20 and 30 mg dose, and triprolidine 10 mg on car driving performance

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1 The effects of a new antihistamine, ebastine (10, 20 and 30 mg), on several parameters of driving performance in actual traffic were studied in 15 healthy male volunteers. Subjects were treated for 5 days, and their driving performance tested on day 1 and day 5. The study was double-blind, placebo controlled and included the antihistamine triprolidine (10 mg sustained release) as an active drug control.

2 General tolerability was good except in one case following the reference compound triprolidine. No significant changes in driving performance were found with the new antihistamine ebastine at any dosage, on day 1 or day 5. Triprolidine (10 mg) significantly increased both the amount of weaving and the delay in following speed manoeuvres of a leading car, compared with placebo.

3 The results suggest that ebastine in doses up to 30 mg may be relatively safe for use by those who drive motor vehicles while under medication. The results do not warrant such a conclusion for triprolidine 10 mg.

Keywords triprolidine ebastine driving performance

Introduction

Antagonists of H_1-histamine receptors, the antihistamines, are widely used for the treatment of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria. However, most of the older and most widely used drugs in this field, such as diphenhydramine, chlorpheniramine, promethazine and triprolidine produce unwanted side-effects of which sedation is the most pronounced [1, 2]. They interfere with important psychological functions and cause impairment of skilled performance that can reduce safety in certain common and critical tasks such as driving [3, 4]. Recently antihistamines have been developed that have little or no central effects, e.g. terfenadine, astemizole and mequitazine [5, 6]. Other antihistamines with high efficacy and low toxicity are currently under investigation, such as telemastine [7], loratadine [8] and ebastine [9]. Of the newer antihistamines terfenadine and loratadine seem to have no effect on actual driving in a standard on-the-road driving test [4, 10]. In a closed-course driving test Betts *et al.* [3] compared triprolidine and terfenadine and reported that triprolidine greatly impaired driving behaviour, whereas the newer antihistamine did not.

The pro-drug ebastine (4-diphenylmethoxy-1-(3-(4-terbutylbenzoyl)-propyl)piperidine) is a potent and selective histamine H_1-receptor antagonist. In humans plasma concentrations of unchanged ebastine were extremely low after oral administration. Peak plasma concentrations of carebastine, the major active metabolite, occurred 3–4 h after oral administration and the metabolite had a half-life between 10–16 h. So far no serious side-effects and no accumulation of ebastine or carebastine occurring after repeated treatment have been reported [9, 11].

The Traffic Research Centre has developed and repeatedly applied an 'on-the-road' test for measuring effects of drugs on driving performance [12, 13, 14, 15, 16]. The ability of the driver to control weaving of the car, measured as the standard deviation of lateral position, is a very sensitive indicator of drug-induced sedation [13]. Recently the test has been expanded to include a car-following test to study the reaction of the driver to driving behaviour of other road users [15, 17, 18]. Drug sedation or activities such as using a car telephone have been shown to impair these reactions [18].

A few studies have shown that up to 90 mg ebastine in comparison with placebo caused no important altera-

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tion of psychomotor function [9, 11]. These experiments involved eye-hand coordination, pursuit tracking and cognitive performance. Although analogous to skills necessary for safe driving, these relatively simple laboratory tests are inadequate to assess human skilled performance that can impair driving. The aims of this study were to ascertain the acute and subchronic effects of ebastine in three dosages, 10 mg, 20 mg and 30 mg, on the ability of subjects to control a vehicle during uninterrupted, high-speed driving, on a normal road, in traffic, and, separately, in a car-following situation; and, to compare these effects with those of the antihistamine triprolidine (10 mg, slow release formulation), measured in the same way.

Method

Fifteen healthy male volunteers aged 25–40 years were recruited. They responded to public advertisement and were selected by individual interview with the investigators, a medical questionnaire, and assessment by the project's medical supervisor. The study had a double-blind, randomized 5-way, cross-over design. The following treatments were each given for 5 days;

Ebastine	10 mg once daily;
Ebastine	20 mg once daily;
Ebastine	30 mg once daily;
Triprolidine:	10 mg once daily (sustained release) and
Placebo.	

As a rule there were 10 days between treatments. All treatments were administered as identical appearing capsules. Dosage was 1 capsule every morning, swallowed with 150 ml of water before breakfast from day 1 to day 5. Treatment was taken 2 and 6 h prior to the beginning of two driving tests. Driving performance was tested on day 1 and on day 5, in the morning 2 h after administration and in the afternoon 6 h after administration.

Specific instructions were given to each subject regarding food, beverages, activities and sleep during the treatment periods. One subject was withdrawn because of non-compliance.

The standard driving test has been fully described [13, 19]. The task was to drive a specially instrumented 1984 Volvo station wagon over a 72 km high-way circuit. Subjects had to maintain a constant speed (95 km h^{-1}) and steady lateral position in the right (slower) traffic lane. They were allowed to deviate from this only when passing a slower vehicle and after 36 km at the mid-circuit turning point.

The second separately-administered test was car-following, where subjects were required to maintain a safe, constant headway behind a lead vehicle travelling at variable speed. Instrumentation within the vehicle permits continuous recording of distance, steering wheel movements, speed, and lateral position relative to delineated lane-boundaries. A radio transmitter allows simultaneous recording of electronic signals, such as speed and events, from the second vehicle in front of the test car in the car-following test.

The two speed signals, one from the test-vehicle and one from the lead car were examined by an analysis of coherence, calculating the coherence and phase-shift between the signals in the frequency domain [20]. The analysis was confined to the frequency band from 0.02 to 0.04 Hz, i.e. the actual and deliberate speed variations with a cycle time of between 25 and 50 s of the lead car.

On completion of the driving test subjects were driven back to the laboratory, a blood sample was taken and centrifuged for 15 min, and the serum was stored at −20°C. Concentrations of carebastine, the active main metabolite of ebastine, were measured using a high performance liquid chromatography assay. In addition to objective performance parameters, subjective mood or feeling parameters were recorded with every test, including:

- subjective rating of mental activation, using Bartenwerfer's [21] continuous scale;
- subjective driving quality, using a continuous scale developed by the investigators in a previous study [19];
- subjective rating of effort driving the test circuit;
- a questionnaire to estimate side-effects or adverse effects.

Informed consent in writing was obtained, and the investigation was approved by the Ethical Review Committee of the Traffic Research Centre. A licensed driving instructor accompanied the subject on every test drive to ensure the subject's safety, using dual controls which were available for that purpose if necessary.

Statistical analysis

Driving performance parameters were analyzed using separate applications of multivariate analysis of variance (MANOVA), using the MULTIVARIANCE program series, as described by Finn [22] and Finn & Mattsson [23]. The two main parameters are control over the lateral position of the test-vehicle (SD lateral position) and the ability to follow manoeuvres of the lead vehicle (phase-shift, or delay, between the speed signals of the two cars). The relationship between SD lateral position and serum drug concentrations was analyzed by calculating Pearson product-moment correlations.

Results

Weaving

The amount of weaving, indexed by the standard deviation of lateral position (SDLP), was affected by treatments. The overall effect of drugs on SDLP was significant ($F(4,11) = 4.67$, $P < 0.019$). Pairwise comparison of the treatments showed a significant difference between triprolidine 10 mg and ebastine 10 mg ($F(1,14) = 8.33$, $P < 0.012$). Control over the vehicle's lateral position after triprolidine 10 mg was non-

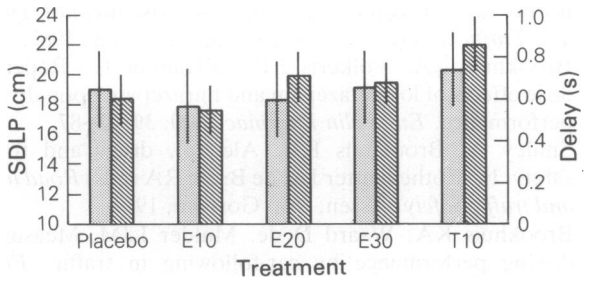

Figure 1 Mean scores and standard errors of standard deviation lateral position (SDLP, in cm, ▦) and delay in speed adaptation (DELAY, in s, ▧), as measured in placebo, ebastine 10, 20 and 30 mg and triprolidine 10 mg treatment conditions during the driving test.

significantly decreased by 6% compared with placebo, whereas it improved non-significantly by 6% after ebastine 10 mg (see Figure 1). In the afternoon SDLP was higher than in the morning ($F(1,14) = 8.96$, $P < 0.009$). No effect of days of treatment (day 1 *vs* day 5) was found.

Coherence and delay in the car-following test

Coherence of the speed signals was always very high, over 0.90, irrespective of treatments, indicating that subjects were well capable of perceiving and adapting to the speed variations of the lead car. The delay between the two signals was mildly and non-significantly influenced by treatments ($F(4,11) = 3.08$, $P < 0.062$). Pairwise comparisons showed a definite effect of triprolidine 10 mg compared with placebo ($F(1,14) = 13.19$, $P < 0.003$). The reactions of subjects to speed variations of the lead car ranged from 0.55 s with ebastine 10 mg treatment to 0.86 s with triprolidine 10 mg treatment (see Figure 1). After triprolidine 10 mg subjects were slower by 0.25 s compared with placebo, i.e. by 42%. No effect of days of treatment (day 1 *vs* day 5) was found, and in Figure 1 the results are given as the mean of day 1 and day 5.

Subjective estimates

There was a slight but non-significant treatment effect on the subjective driving quality scale ($F(4,11) = 2.81$, $P < 0.078$), but pairwise comparisons showed that triprolidine differed significantly from placebo ($F(1,14) = 6.83$, $P < 0.020$). Subjects judged their driving with triprolidine 10 mg condition as poorer than normal. In the afternoon they felt that they drove slightly worse than in the morning ($F(1,14) = 4.81$, $P < 0.045$). No effects of drug treatments were found on the other subjective scales.

Table 1 Serum drug concentrations (ng ml^{-1}), averaged across subjects, in each treatment condition

	Ebastine		
	10 mg	*20 mg*	*30 mg*
Day 1 Morning	60.9	107.6	118.1
Day 1 Afternoon	70.3	108.1	138.8
Day 5 Morning	84.7	205.5	231.0
Day 5 Afternoon	126.8	216.7	257.1

Blood assays

Average concentrations of carebastine, the active main metabolite of ebastine, are given in Table 1. There were highly significant effects of dose ($F(2,12) = 21.15$, $P < 0.001$) and of day of treatment (day 1 *vs* day 5, $F(1,6) = 26.06$, $P < 0.002$).

The correlation between serum drug concentrations and SDLP across all data, i.e. subjects and conditions, was virtually zero ($r = 0.02$). The correlation between serum drug concentrations and SDLP averaged across subjects was also very low and insignificant ($r = 0.29$).

Discussion

Generally, the treatments as they were given to the 15 subjects showed a mildly significant overall effect on a few relevant driving parameters. These were the most well-known in the field, the ability of the driver to control weaving of the car, indicative of vehicle control and by implication traffic safety, and the ability of the driver to follow manoeuvres of a lead car, indicative of attention and perception, strongly related to accident susceptibility. Subjects after treatment with ebastine 10 mg showed the least impairment, whereas triprolidine 10 mg produced the most impairment. Subjects substantiated the objective measurements by reporting the latter treatment as having the most effect on their driving performance. Contrary to previous findings [9] an accumulation of the metabolite carebastine occurred in this study after 5 days of treatment.

In agreement with previous findings [2, 3], triprolidine impaired performance, whereas ebastine did not [11]. However, studies of driving in actual traffic are the critical tests of safety. The standard driving test described has been shown to be very sensitive in this respect [13, 18], demonstrating clear impairment by some hypnotics [16], anxiolytics [14, 15], analgesics [19] and relatively low amounts of alcohol [24].

We suggest that it may be unsafe to drive after treatment with triprolidine 10 mg. The data from this experiment show no impairment during treatment with ebastine at doses up to 30 mg.

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