REPEATED DOSE EFFECTS OF TWO ANTIHISTAMINES UPON ACTUAL DRIVING PERFORMANCE

Karel A. Brookhuis and Gerbrand de Vries
Traffic Research Centre, Haren, The Netherlands

Summary.

Two antihistamines (triprolidine 10mg, ebastine 10mg, 20mg and 30mg) were tested to their effects on driving performance in actual traffic. Compared to placebo, triprolidine appeared to have impairing effects on driving performance with respect to the ability to control the testvehicle’s lateral position on a quiet highway and the ability to adapt adequately to speed variations of a leading car in a car following test. Ebastine showed no significant effects in these two test parts, compared to placebo. It seems that the newer generation of antihistamines, of which ebastine is an example, has no detrimental effect on driving ability.

Introduction.

Antagonists of H1-histamine receptors, the antihistamines, are widely used for the treatment of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria. However, the most widely used drugs in this field, such as diphenhydramine, chlorpheneramine, promethazine and triprolidine, produce unwanted side-effects of which sedation is the most pronounced (Nicholson, 1979). They possess behaviourally toxic effects in the sense of interference with important psychological functions causing impairment of skilled performance that can reduce ambulant patient’s safety in certain common and critical tasks such as operating motor vehicles (e.g. Betts et al., 1984, Riedel et al., 1987). Recently, new antihistamines have been developed that have little or no central effect, e.g. terfenadine, astemizole and mequitazine (Nicholson & Stone, 1982, 1983). Other antihistamines with high efficacy and low toxicity are currently still under investigation, such as telemastine, loratadine and ebastine. Of the newer antihistamines, terfenadine and loratadine seem to have no effect on actual driving in a standard driving test on-the-road (Riedel et al., 1987). In a closed-course driving test, Betts et al. (1984) compared triprolidine and terfenadine. They reported that the older antihistamine greatly impaired driving behaviour, whereas the newer did not.

Ebastine, a new compound closely related to terfenadine, has not yet been tested to its effect on interference with human skilled performance that can impair driving a motor vehicle. Therefore, the specific objectives of this study were to ascertain the acute and subchronic effects of ebastine in three dosages, 10mg, 20mg and 30mg, on the ability of subjects to control a vehicle during uninterrupted, high-speed operation, in traffic on a quiet highway, and, separately, in a car-following situation; and, to compare these effects with those of an equipotent dose of an older antihistamine, triprolidine (10mg, slow releasing formulation), measured in the same way.

Method.

Fifteen healthy male volunteers between 25 and 40 years old were employed after responding to public solicitation. Adhering to the declaration of Helsinki, they were accepted after indicating their informed consent, in writing, and a medical investigation under the responsibility of the project’s medical
supervisor. All held a drivers' license for 5 years prior to the study. During that period they had driven more than 5000 km per year.

The study was conducted according to a double-blind, 5-way, cross-over design. Treatments consisted regularly of a five-day administration of each of ebastine 10 mg, 20 mg, 30 mg, triprolidine 10 mg (sustained release tablets) or placebo. The times of administration were set so that ingestion of single dose or placebo occurred 2 and 6 hours prior to the beginning of two driving tests. Dosage was 1 cachet every morning, swallowed with 150 ml of water before breakfast from day 1 to day 5. Treatments were administered to two subjects on the same day. One began the test at 9:00 hours, and the other, at 10:00 hours. The second driving test was administered respectively at 13:00 hours and 14:00 hours. Subjects were tested on day 1 and day 5 of each drug treatment period.

The standard driving test has been fully described in previous publications (O'Hanlon et al., 1982, Brookhuis 1986). The subject's task was to operate a specially instrumented 1984 Volvo station wagon over a 72 km primary highway circuit. The subject was instructed to maintain a constant speed (95 km/hr) and steady lateral position in the right (slower) traffic lane. He was allowed to deviate from this procedure only in the case of passing a slower vehicle and at the mid-circuit turning point.

The second, separately administered test comprised a car-following task (cf., Brookhuis et al., 1987), where the subject is required to maintain a safe, constant headway behind a leading vehicle travelling at variable speed.

Instrumentation within the vehicle permits the continuous recording of speed and lateral position relative to delineated lane-boundaries. A radio transmitter allowed simultaneous recording of electronic signals, such as speed and events, from the second vehicle, in front of the test vehicle in the car-following test. Finally, subject's electro-cardiogram was registered and inter-beat-intervals (IBI) were derived on-line and stored.

Two experimenters accompanied the subject on every test ride. One's sole responsibility was to ensure the subject's safety, using if necessary, redundant controls which are available for that purpose. He also recorded distance travelled using a hand-held keyboard. A separate computer-system was used, off-line, to perform data editing and reduction. A first-pass processing routine produced mean and standard deviation (SD) of speed, and standard deviation (SD) of lateral position. The two speed signals, one of the test-vehicle and one of the car-in-front, were processed simultaneously in an analysis of coherence, i.e. calculating the coherence and phase-shift between the signals in the frequency domain (Porges et al., 1980). The analysis was confined to the frequency band around 0.03 Hz, i.e. the actual and deliberate speed variations with a cycle time of around 30 seconds of the car-in-front. Reported are car following performance and response times (RT) to the leading vehicle's movements. Analyzing heart rate variability by means of spectral analysis is informative with respect to differences in, particularly mental, effort of different driving conditions. Especially a frequency band around 0.10 Hz is sensitive to differences in mental effort (Mulder, 1980).

In addition to objective performance parameters, a few subjective mood or feeling parameters were recorded in conjunction with every test, of which will be mentioned here the subjective driving quality scale, using a continuous
Driving performance parameters were analyzed using separate applications of multivariate analysis of variance (MANOVA), using the MULTIVARIANCE program series, as described by Finn (1974) and Finn and Mattsson (1978). The general factor, drug treatments, is tested for significance in this way (simple- or C-contrasts, a priori, using placebo as the control treatment). Other factors that are included in the test are Time-of-test and Day-of-test. Mean-pair comparisons between treatment conditions were accomplished separately by subroutines available in the program (deviation- or D-contrasts, a posteriori).

Results.

The amount of weaving

The control over lateral position, as measured by the amount of weaving, indexed by the SD lateral position, was affected by treatment (see figure 1). The overall effect of drugs on SD lateral position was significant ($F(4,11)=4.67, p<0.019$). Mean pair comparisons of each of the drug treatment conditions, showed a significant effect between triprolidine and ebastine 10 mg only ($F(1,14)=8.33, p<0.012$). In the afternoon SD lateral position was higher than in the morning ($F(1,14)=8.96, p<0.009$). No effect of days of treatment (day 1 - day 5) was found.

Figure 1: Means of SD lateral position across the five treatment conditions, triprolidine 10mg, ebastine 10mg, 20mg, 30mg and placebo.

Speed and standard deviation speed

No effect of treatment on the average speed of the test-rides was found. In all treatment conditions subjects drove quite well according to the experimenter’s instructions, i.e. 95 km/h. Neither an effect of treatment on SD speed was found. Subjects were well capable of keeping a steady speed over all the five treatment conditions. Subjects drove faster in the afternoon than in the morning ($F(1,14)=8.01, p<0.013$), and faster on the 5th day than on the 1st day ($F(1,14)=9.68, p<0.008$). No effects of time of day or test day were found.

Coherence and Phase-shift of the car-following

Coherence of the speed signals was always very high, i.e. over .90, irrespective of treatment condition, indicating that subjects were well capable of perceiving and adapting to the speed variations of the car-in-front. The phase-shift between the two signals, in radians and therefore converted to reaction time (RT) in seconds (see figure 2), is mildly and non-significantly influenced by treatment condition ($F(4,11)=3.22, p<0.056$). Mean pair comparisons of the placebo condition with the other treatment conditions, showed a definite effect of placebo with triprolidine ($F(1,14)=13.19, p<0.003$). The reactions of the subjects to speed variations of the car-in-front ranged from 0.601 seconds in the placebo treatment condition to 0.855 seconds in the triprolidine treatment condition. After treatment with triprolidine, subjects were slowed with 0.254 seconds, compared to treatment with placebo, i.e. 42 %.

Figure 2: Means of reaction times (RT) across the five treatment conditions, triprolidine, ebastine 10mg, 20mg, 30mg and placebo.
Driving quality, subjective estimate

There was only a very slight and non-significant main effect of treatment on the subjective driving quality scale (F(4,11)=2.81, p<0.078), but mean pair comparisons showed that placebo differed significantly from treatment with triprolidine (F(1,14)=8.68, p<0.011). Subjects judged their own driving quality after triprolidine as lower than normal, in the other conditions they judged their driving quality similar as normal, indicating that they did their best and felt they were able to do so. In the afternoon they felt that they drove slightly worse than in the morning (F(1,14)=4.81, p<0.045).

Cardiac inter-beat-interval

No main effect was found for treatment nor any difference among the drug treatment conditions. The drug treatments did not necessitate, or at least did not inflict, an elevation in mental effort to carry out the task at hand. However, the differential requirements of the two test parts, car-following and quiet highway, were apparent in the frequency-band around 0.10 Hz (F(1,14)=15.16, p<0.002).

Conclusion.

Generally, the treatments as they were given to the 15 subjects, showed a mildly significant overall effect on some of the relevant driving parameters, among which the most important to date, the control over the vehicle’s lateral position, indicative for vehicle control and by implication traffic safety, and the most promising for the near future, reactions to a car-in-front, indicative for attention and perception, and therefore related to accident-proneness. It turned out that placebo and ebastine 10mg generally were the least affected treatment conditions, contrary to the triprolidine treatment condition, which was the most impairing treatment condition. Subjects confirmed the objective measurements by reporting the latter treatment as the most affecting. Tentatively, it would be unsafe to drive after treatment with the older generation antihistamine, triprolidine 10mg, whereas the data from this experiment do not warrant such a position for the treatment with the newer generation antihistamine, ebastine up to 30mg.

References.


