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Ebastine: the effect of a new antihistamine on psychomotor performance and autonomic responses in healthy subjects

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1 Ebastine, through its carboxylic acid metabolite has antihistamine (H_1-receptor) activity in man.
2 We have examined in a single blind placebo controlled study the effects of 10 mg and 50 mg of ebastine on cardiovascular, autonomic and psychomotor function in healthy subjects.
3 Ebastine had no effect on blood pressure or heart rate and there was no evidence of any anticholinergic activity on circulatory reflexes or salivation.
4 Ebastine did not impair psychomotor performance as assessed by critical flicker fusion at either dose.
5 Ebastine 10 mg had no effect on sedation measured by visual analogue scale or direct questioning, however ebastine 50 mg did cause a modest increase in indices of sedation.
6 Ebastine did not have detectable sedative properties at the 10 mg dose where long-lasting antihistamine effects can be demonstrated.

Keywords antihistamine sedation autonomic nervous system psychomotor function

Introduction

Ebastine, (4-diphenylmethoxy-1-[3-(4-terbutyl-benzoyl)-propyl] piperidine) (LAS-W-090) is a new antihistamine which blocks H_1-receptors (Figure 1). In experimental pharmacology and preliminary clinical investigations ebastine appears to be a potent long-acting drug with no apparent sedative properties in the antihistamine dose range (Roberts *et al.*, 1987). Antihistamines have been used for over 30 years but impairment of psychomotor performance, sedation and anticholinergic effects have been associated with most earlier compounds (Peck *et al.*, 1975; Carruthers *et al.*, 1978; Clarke & Nicholson, 1978; Nicholson & Stone, 1982, 1986; Paton & Webster, 1985). Antihistamines without sedation or psychmotor impairment constitute an important clinical development. These properties have been claimed for terfenadine (Weiner, 1982) and astemizole (Richards *et al.*, 1984). This study was carried out with two doses of ebastine, 10 mg and 50 mg, which were compared with placebo to evaluate the psychomotor and autonomic effects of ebastine in healthy normal volunteers. The

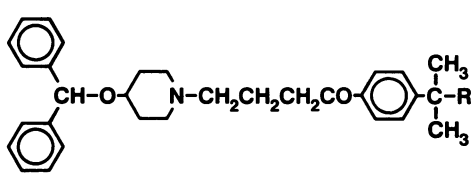

Figure 1 The chemical structure of ebastine (LAS-W-090) R = CH_3. For the metabolite carebastine (LAS-X-113)C, R = CO_2H.

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lower dose (10 mg) appears to be an effective antihistamine dose when given once daily (Vincent *et al.*, 1988).

Methods

Nine healthy males with no evidence of physical or psychiatric disease on clinical history and examination and in whom pre-study haematology, biochemistry and electrocardiogram were within normal limits were studied. None of the subjects was on any medication for at least 2 weeks before and all through the study. None of the subjects abused alcohol or smoked tobacco. Haematology and biochemistry tests were repeated 24 h after drug or placebo administration and again 2 weeks after the study.

The subjects were aged 19–23 years (mean 24.1 ± 5.3 years) and weighed 56–85 kg (mean 67.7 ± 8.4 kg). Each subject gave written informed consent and the study was approved by the Research and Ethics Committee of the Greater Glasgow Health Board. Subjects attended the Clinical Pharmacology Research Unit on at least one occasion before the study and practised using the Leeds Psychomotor Tester until consistent scores were obtained. This was done to reduce possible practice or training effects in the analysis.

Each subject was studied on three different study days at least 1 week apart. Subjects were advised to avoid alcohol for at least 48 h, and food and tobacco from 22.00 h the evening preceding the study. An intravenous cannula was inserted in a forearm vein for blood sampling and precordial ECG leads attached for continuous ECG monitoring. Each subject rested for at least 30 min in the supine position before baseline measurements were made.

The subjects received under single (subject) blind conditions either ebastine 10 mg, 50 mg or a matching placebo orally. Ebastine was supplied as a solution containing 2 mg ml^{-1}. The appropriate dose was diluted to a constant volume of 40 ml with water. The drug dosing and test series were staggered at 30 min intervals to allow measurements of psychomotor performance in each subject at the appropriate time. The order of measurements was randomised but the sequence was constant for each subject and on each occasion. Blood pressure was measured with a semi-automatic sphygmomanometer (Sentron) in duplicate after resting supine for at least 10 min and on standing for up to 2 min. The corresponding heart rate was counted from the ECG trace. Blood samples were taken at intervals for up to 24 h, the plasma separated and stored at −20° C until assayed for active metabolite carebastine (LAS-X-113) Breakfast was provided 120 min after drug or placebo administration and lunch 4 h later.

Psychomotor tests

Psychomotor performance was assessed by means of both objective and subjective tests.

Subjective tests These included assessment of sedation using the visual analogue scale and categorical questioning on mood.

Objective tests The objective tests carried out included the critical flicker fusion (c.f.f.) threshold, choice reaction time and recognition time.

Autonomic tests

These included blood pressure and heart rate as described above, salivary secretion and the standing-to-lying test.

These procedures were undertaken before and at 1, 2, 3, 6, 8 and 24 h after drug or placebo administration.

Critical flicker fusion (c.f.f.)

This was evaluated using a Leeds psychomotor Tester as described by Hindmarch (1980, 1982) and Hindmarch & Parrot (1978). The subject was required to discriminate flicker in a set of four-light emitting diodes in foveal fixture at about 1 m in a quiet room with a constant ambient illumination. The frequency of the flicker fusion threshold was detected for ascending and descending scales using the psychological method of limits (Woodworth & Schlosberg, 1958). A mean of twenty readings was taken as the flicker fusion threshold (Hz).

Choice reaction time (CRT)

This was also assessed on the Leeds Psychomotor Tester (Hindmarch & Parrot, 1978). This instrument measures both motor movement (MRT) and recognition time (RRT). Subjects were required to extinguish one of six coloured lights iluminated at random by touching the appropriate response key. The reaction time recorded was the mean of 30 stimulus responses.

Visual analogue scale and questionnaire for sedation

This was evaluated by asking the subject to place a mark on an upgraded 100 mm line which read

'wide awake' at the left end and 'almost asleep' at the right end. The distance from the left end was used as a measure of sedation in the analysis. The subjects did not see their previous estimates.

The subjects were also required to tick one of the five categorical questions which were later scored 0–4 before analysis. The categorical questions on mood and their scores were:

1. I can hardly stay awake (4)
2. I feel a bit drowsy (3)
3. I don't feel different from usual (2)
4. I feel more alert than usual (1)
5. I feel very alert and cannot possibly sleep (0).

Saliva flow

This was measured with cotton dental rolls as described by Dollery *et al.* (1976) using duplicate 1 min collections with pre-weighed dental rolls. The average change in weight was expressed as salivary flow in g min^{-1}.

Standing-to-lying test

Continuous measurement of heart rate was made and this test was evaluated by the method described by Bellavere & Ewing (1982).

Statistical analysis

The autonomic effects of ebastine were analysed using repeated measures analysis of variance.

The psychomotor performance tests were analysed using analysis of covariance on the RUMMAGE package. Treatment, day and time were included in the model as fixed effects, and the baseline (pre-dose) value was included as a covariate. It was necessary to include the baseline values in the model because of the marked variations in performance of the tests during the day and also between study days.

Results

Ebastine was generally well tolerated at both doses. Subjective effects reported by the volunteers were present on both active treatments and also after placebo, and included tiredness and occasional comments of drowsiness. They were not more frequent or severe on either of the active treatment days.

Blood pressure and heart rate

At both doses studied, ebastine had no consistent effect on either supine or erect blood pressure or heart rate. Statistical evaluation by the repeated measures analysis of variance (ANOVA) did not reveal any significant treatment effect compared with placebo.

Table 1 Mean ± s.d. critical flicker fusion (Hz) after ebastine 10 and 50 mg and placebo, $n = 9$

Time	*Ebastine*		
(h)	*10 mg*	*50 mg*	*Placebo*
0	29.8 ± 3.2	32.0 ± 2.0	31.9 ± 3.5
1	30.2 ± 2.6	31.6 ± 1.8	33.4 ± 4.8
2	30.4 ± 2.3	31.8 ± 3.2	32.0 ± 3.1
4	30.1 ± 2.9	31.9 ± 2.2	32.1 ± 3.3
6	31.0 ± 2.8	31.3 ± 3.4	31.5 ± 2.3
8	33.1 ± 3.8	32.3 ± 2.6	31.9 ± 2.8
24	32.1 ± 2.6	33.9 ± 2.7	33.4 ± 3.0

Critical flicker fusion

There was no significant difference between the effects of both doses of ebastine compared with placebo (Table 1).

Choice reaction time

In comparison with placebo, neither dose of ebastine had a statistically significant effect on the mean rcognition time. However, both doses resulted in a marginally significant increase in the choice reaction time; for 50 mg ebastine the difference from placebo was significant at 4 h and 8 h (95% C.I. for the difference at both time

Table 2 a) Mean ± s.d. choice reaction time (s) and b) mean ± s.d. recognition time (s) after ebastine 10 and 50 mg and placebo in nine healthy men

a) Choice reaction time

Time	*Ebastine*		
(h)	*10 mg*	*50 mg*	*Placebo*
0	0.58 ± 0.1	0.57 ± 0.1	0.64 ± 0.1
1	0.58 ± 0.1	0.61 ± 0.1	0.61 ± 0.1
2	0.58 ± 0.1	0.62 ± 0.1	0.61 ± 0.1
4	0.58 ± 0.1	0.61 ± 0.2	0.56 ± 0.1
6	0.57 ± 0.1	0.57 ± 0.1	0.55 ± 0.1
8	0.56 ± 0.1	0.56 ± 0.1	0.52 ± 0.1
24	0.52 ± 0.1	0.55 ± 0.1	0.54 ± 0.1

b) Recognition time

0	0.40 ± 0.1	0.39 ± 0.1	0.44 ± 0.1
1	0.40 ± 0.1	0.43 ± 0.1	0.41 ± 0.1
2	0.40 ± 0.1	0.44 ± 0.1	0.43 ± 0.1
4	0.42 ± 0.1	0.43 ± 0.2	0.39 ± 0.1
6	0.39 ± 0.1	0.40 ± 0.1	0.38 ± 0.1
8	0.39 ± 0.1	0.38 ± 0.1	0.36 ± 0.1
24	0.37 ± 0.1	0.40 ± 0.1	0.39 ± 0.1

points (0.01, 0.25)), whereas for 10 mg ebastine the difference was only just significant at 8 h (95% C.I. (0.01, 0.23)). This assessment time coincided with the fastest of the reaction times recorded with placebo.

Sedation

Assessment of sedation by visual analogue scale confirmed no detectable effect of ebastine 10 mg compared with placebo. However, ebastine 50 mg significantly increased the sedation scores ($P < 0.05$) compared with the 10 mg dose and placebo (Figure 2). Analysis of the categorical questions on mood showed that the subjects felt more drowsy 4-6 h after ebastine 50 mg compared with the 10 mg dose. Some subjects also felt drowsy on placebo (Figure 3). Four subjects felt drowsy both on placebo and ebastine 50 mg. One subject felt drowsy on all three treatments and five subjects felt that they had a more than usually long sleep the night after taking ebastine 50 mg.

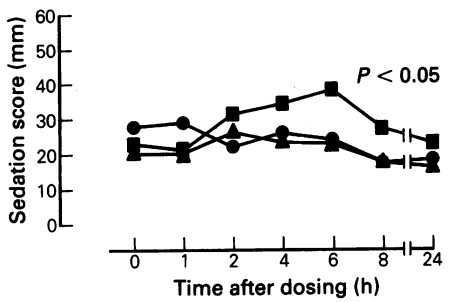

Figure 2 Effect of ebastine 10 mg (●), 50 mg (■) and placebo (▲) on sedation scores in normal volunteers. The effect of ebastine 50 mg was significantly different ($P < 0.05$) compared with 10 mg dose or placebo.

Autonomic tests and saliva production

There was no change in the response to lying down (standing and lying test) after placebo or either active treatment. There was no drug related effect on salivary flow although there was a significant time effect ($P < 0.02$) after placebo and both active treatments indicating that the saliva produced varied throughout the study day.

Discussion

In this study neither dose of ebastine significantly impaired the critical flicker frequency threshold while there was only a marginal effect on the overall choice reaction time most apparent at the higher dose and of doubtful clinical relevance. These tests have been used extensively for the objective evaluation of the psychomotor effects of several drugs (Turner, 1968; Hedges *et al.*, 1971; Ogle & Turner, 1974; Smith & Misiak, 1976; Hindmarch, 1980). The re-

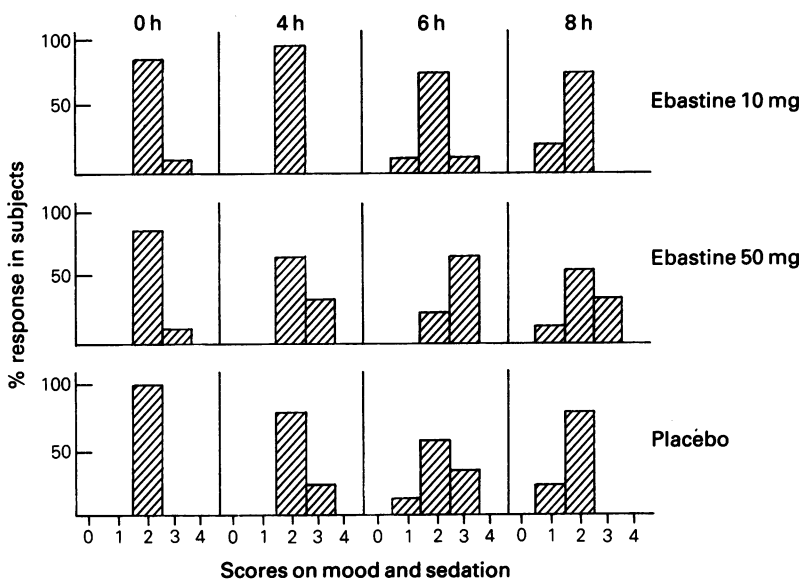

Figure 3 Relationship between scores of categorical questions on mood and sedation in individual subjects to the percentage response in all subjects.

liability and validity of scores obtained with the Leeds Psychomotor Tester have also been established in previous studies (Hindmarch & Parrot, 1978; Hindmarch, 1982; Subhan & Hindmarch, 1985).

The results with visual analogue scales are consistent. This is a flexible method permitting a subject to report on mood states (Mann, 1985) and its usefulness has been confirmed in several studies (Bond & Lader, 1974; Bye *et al.*, 1974; Cohen *et al.*, 1985; Littman *et al.*, 1985). Using this scale ebastine 10 mg orally which significantly inhibited the histamine-induced wheal and pain (Roberts *et al.*, 1987; Vincent *et al.*, 1987) did not induce detectable sedation. However, the higher dose of 50 mg significantly increased sedation scores both on the visual analogue scale and on the categorical scales. This observation suggests a dissociation between antihistamine and sedative effects and confirms a discrepancy between the central and peripheral effects of ebastine. Ebastine may show a separation between the therapeutic dose and a dose likely to cause central nervous system impairment. A similar observation has earlier been made with terfenadine (Nicholson & Stone, 1982; Weiner, 1982) and astemizole (Richards *et al.*, 1984). The reason for the selective action of the therapeutic dose of 10 mg is not clear but may include factors such as lipid solubility or reflect different mechanisms of drug action at the periphery and in the central nervous system (Levander *et al.*, 1985). We observed no detectable correlation between plasma concentration of the active metabolite carebastine and the sedation scores in individual subjects (unpublished data). However this has been demonstrated previously with diphenhydramine (Carruthers *et al.*, 1978).

Ebastine has little or no effect on muscarinic receptors. This was shown by its lack of effect on autonomic responses under parasympathetic control such as resting heart rate and salivary production (Tyrer, 1976), and the standing-to-lying test (Bellavere & Ewing, 1982). This absence of anticholinergic actions may also contribute to its lack of sedative effects at least in therapeutic doses (Paton & Webster, 1985). In addition, the absence of a significant effect on the blood pressure or heart rate also suggests that ebastine does not impair the function of the sympathetic nervous system.

In conclusion, ebastine 10 mg, a dose that significantly inhibited histamine-induced wheal size and pain for up to 24 h (Vincent *et al.*, 1988) did not show any autonomic impairment or sedative effects in healthy volunteers, although a higher dose of 50 mg increased sedation. These features support further evaluation of ebastine in patients with rhinitis, urticaria and other allergic states.

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