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# Placebo controlled comparison of acute effects of ebastine and clemastine on performance and EEG

**H. Hopes, G.-H. Meuret, W. Ungethüm, G. Leopold, and H. Wiemann**

Divison of Clinical Research, Department of Clinical Pharmacology, Laboratory for Experimental Psychopharmacology, E. Merck, Darmstadt, FRG

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**Summary.** The effects of single oral doses of 10 and 20 mg ebastine were compared with placebo and 2 mg clemastine in a double-blind cross-over study in 16 healthy male volunteers.

Clemastine produced the known pattern of changes, namely impairment of psychomotor performance, drowsiness, and a selective effect on cognitive processes. Earlier encoding in a perceptual stage was slowed whereas abstract classification processes were not affected. Electrophysiological measures of vigilance showed a general decrease in vigilance especially 2.5 and 4.5 h after dosing.

In contrast at no time was any effect of ebastine different from that of the placebo.

Ebastine 10 and 20 mg differed positively from clemastine in its effect on pursuit tracking, subjective rating of drowsiness and general discomfort. Ebastine 10 mg also differed positively from clemastine in the EEG features of vigilance.

It is concluded that 10 and 20 mg ebastine were free from sedative adverse effects.

**Key words:** Ebastine, Clemastine; $H_1$-receptor antagonist, psychomotor performance, healthy volunteers, vigilance, cognitive performance adverse effects

$H_1$-receptor antagonists can both stimulate and depress the CNS. Central depression is the usual accompaniment of therapeutic doses of the older $H_1$ antagonists. Diminished alertness, slowed reaction times and somnolence are common manifestations [Douglas 1985]. Although this may be a desirable adjunct in the treatment of some patients, it may interfere with day time activities and increases the risk of errors, lack of concentration and accidents.

Antihistamines have recently been developed without the side effect of sedation [Cheng and Woodward 1982, Van Wauwe et al. 1981]. It is important, therefore, to test all newly developed $H_1$-antihistamines for CNS side effects.

Ebastine is a new selective $H_1$-receptor antagonist of proven antihistamine efficacy in doses of 10 and 30 mg per day [Farnells 1987, E. Merck, Darmstadt, data on file].

Clinical pharmacology studies in healthy volunteers have shown that the antihistamine efficacy of ebastine lasts for up to 24 h, so a once daily treatment regimen can be recommended [Vincent 1988].

Several experimental studies in healthy volunteers have shown that ebastine is well tolerated in doses up to 9-fold (90 mg as a single dose) of that showing optimum antihistamine activity (skin weal test after intradermal antihistamine injection) [Carrencá et al. 1985, 1986, 1987, E. Merck, Darmstadt, data on file].

In clinical trials in some 1400 patients ebastine has shown good efficacy and tolerability in patients with seasonal allergic rhinitis, perennial allergic rhinitis and chronic urticaria. The clinical studies lend support to the proposed dosing schedule of 10 mg ebastine oncy daily [Bakke 1987, de Molina Gorina 1987, E. Merck, Darmstadt, data on file].

The present study was designed to detect possible CNS effects in healthy volunteers after single doses of 10 and 20 mg ebastine in comparison to placebo and 2 mg clemastine. The objective was to cover the most relevant aspects of behaviour: vigilance as measured by quantitative pharmaco-EEG, cognitive performance, visual motor coordination, and subjective estimates of sedation. Clemastine was included as a positive control because it has been reported to affect visual-motor coordination, reaction time and to cause subjective tiredness [Peck et al. 1975, Clarke and Nicholson 1978, Seppäla et al. 1981].

## Subjects and methods

The subjects were 16 healthy male volunteers, aged 21 to 43 y (mean 32 y) and weighing 63 to 97 kg (mean 78 kg). They had been selected on the basis of a stable, normal α-EEG, and were assessed as having good health and cardiovascular stability in a screening examination before the start of the study. No other medication was allowed for 2 weeks prior to the study or during it. Subjects had to refrain from smoking during the laboratory periods and to refrain from taking alcohol on the laboratory days, on the preceding evening, and for the subsequent 3 days. The study was carried out in accordance with the revised Declaration of Helsinki. All subjects were fully informed about the purpose of the study and the possible effects of the administered drugs. They gave their written consent to participation. The

study was approved by an independent Ethical Committee. All subjects were trained to perform the tests before entering the trial. Before and after the study each subject underwent a thorough medical and laboratory examination.

### *Medication*

Single oral doses were administered of 10 mg ebastine, given as 2 capsules of 5 mg, 20 mg ebastine, as 2 capsules of 10 mg, 2 mg clemastine as 2 capsules of 1 mg, and placebo as 2 capsules, all of identical appearance. All treatments were administered under supervision with 200 ml water. Subjects received a light breakfast 1.5 h after medication and a standard lunch after 3.5 h.

### *Design and experimental procedures*

The study was conducted as a double blind, placebo controlled, Latin square design. The wash-out period between treatments was one week. Measurement periods were immediately before and 2.5, 4.5 and 6.5 h after medication. Each test period lasted 55 min. All procedures were standardized and were the same on each day and in each measurement period. Four subjects were examined on each day of the study. Drug administration and test sessions were staggered at 20 min intervals because equipment was available for only one subject at a time. Subjects were given two questionnaires to complete at home 12 h after medication, and a sleep questionnaire to be filled in on the morning before and after the laboratory day.

### *Assessments*

*EEG. Indicator of vigilance.* Disappearance of the occipital α-rhythm and its replacement by low voltage, mixed frequency EEG in α-carriers has been generally accepted as an indicator of reduced vigilance [e.g. Matejcek 1982]. The change is quantifiable by power spectral density analysis. The delta$^F$ power was used as a unidimensional vigilance indicative variable in the EEG (in accordance with Herrmann et al. 1986).

*EEG. Recording and Quantification.* The EEG was recorded under vigilance-controlled conditions. The subject sat with eyes closed in a reclined chair and was instructed to count along with tones of 50 ms duration, which were given at average random intervals of 4 s. Subjects were asked to respond to every 20th tone by pressing a button as fast as possible.

The EEG was recorded from the lead $P_3$–$O_1$ using Ag-AgCl electrodes placed according to the international 10/20 system.

To control artifact, eye movements (EOG) were recorded using a piezoelectrode (Siemens Elema 230) attached to the right eyelid. And, as a further control, the Lead 1 ECG was also recorded. The EEG, EOG and ECG were printed out on a Schwarzer EEG printer (type E 12000) and recorded for further processing on an analogue tape recorder (Bell and Howell 4020). The EEG was amplified to $50\ \mu V \cdot 7\ mm^{-1}$; time constant 0.3 s; upper frequency limit 70 Hz. The amplifier sensitivity for the EOG was $500\ \mu V \cdot cm^{-1}$; time constant 0.1 s; upper frequency limit 30 Hz. Amplifier sensitivity for the ECG lead was $1\ mV \cdot cm^{-1}$; time constant 1.5 s; upper frequency limit 70 Hz. The second and third minutes of artifact-free EEG were submitted to spectral density analysis. As variables related to vigilance the absolute and relative power of the following frequency bands were extracted:

Delta$^F$ (1.5–6.0 Hz)
Theta$^F$ (6.0–8.5 Hz)
Alpha$_1^F$ (8.5–10.5 Hz)
Alpha$_2^F$ (10.5–12.5 Hz)

The frequency band limits are based on the factor analysis studies of Herrmann et al. (1980). The main target variable was the relative delta$^F$ power.

*Matching paradigm.* Modified from Posner (1967), a task with two levels of information processing was used. It consisted of simultaneous visual presentation of pairs of digits. The digits remained present until subjects responded by pressing a response key (mouse). The subjects were instructed to classify pairs of stimuli either as "same", by pressing a response-key labelled "same", or as "different" by pressing a key labelled "different". The Level 1 instruction was to classify each pair of stimuli as "same" if they were physically identical. The Level 2 instruction was to classify pairs of digits as "same" if they were both even, or if they were both odd (i.e. belonging to the same category). If pairs of digits consisted of one odd and one even digit they were neither physically nor categorically the same and so had to be classified as "different". The sequence of pairs was randomized. Each session consisted of 24 pairs of identical even numbers, 24 pairs of identical odd numbers, 24 pairs of non-identical even numbers and 24 pairs of non-identical odd numbers. They were mixed at random with 96 pairs of odd/even numbers. At the beginning of every session 32 stimuli were given for warming up and the results were discarded. The subjects were instructed to classify each pair as rapidly as possible, trying to keep errors to a minimum. After each stimulus they were provided with feedback (information on the correct response). 500 msec before each stimulus a fixation cross was demonstrated for 500 ms. The interval between the feedback and the fixation point for the next stimulus was 1.5 s. One block consisted of 96 stimuli. In each session two blocks were administered, with a pause of 15 s between each. For each session of 192 stimuli the number of correct responses, reaction time and standard deviation of correct responses were calculated. These variables are reported for the two levels of information processing: stimulus recognition (matches based on physical identity) and stimulus classification (matches based on common rule). The test program was developed in ERTS (Experimental Run Time System, Beringer, 1988).

The principal aim was to differentiate between distinct stages of information processing and to test whether the drugs would affect stages in a differential way.

*Pursuit rotor.* This test is part of the Motor Performance Series of Schoppe (1974).

An illuminated square (1.5 cm × 1.0 cm) was rotated clockwise at 15 cpm on a diamond shaped trace. Subjects had to adapt the speed and rhythm of arm movement to the rotating light in order to keep it covered with a photoelectric scanner. Each deviation from the rotating light was counted as a mistake, and the time off the target (duration of mistakes in s) was accumulated over the 64 s of the task.

*Pursuit tracking.* The pursuit tracking task was developed by Beringer (1988) using the tracking function of ERTS (Experimental Run Time System).

In the center of the monochrome monitor of a personal computer a window of 4 cm depth across the total width of the screen was shown. A wiggly line moved from bottom to top and, depending on the amplitude of the curve, continuously reached the upper frame of th window at different points. The subject controlled a marker (in the form of a downward pointing arrow) with the mouse of the computer. The marker could be moved horizontally along the upper frame of the window. The subject had the task of superimposing the marker on the endpoint of the curve and to follow it as closely as possible. The adaptation period was 20 s; the score was the root mean squared (RMS) error, i.e. the mean deviation from the track over a 30 s trial period. A lower score indicates more accurate tracking.

*Subjective ratings.* The adjective checklist [Janke and Debus 1978] was employed to measure activation, disactivation, drowsiness (tiredness) and confusion.

The list of somatic symptoms [Lehmann 1973, revised by Hopes and Görtelmeyer 1986, E. Merck, Darmstadt, data on file] was used as a self-reporting scale for adverse somatic effects.

The sleep questionnaire [Görtelmeyer 1986] was filled out on the mornings before and after medication days. It was used to compare subjective assessment of exhaustion in the evening and the quality of sleep and vigilance in the morning following each treatment.

*Health examination.* A screening and a final examination were performed to document the state of health of the subjects and the safety of the drug.

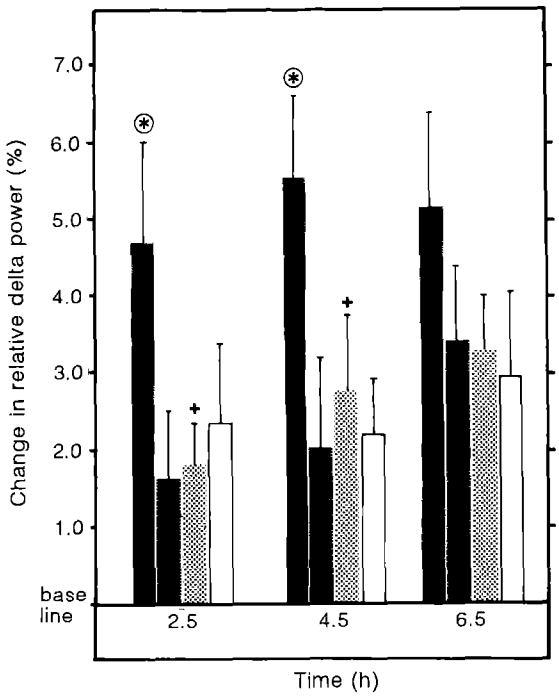


**Fig. 1.** EEG: Changes in relative delta$^F$-power (1.5 Hz – 60 Hz) at 2.5 h, 4.5 h, 6.5 h after 2 mg clemastine (■), 20 mg ebastine (▤), 10 mg ebastine (▨) and placebo (□). ($N = 16$)
* = comparison clemastine to placebo $P \leq 0.05$
+ = comparison clemastine to ebastine 10 mg $P \leq 0.05$

The health status of each subject was assessed by a medical check-up, clinico-physiological examinations (blood pressure, heart rate, ECG, lung function test) and laboratory data (clinical chemistry, haematology, urinalysis).

### *Statistical analysis*

Results were expressed as differences from baseline on each test day. Because of missing data the Latin square structure was not used in the analysis. Pairwise comparisons at each time point after treatment were performed by paired $t$-tests. The level of significance was $\alpha = 5\%$, two-tailed (descriptive).

## Results

### *EEG*

The increase in relative delta$^F$ power (Fig. 1) was most pronounced after clemastine, with a maximum at 4.5 h. The mean differences after 10 and 20 mg ebastine at all measurement points were close to those of placebo. At 2.5 h and 4.5 h after dosing the increase in delta$^F$ was significantly larger after clemastine than after placebo and 10 mg ebastine. A corresponding decrease in the relative power of the alpha$_1$ frequency band was seen.

### *Matching paradigm*

Mean changes from predrug for the two components of information processing "recognition" and "classification" are given in Figs. 2 and 3.

Neither stage of information processing was impaired after 10 mg and 20 mg ebastine. In fact, as after placebo, the reaction time decreased on repeated testing.

Clemastine affected the recognition process and not the classification process. In the session 4.5 h after medication clemastine slowed recognition speed even below the baseline level.

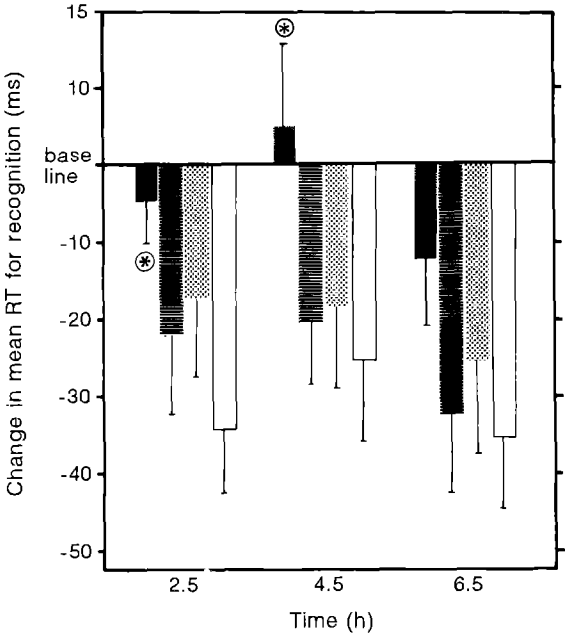


**Fig. 2.** Matching Paradigm: Changes in mean (SEM) RT for recognition of physically identical matches at 2.5 h, 4.5 h, 6.5 h after 2 m clemastine (■), 20 mg ebastine (▤), 10 mg ebastine (▨) and placebo (□). ($N = 16$)
* = comparison clemastine to placebo $P \leq 0.05$

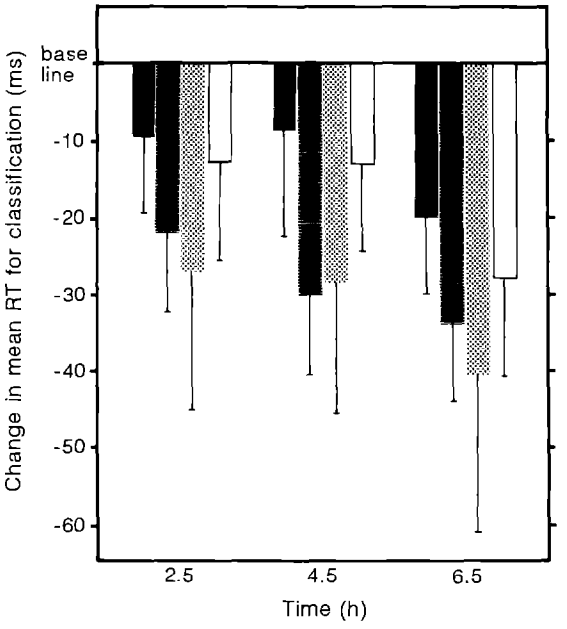


**Fig. 3.** Matching Paradigm: Changes in mean (SEM) RT for classification of categorially identical matches at 2.5 h, 4.5 h, 6.5 h after 2 mg clemastine (■), 20 mg ebastine (▤), 10 mg ebastine (▨) and placebo (□). ($N = 16$)

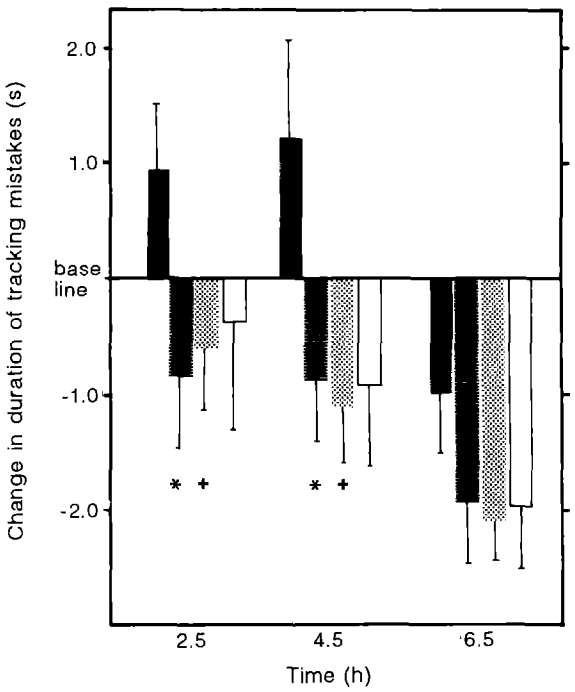


**Fig. 4.** Pursuit Rotor: Changes in mean (SEM) duration of tracking mistakes cumulated over 64 sec tracking time, 2.5 h, 4.5 h, 6.5 h after 2 mg clemastine (■), 20 mg ebastine (■), 10 mg ebastine (▨) and placebo (□). ($N = 16$).
* = comparison clemastine to ebastine 20 mg; $P \leq 0.05$
\+ = comparison clemastine to ebastine 10 mg; $P \leq 0.05$

No significant drug effect was seen on reaction accuracy in either reaction task. A speed-accuracy trade-off was not found.

*Pursuit rotor and pursuit tracking*

In both tests psychomotor performance was impaired by clemastine, peaking at 4.5 h, and with a tendency to normalise at 6.5 h. Ebastine 10 and 20 mg was no different from placebo but differed from clemastine at 2.5 and 4.5 h. Visual-motor coordination in these tasks was significantly better after ebastine than after clemastine. As results of both tasks were in good agreement, only those of the pursuit rotor task are shown (Fig. 4).

*Adjective check-list*

Of the four activation scales used, the scale "drowsiness" (tiredness) was the most sensitive. Drowsiness scores as mean changes from the predrug state are given in Table 1. The scores were most increased after 2 mg clemastine and were below baseline only after 20 mg ebastine; the difference was significant. Twelve h after medication, when the list was filled out at home, the highest drowsiness scores were found after clemastine and placebo, and the lowest after 10 and 20 mg ebastine.

*List of somatic symptoms*

General discomfort (Table 2) after 10 and 20 mg ebastine was not significantly different from placebo.

Clemastine caused an increase in discomfort score as early as 2.5 h, which differed from placebo and 10 and 20 mg ebastine. At 4.5 and 6.5 h the score was still different from that of placebo and 20 mg ebastine.

*Sleep questionnaire*

The sleep questionnaire was completed for the nights before and after treatment. Sleep quality was rated best after clemastine and worst after placebo. The feeling of being stressed in the evening was most pronounced after clemastine and least after 10 mg ebastine. The feeling of being refreshed after sleep was increased after all medications, with the highest value after 20 mg ebastine.

**Table 1.** Changes in subjective ratings: adjective check list
Scale: Drowsiness

| Measurements (post application) (h) | Medication | | Differences from baseline | |
|---|---|---|---|---|
| | | | $\bar{x}$ | SEM |
| 2.5 | Clemastine | 2 mg | 0.69 | 0.3 |
| | Ebastine | 20 mg | −0.44 | 0.4 |
| | Ebastine | 10 mg | 0.13 | 0.3 |
| | Placebo | | 0.06 | 0.3 |
| 4.5 | Clemastine | 2 mg | 1.38 | 0.4 |
| | Ebastine | 20 mg | −0.06 | 0.3 |
| | Ebastine | 10 mg | 0.56 | 0.3 |
| | Placebo | | 0.31 | 0.4 |
| 6.5 | Clemastine | 2 mg | 1.00 | 0.5 |
| | Ebastine | 20 mg | −0.31 | 0.3 |
| | Ebastine | 10 mg | 0.63 | 0.4 |
| | Placebo | | −0.25 | 0.4 |
| 12 | Clemastine | 2 mg | 1.13 | 0.6 |
| | Ebastine | 20 mg | 0.13 | 0.4 |
| | Ebastine | 10 mg | −0.13 | 0.3 |
| | Placebo | | 0.75 | 0.6 |

**Table 2.** Changes in subjective ratings: list of somatic symptoms
Scale: General discomfort

| Measurements (post application) (h) | Medication | | Differences from baseline | |
|---|---|---|---|---|
| | | | $\bar{x}$ | SEM |
| 2.5 | Clemastine | 2 mg | 4.75 | 1.4 |
| | Ebastine | 20 mg | −0.44 | 0.7 |
| | Ebastine | 10 mg | 1.75 | 0.8 |
| | Placebo | | −0.94 | 1.3 |
| 4.5 | Clemastine | 2 mg | 5.88 | 1.8 |
| | Ebastine | 20 mg | 0.44 | 1.1 |
| | Ebastine | 10 mg | 1.94 | 1.5 |
| | Placebo | | 0.44 | 1.4 |
| 6.5 | Clemastine | 2 mg | 4.38 | 1.9 |
| | Ebastine | 20 mg | 0.13 | 0.8 |
| | Ebastine | 10 mg | 1.06 | 1.2 |
| | Placebo | | −1.19 | 1.8 |
| 12 | Clemastine | 2 mg | 3.33 | 1.9 |
| | Ebastine | 20 mg | 0.13 | 1.1 |
| | Ebastine | 10 mg | −0.40 | 1.3 |
| | Placebo | | −1.25 | 1.4 |

*Documentation of state of health*

The results of the final examination revealed no unusual findings and corresponded to the results of the screening examination. Cardiovascular examination (blood pressure, heart rate, ECG) and lung function as well as laboratory values did not reveal any notable change in the before/after comparison.

## Discussion

An acute oral dose of 10 mg or 20 mg ebastine had no statistically significant central activity in this controlled study. Neither dose led to results that differed significantly from each other or from placebo in any of the measures employed. Subjects even seemed to perform better after 20 mg than after placebo or 10 mg ebastine.

Clemastine, on the other hand, caused a decline in vigilance, as measured by a significant increase in relative delta$^F$ power, complemented by a decrease in $\alpha_1$-power in the EEG. It impaired visual-motor coordination in two tracking tasks and increased subjective drowsiness. Clemastine did not impair comprehension processes in a cognitive performance test. However, there was a tendency for clemastine to slow down stimulus processing in an earlier encoding stage. A similarly selective action on the perceptual processing stage has been reported for barbiturates [Frowein 1981].

The time course profiles of all variables were in good agreement, showing the maximum effect of clemastine in the period 4.5 to 5.5 h after medication. The increase of subjective side effects after clemastine was significant but small. This is in agreement with Clarke and Nicholson (1978), who found little evidence of impaired subjective assessment of well-being after 1 mg clemastine. In agreement with findings of Seppälä et al. (1981), drowsiness was still reported 12 h after treatment by subjects filling out the adjective check-list at home.

In contrast, ebastine 10 and 20 mg caused no significant increase in adverse effects.

Clarke and Nicholson (1978) reported a significant effect of 1 mg clemastine in a visual-motor coordination task, with a maximum after 5 h p. a. Here, 2 mg clemastine had a clear effect on visual-motor coordination, but 10 and 20 mg ebastine did not cause any decrement in performance.

It is concluded that ebastine in clinical doses belongs to the class of non-sedative antihistamines, because no evidence of sedation was found in the EEG nor in behaviour or subjective measures.

In further trials performance after multiple administration will be investigated.

As the study was double-blind, placebo controlled and used a positive standard (clemastine) in a multidimensional approach to measure changes, it is anticipated that neither 10 nor 20 mg ebastine will cause problems for safe driving or handling complicated machinery. It may also be assumed that both doses will be well tolerated and will have no influence on sleep quality or vigilance on the following morning.

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H. Hopes
Department of Clinical Pharmacology
Laboratory for Experimental Psychopharmacology
E. Merck
Post Office Box 4119
W-6100 Darmstadt, FRG