Diazepam effects on the performance of healthy subjects are not enhanced by treatment with the antihistamine ebastine

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- 1 We have given 12 healthy subjects the H₁-antihistamine ebastine (20 mg) or placebo in a randomized double-blind and crossover study for 1 week each. The subjects were tested for drug effects on day 6 of each period, and for interactions of ebastine with oral 15 mg diazepam (DZ) on day 7. On both days, the testing runs were at baseline and 1.5, 3, 4.5 and 6 h after intake.
- 2 The performance was evaluated both objectively (digit symbol substitution, flicker fusion, Maddox wing, simulated driving, body balance) and subjectively (visual analogue scales, questionnaires). Venous blood was sampled daily during the maintenance and during each testing round for the assay of plasma carebastine (the active metabolite of ebastine) by high pressure liquid chromatography and plasma diazepam by radioreceptor assay. Three-way ANOVA, paired *t*-test, Wilcoxon rank sign test and Fisher's fourfold table test were used for data analysis.
- 3 Plasma carebastine reached steady levels from day 3 onwards. The mean concentrations in the morning were 82 µg l⁻¹ on day 6 and 85 µg l⁻¹ on day 7. The rise (+ 150%) in plasma carebastine after an extra 20 mg ebastine was not modified by DZ. Ebastine did not affect performance objectively or subjectively, yet borderline drowsiness was recorded during the first 3 h. On day 7, plasma DZ concentrations peaked (mean 480 µg l⁻¹) at 1.5 h after the intake. DZ produced impaired performance in various objective tests, and drowsiness, weakness, clumsiness, mental slowness and poor performance were reported on visual analogue scales. Ebastine neither modified plasma DZ concentrations nor increased DZ effects.
- 4 We conclude that treatment with 20 mg ebastine once daily for 1 week provides steady concentrations of carebastine in plasma, without impairment of skilled performance or important interactions with diazepam.

Keywords ebastine carebastine diazepam interaction pharmacokinetics psychomotor performance

Introduction

The sedative action of old antihistamines has led to the development of newer non-sedative drugs, such as astemizole and terfenadine. Ebastine is a selective and long-acting H₁-receptor antihistamine, chemically related to terfenadine. It penetrates the brain poorly and thus allows an effective blockade of H₁-receptors in peripheral tissues without important central side-effects (Vincent *et al.*, 1988 a,b; Wood-Baker & Holgate, 1990). Ebastine is well absorbed and extensively converted to its active carboxylic acid metabolite carebastine during the first pass through the liver. The elimination half-life of carebastine in man is 10 to 16 h (Vincent *et al.*, 1988b); it is moderately accumulated during the

treatment with therapeutic doses of ebastine once daily for 1 week, and the local responses to intradermal histamine are suppressed by over 50% for 24 h (Vincent *et al.*, 1988b) with plasma concentrations of carebastine (100 µg l⁻¹) resulting from a daily dose of 20 mg ebastine. Subjective sedation has not been reported after therapeutic daily doses (10–20 mg) of ebastine, but larger (50 mg) doses may produce drowsiness and psychomotor impairment (Vincent *et al.*, 1988 b).

Ebastine administered once daily to healthy subjects for 7 days does not interact with 0.8 g l⁻¹ of alcohol (Mattila *et al.*, 1992). The present study was conducted to determine if 1 week treatment with ebastine once

daily might increase diazepam-induced impairment of human psychomotor performance.

Methods

Subjects

Twelve healthy subjects, six females and six males, aged 22–26 years and weighing 60–80 kg, volunteered for the trial and were paid for their time. The subjects were free of physical or mental diseases, and they did not use any medicines regularly, or alcohol in excess. They gave their written informed consent, and the trial design was accepted by the Ethics Committee of the Department of Pharmacology and Toxicology, University of Helsinki.

The subjects were trained to the tests, four of them having participated previously in similar trials. They underwent clinical examination and laboratory tests for haematology (haemoglobin, red blood cells, leucocytes with differential count, platelets) as well as biochemical tests for hepatic (bilirubin, alkaline phosphatase, gamma-GT, ALAT, ASAT) and renal (creatinine, K, Na, Cl, Ca, inorganic phosphate) functions. The subjects were advised to avoid drinking coffee and tea in the morning of the days of psychomotor testing.

Trial design

This double-blind crossover trial comprised two randomized maintenance treatment periods, 1 week each, with 1 week wash-out between them. During both maintenance periods, the subjects were tested on day 1 (baseline only), on day 6 (drug + placebo capsule; baseline and four post-treatment runs), and on day 7 (drug + diazepam capsule; tests as on day 6). The order of challenge with placebo and diazepam within the same treatment period was not randomized; the tests after treatment were 1.5, 3, 4.5 and 6 h after the intake. During each period the treatment began after the baseline testing on day 1 (Monday afternoon), continued supervised in the morning of days 2, 3, 4 and 5, and further after the baseline round on the actual testing days 6 and 7 (Saturday and Sunday). This administration ensured the compliance. Venous blood was sampled at the end of each testing run and before drug intake on each day of the maintenance periods. A snack was served during test sessions after the 3 h tests.

Drugs

Ebastine (20 mg) and respective placebo were given in gelatine capsules once daily as explained above. Diazepam (15 mg) in a large gelatine capsule was given on day 7, and the dummy capsule on day 6, respectively.

Tests

The session began with the *digit symbol substitution test* with pencil and paper, the number of symbols correctly substituted in 3 min being recorded. Matched different versions of test chart were provided for the consecutive tests. *Flicker fusion threshold* was measured against red

flickering light with a battery-driven automatized calculator (Leeds tester) controlled by the subjects themselves (Hindmarch, 1982). The distance was 100 cm, the lighting conditions were standard, and the pupil diameter was standardized with special glasses. The fusion frequency recorded was the mean of the measurements upwards and downwards once each. *Maddox wing test* measures the balance of extraocular muscles and drug-induced shifts towards exophoria and esophoria, expressed in dioptries (Hannington-Kiff, 1970).

Body balance was measured with the subjects standing on an electronic platform, with the eyes open and closed, for 30 s each (Savolainen & Linnavuo, 1979). The body sway was separated to lateral and sagittal movements, but the total shifts of the gravity point were taken for data analysis.

A simulated driving task (Linnavuo *et al.*, 1987) was undertaken, composed of two halves lasting for 2.5 min each. The first half comprised simple *tracking* only. The second half was made complex by the appearance of 60 mixed light and sound *reaction stimuli* to be answered to, according to complex rules, by pushing two buttons or two foot pedals while tracking. The computerized test provided a moving road on the colour TV screen, and an alignment mark ('car') was to be kept on the road by turning the steering wheel. The numbers of errors (deviations from the road) and error percentages (relative length of the track driven off the road) were recorded separately for the both halves of the track. The tracking error severity index covering the whole track was also computed.

For subjective assessment, *visual analogue scales* (VAS) (Bond & Lader, 1974) were used to quantitate the effects of ebastine and diazepam. Horizontal 100 mm ungraded lines were used, and the pairs of extremes thus used (in Finnish) were alert/drowsy, calm/excited, strong/weak, muzzy/clear-headed, skilful/clumsy, lethargic/energetic, contented/discontented, troubled/balanced, mentally slow/quick-witted, tense/relaxed, attentive/dreamy, incompetent/proficient, happy/sad, antagonistic/friendly, interested/bored, withdrawn/social, and very good/very bad performance. The subjects also filled in a *13-item questionnaire*, ticking and scoring (0–5) various bodily symptoms during each testing run.

Plasma concentrations of carebastine and diazepam

Venous blood was drawn into heparinized 10 ml vacuum tubes, centrifuged at 4° C, and the plasmas were stored at –20° C for several weeks until assayed for carebastine (Vincent *et al.*, 1988a). The assay method involves an automatic solid-phase extraction of ebastine and carebastine from plasma samples on a C2 bonded phase (AASP system, Varian) and a subsequent separation by reverse phase h.p.l.c. with u.v. detection of both compounds. The sensitivity limit is 5 g l⁻¹ for the unchanged drug and 20 g l⁻¹ for the metabolite in human plasma. Quality control studies indicate the stability of ebastine (over 5 months) and of carebastine (over 16 months) in human plasma at –20° C.

Plasma concentrations of diazepam were measured with direct radioreceptor assay (RRA), without previous extraction, against four diazepam standards which ran parallel in each assay (Mattila, 1988). Briefly, plasma

samples in triplicate were incubated with [^3H]-flunitrazepam and receptor homogenate (rat cerebral cortex) for 60 min, filtered in vacuum, and the radioactivity in the filter was counted with liquid scintillator. Differences from the subjects' baseline samples were used to estimate plasma diazepam concentrations against the log probit graphs for diazepam standards. RRA also accounts the small amounts of nordiazepam generated from diazepam during the session (Mattila, 1988).

Statistics

Mean ($\pm$ s.e. mean) values were computed for absolute test performances, and for the Δ -values (changes from respective baselines) at each post-drug testing time. These changes represent the responses to the drug (diazepam; the maintenance dose of ebastine) or placebo, and their statistical significance *vs* zero were evaluated with the paired two-tailed *t*-test. The contribution by the treatment period to these Δ -values was evaluated by comparing (paired *t*-test) the Δ -values of the two periods, irrespective of the drugs given.

The primary comparisons were between placebo and ebastine, and between diazepam and diazepam + ebastine. Repeated measures three-way (subject $\times$ period $\times$ drug) ANOVA (SAS general linear models) was computed for the Δ -values of day 6 (placebo *vs* ebastine) and day 7 (placebo + diazepam *vs* ebastine + diazepam) at separate testing times (see Table 1) and also with the times combined. Since the order of challenge with extra placebo and diazepam was not randomized between the testing days, the diazepam effects were evaluated from the significance of the Δ -values on day 7 during the placebo period. They were confirmed by repeated measures two-way ANOVA (subject $\times$ drug) computed for the combined test times to compare the Δ -values of day 6 and day 7 during the placebo period. Comparison of the days 6 and 7 during the ebastine period (ebastine *vs* ebastine + diazepam) was also made, but the lack of randomization between day 6 and day 7 might have confounded these analyses.

These analyses were applied for the objective data and subjective VAS data. Data from the questionnaire for side-effects were analyzed with Fisher's fourfold table test.

Results

Certain objective test functions which require skill and motivation improved during the trial. The use of Δ -values for analysis reduced but not abolished the contribution by the treatment period to the overall variation. Statistically significant changes from the baselines (paired *t*-test) on day 6 after placebo and ebastine were few and small. The results of the clinical chemistry tests were within the normal range except for some borderline values which were interpreted as being normal, however.

Effects of ebastine

The baselines and responses recorded on day 6 during the maintenances with placebo and ebastine did not

Table 1 Effects of ebastine (EBA) and 15 mg diazepam (DZ) in some objective tests and visual analogue (VAS) assessments. Mean $\pm$ s.e. mean values of 12 subjects are given; a, b, and c refer to significant (paired *t*-test) differences from the baseline at 5%, 1% and 0.1% levels. F_D refers to drug effects, and S and W to significant subject and week effects in three-way ANOVA

Test/Drug	Baseline	1.5 h	3 h	4.5 h	6 h
<i>Tracking error severity</i>					
EBA	25 $\pm$ 6	24 $\pm$ 4	24 $\pm$ 4	21 $\pm$ 3	24 $\pm$ 4
EBA + DZ	22 $\pm$ 3	32 $\pm$ 5 ^a	21 $\pm$ 2	19 $\pm$ 2	21 $\pm$ 3
Plac	23 $\pm$ 3	24 $\pm$ 3	25 $\pm$ 4	23 $\pm$ 3	26 $\pm$ 3
Plac + DZ	21 $\pm$ 2	32 $\pm$ 5 ^a	22 $\pm$ 3	21 $\pm$ 4	23 $\pm$ 5
Day 6 F_D		0.48	0.40	0.59	0.85
Day 7 F_D		0.02(S)	0.95	0.67	2.14
<i>Body sway, eyes open</i>					
EBA	96 $\pm$ 6	92 $\pm$ 8	89 $\pm$ 5	95 $\pm$ 8	96 $\pm$ 7
EBA + DZ	85 $\pm$ 8	94 $\pm$ 10	101 $\pm$ 10	94 $\pm$ 6	104 $\pm$ 8 ^a
Plac	88 $\pm$ 6	84 $\pm$ 7	88 $\pm$ 8	111 $\pm$ 14	96 $\pm$ 11
Plac + DZ	98 $\pm$ 6	95 $\pm$ 8	91 $\pm$ 7	92 $\pm$ 5	100 $\pm$ 10
Day 6 F_D		0.01	0.08	1.90	0.34
Day 7 F_D		2.34	7.33	2.77	2.14
<i>Clumsiness (mm VAS)</i>					
EBA	34 $\pm$ 5	35 $\pm$ 5	29 $\pm$ 5	33 $\pm$ 5	39 $\pm$ 5
EBA + DZ	34 $\pm$ 5	55 $\pm$ 7 ^b	50 $\pm$ 7 ^b	38 $\pm$ 7	41 $\pm$ 6
Plac	34 $\pm$ 5	33 $\pm$ 5	35 $\pm$ 5	40 $\pm$ 6	37 $\pm$ 5
Plac + DZ	33 $\pm$ 5	55 $\pm$ 7 ^b	45 $\pm$ 6 ^b	40 $\pm$ 7	37 $\pm$ 6
Day 6 F_D		0.30	2.15(W)	1.66	0.25
Day 7 F_D		0.08(W)	1.42	0.30(W)	0.39
<i>Mental slowness (mm VAS)*</i>					
EBA	64 $\pm$ 5	64 $\pm$ 4	65 $\pm$ 5	65 $\pm$ 4	63 $\pm$ 4
EBA + DZ	68 $\pm$ 5	50 $\pm$ 6 ^a	53 $\pm$ 7 ^a	59 $\pm$ 7 ^a	60 $\pm$ 6
Plac	63 $\pm$ 5	61 $\pm$ 5	66 $\pm$ 5	62 $\pm$ 5	59 $\pm$ 4
Plac + DZ	70 $\pm$ 4	50 $\pm$ 7 ^b	52 $\pm$ 6 ^c	60 $\pm$ 6	63 $\pm$ 5
Day 6 F_D		0.77(S)	0.43	0.37(S)	0.35
Day 7 F_D		0.26	0.54	0.21	0.00

*Shift downwards indicates mental slowness.

differ from each other in any objective test variable (Figure 1, Table 1). Individual differences and period effects considerably contributed to the total variation. The borderline significant shift after ebastine towards drowsiness at 3 h ($F_D = 4.94$; $P = 0.050$) could be a coincidence partly due to different baselines (Figure 2).

When the ANOVA was computed for all the consecutive post-drug testing times together on day 6, ebastine differed from placebo objectively in the flicker fusion test ($F_D = 7.36$; $P < 0.01$) and in the body sway with the eyes closed ($F_D = 7.28$; $P < 0.01$). Subjective differences were found in drowsiness ($F_D = 4.42$; $P < 0.05$), proficiency ($F_D = 10.62$; $P < 0.01$); and antagonism ($F_D = 16.40$; $P < 0.001$). In all these differences the real changes were small. Compared to the respective shifts after placebo, ebastine tended to lower the flicker fusion threshold, to reduce body sway, and to shift the subjective assessments towards drowsiness, proficiency and antagonism.

Effects of diazepam

Significant changes from the baselines (*vs* zero; paired *t*-test) on day 7 during the placebo period indicate significant diazepam effects in various objective and subjective tests (Figures 1 and 2, Table 1). Diazepam reduced the number of digits substituted, increased

Figure 1 Effects and combined effects of treatment with ebastine (20 mg daily) and a single dose of 15 mg diazepam on the digit symbol substitution (a) and the flicker fusion threshold (b). Mean values of 12 subjects are given. Open triangles (Δ) refer to placebo, open circles ($\circ$) to ebastine, solid triangles ($\blacktriangle$) to diazepam, and solid circles ($\bullet$) to ebastine + diazepam. The symbols *, † and ** refer to the differences from baseline (Δ -values) at 5%, 1% and 0.1% level, respectively.

exophoria (relaxation of extraocular muscles), lowered the flicker fusion threshold, slightly increased the number and severity of tracking errors, and shifted subjective assessments on VAS towards sedation, clumsiness and poor performance (Figures 1 and 2, Table 1). When analyzing (paired *t*-test) the combined Δ -values of the four post-drug testing times of day 6 *vs* day 7 during the placebo period, the diazepam effects on digit substitution and subjective sedation were unequivocal; flicker fusion was less affected, and tracking error severity and body sway were not impaired significantly. When similar comparisons were made during the ebastine period (ebastine *vs* diazepam + ebastine), the results were very similar to those mentioned above.

Ebastine-diazepam interactions

Three-way ANOVA revealed few if any significant differences between the diazepam effects on day 7 measured during the treatments with ebastine or placebo. In general, significant contribution by subject and period

Figure 2 Effects of ebastine and diazepam, alone and in combination, on subjective drowsiness (a) and overall performance (b) assessed on the visual analogue scales (VAS). The symbols *, † and ** refer to the differences from baseline (Δ -values) at 5%, 1% and 0.1% level, respectively.

factors were frequent, particularly in subjective assessments on the VAS scales. The only significant ebastine-diazepam interaction event was found in the body sway with the eyes open at 3 h ($P = 0.022$): ebastine + diazepam increased body sway over that recorded after diazepam alone.

When computing ANOVA for the four post-drug testing times together, this interaction ($F_D = 14.96$; $P < 0.001$) was unequivocal. A significant ($P < 0.01$) subject effect but negligible period effect were associated with this drug effect. Measurement of body sway with the eyes closed revealed no drug effect. Diazepam-induced borderline shift towards subjective incompetence was prolonged by ebastine ($F_D 5.84$; $P < 0.01$).

Side-effects

Baseline and post-dose sedative complaints were commoner than expected on day 6 of the placebo period. The symptoms related to sedation after placebo were similar to those reported after ebastine but less than those produced by diazepam. Active drugs did not differ significantly from placebo at any testing time.

Table 2 Mean $\pm$ s.d. plasma concentrations ($\mu\text{g l}^{-1}$, $n = 12$) of carebastine on days 6 and 7 of the maintenance with 20 mg ebastine once daily. Ebastine was given alone on day 6, and with 15 mg diazepam on day 7. No statistically significant differences were found between the days 6 and 7

	Plasma carebastine ($\mu\text{g l}^{-1}$)				
	Baseline	2 h	3.5 h	5 h	6.5 h
Ebastine	82 $\pm$ 23	156 $\pm$ 59	201 $\pm$ 59	225 $\pm$ 55	224 $\pm$ 59
Ebastine + diazepam	85 $\pm$ 19	141 $\pm$ 51	209 $\pm$ 67	232 $\pm$ 51	241 $\pm$ 51

Table 3 Mean $\pm$ s.e. mean plasma concentrations ($\mu\text{g l}^{-1}$, $n = 12$) of diazepam in 12 healthy subjects after the intake of diazepam (15 mg) on day 7 during the treatment with placebo or ebastine 20 mg daily. The radioreceptor assay (RRA) used also counts nordiazepam generated from diazepam during the session

Treatment	Plasma diazepam ($\mu\text{g l}^{-1}$)			
	2 h	3.5 h	5 h	6.5 h
Diazepam	470 $\pm$ 60	310 $\pm$ 40	190 $\pm$ 70	190 $\pm$ 60
Diazepam + ebastine	480 $\pm$ 70	370 $\pm$ 50	150 $\pm$ 30	120 $\pm$ 30

Plasma concentrations of carebastine and diazepam

The plasma carebastine concentrations on days 6 and 7 are given in Table 2. It appears, that the mean baseline values on these days were similar, thus indicating a steady kinetic state. The rise in plasma carebastine after further 20 mg ebastine was similar on days 6 and 7, thus indicating that diazepam did not modify the absorption or metabolism of ebastine. The plasma concentrations of diazepam measured with radioreceptor assay (Table 3) were as expected and similar to those we have previously measured (Mattila, 1988; Mattila *et al.*, 1988). Ebastine did not modify the plasma concentrations of diazepam significantly.

Discussion

This double-blind crossover trial was randomized for the maintenance treatments with placebo and ebastine but not for the extra placebo (on day 6) and diazepam (on day 7). Randomization of the treatment with diazepam was omitted because its residual effects from day 6 could not have been excluded on day 7. The design, however, allowed an adequate comparison of ebastine vs placebo, and ebastine + diazepam vs diazepam

alone. The design for the comparison of diazepam vs placebo was less robust but feasible. The baseline performances on day 6 and day 7 may represent 'trough effects' during the maintenance while the responses to treatment (Δ -values) on day 6 might represent the effects of rising (+ 150% or more) concentrations of carebastine after a single daily dose of ebastine.

The present results resemble those recorded and discussed in our previous ebastine-alcohol interaction study (Mattila *et al.*, 1992). Ebastine proved nearly inactive on objective and subjective measures of human performance. The borderline differences were occasionally found between placebo and ebastine, at separate test times or with the times combined, but the real differences were small and the significances partly result from different baseline values or from a statistical α -inflation. They could, however, refer to small concentrations of carebastine in the central nervous system, and since Vincent *et al.* (1988b) reported impaired performance from larger doses of ebastine, it might be preferable to take daily doses in the evening. The effects of diazepam, though not very strong in the present trial, clearly differed from those recorded after placebo and ebastine.

Treatment with ebastine did not enhance the effects of 15 mg diazepam, and our results are thus comparable with those reported by Moser *et al.* (1978) who documented the lack of interaction between the single doses of 10 mg diazepam and terfenadine. In our study, a significant increase of the body sway with the eyes open, but not with the eyes closed, was found with ebastine and diazepam as compared with diazepam alone. We have previously reported a similar phenomenon when giving diazepam (15 mg) in combination with the antipsychotic remoxipride (Mattila *et al.*, 1988) and sedative antidepressants (Mattila *et al.*, 1989) while the drugs separately minimally affected body sway in these conditions. Alcohol did not exhibit such a selective interaction (Mattila *et al.*, 1988). We tend to attribute this curious action of diazepam on body sway to its moderate dose and well-known acute tolerance, as well as to its action, even at low doses, on corrective visual pathways, possibly on the retinal GABAergic system (Fisch *et al.*, 1983).

We conclude that treatment with ebastine 20 mg daily for 7 days had minimal or no effects on human performance and did not interact importantly with an oral single dose of 15 mg diazepam. The side-effects were negligible.

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