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Lack of pharmacodynamic and pharmacokinetic interactions of the antihistamine ebastine with ethanol in healthy subjects

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Summary. We have given 12 healthy subjects the H_1-antihistamine ebastine (20 mg) or placebo in a double-blind, crossover study for one week each. The subjects were tested for drug effects on Day 6 of each period, and for interactions of ebastine with ethanol (0.8 g · kg^{-1}) on Day 7. On both days, the testing runs were done at baseline and at 2, 4, and 6 h after the drug. Performance was evaluated both objectively (digit symbol substitution, flicker fusion, Maddox wing, nystagmus, simulated driving, body balance) and subjectively (visual analogue scales) and with questionnaires. Venous blood samples were taken daily during maintenance and during each test run for assay of plasma carebastine. Blood ethanol concentrations were assayed with an Alcolmeter in the breath and directly in the blood. Plasma carebastine concentration reached a steady-state from Day 3 on; the mean concentrations in the morning were 92 μg · l^{-1} on Day 6 and 104 μg · l^{-1} on Day 7. The rise in plasma carebastine after an extra 20 mg of ebastine was accelerated but not increased by ethanol. Ebastine did not impair performance objectively or subjectively. It slightly improved body balance and reduced errors during simple tracking at 4 h. Blood ethanol concentrations peaked (mean 0.76 g · l^{-1}) at 1.5 h after ethanol intake. Ethanol impaired performance in most objective tests and produced clumsiness, muzziness, and mental slowness, but little drowsiness. Ebastine neither modified the blood ethanol concentrations nor increased the effects of ethanol. We conclude that treatment with 20 mg ebastine once daily for one week provides steady concentrations of carebastine in plasma without impairment of skilled performance or important interactions with alcohol.

Key words: Ebastine, Ethanol interaction; carebastine, psychomotor performance, pharmacokinetics

Ebastine is a selective and long-acting H_1-antihistamine, chemically related to terfenadine. It penetrates the brain poorly and thus allows effective blockade of H_1-receptors in peripheral tissues without important central effects [2–3 and Roberts et al. 1987 unpublished data]. It is well absorbed and extensively converted to its active carboxylic acid metabolite carebastine (Fig. 1) during its first pass through the liver. The half-life of carebastine is 10 to 16 h [2], it is subject to moderate accumulation during the administration of therapeutic doses of ebastine once daily for one week, and local responses to intradermal histamine are suppressed by over 50 % for 24 h [2] with concentrations of carebastine (100 μg · l^{-1}) resulting from a daily dose of 20 mg of ebastine. The toxicity of ebastine in animals is low [1], and studies in man have not shown pathological alterations in conventional clinical laboratory tests. Subjective sedation has not been reported after therapeutic daily doses (10–20 mg) of ebastine, but larger doses (50 mg) may produce mild drowsiness and psychomotor impairment [3].

The present study was conducted to find out if treatment with ebastine 20 mg once daily for one week might cause objective or subjective impairment of human performance and might increase the detrimental effects of alcohol on performance. The results have been briefly communicated elsewhere [5].

Materials and methods

Subjects

Twelve healthy subjects, 5 f, 7 m, aged 19–26 y and weighing 55–78 kg, volunteered for the trial and were paid for their time. The subjects had no physical or mental diseases and they did not use any medicines regularly or take 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 in the tests, most of them having previously participated in similar trials. They also underwent clinical examination and laboratory tests for haematology (haemoglobin, red blood cell count, haematocrit, differential leucocyte count, platelet count, and ESR) as well as biochemical tests (bilirubin, alkaline phosphatase, γ-GT, AlT, AsT, blood urea nitrogen, creatinine, potassium, sodium, chloride, calcium, inorganic phosphate, fasting blood glucose, total cholesterol, and uric acid). They were advised to avoid drinking coffee and tea in the mornings of the test days.

Trial design

This double-blind crossover trial comprised two randomized maintenance treatment periods, one week each, with one week of washout between them. During both maintenance periods the subjects were tested on Day 1 (baseline), on Day 6 (drug + placebo drink; baseline and three post-treatment runs), and on Day 7 (drug + alcoholic drink; testing as on Day 6). The tests after treatment were at 2, 4, and 6 h after the maintenance dose. The drinks given on Days 6 and 7 were not randomized. During each period treatment began after baseline testing on Day 1 (Monday afternoon), was continued in the mornings of days 2, 3, 4, and 5, and continued after the baseline run on the actual test days 6 and 7 (Saturday and Sunday). Supervision of administration ensured compliance. Venous blood was sampled during each test run and before drug intake on each day of the maintenance periods.

Drugs

Ebastine (20 mg) and respective placebo were given in gelatine capsules once daily as explained above. Ethyl alcohol ($0.8\ g \cdot kg^{-1}$) diluted (20%) in fruit juice was given on Day 7 of both periods, and the amount of fluid thus given was about $6\ ml \cdot kg^{-1}$. Both alcoholic (Day 7) and non-alcoholic (Day 6) drinks were taken with a light breakfast within 30 min, beginning 30 min after the capsule. No attempt was made to blind the non-alcoholic drink with a drop of alcohol, since the subjects recognize this dose of alcohol from its effects.

Tests

Digit symbol substitution test measures the recognition of sensory information and the ability to concentrate [6]. We used a prolonged test in which the number of symbols correctly substituted in 3 min were recorded. Matched different versions of the test chart were provided for consecutive tests.

Critical flicker fusion threshold refers to cortical arousal state and alertness; it was measured against red flickering light with a battery-driven automatized calculator controlled by the subjects themselves [7]. The distance was 100 cm, the lighting conditions were standard, and pupil size was standardized with special glasses. The fusion frequency recorded was the mean of the measurements upwards and downwards, once each.

The *Maddox wing test* measures the balance of the extraocular muscles, and drug-induced shifts towards exophoria and esophoria (expressed in dioptres) result from altered muscle tone [8].

Body balance was measured with the subjects standing on an electronic platform, with the eyes open and closed, for 30 s each [9]. The variations in body balance in both the lateral and sagittal directions were recorded on paper and the lengths of these lines were measured.

Lateral gaze nystagmus was estimated as the angle in which horizontal nystagmus appeared, with finger perimetry on a graded arch fixed on the subject's forehead [10].

A simulated driving task [11] 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 both halves of the track. The tracking error severity index (TESI) covering the whole track was also computed.

For subjective assessments, *visual analogue scales* [12] were used to quantify the subjective effects of ebastine and ethanol. 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/competent, happy/sad, hostile/friendly, interested/bored, withdrawn/social, and very good/very bad performance. The subjects were also given a *13-item questionnaire* in which they had to tick and score (0–3) various bodily symptoms, filling in the form at the end of each test run.

Pharmacokinetics

Venous blood was drawn into heparinized 10 ml vacuum tubes and centrifuged at 4 °C. The plasma was stored at −20 °C for several weeks until assayed for carebastine [2]. On the test days, the sampling was after each testing round, and also at 1.5 h. 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 HPLC with UV detection for both compounds. The sensitivity limit is $5\ \mu g \cdot l^{-1}$ for the unchanged drug and $20\ \mu g \cdot l^{-1}$ for the metabolite in human plasma. Quality control studies showed that ebastine is stable over 5 months and carebastine over 16 months in human plasma at −20 °C. Multiple-dose kinetics were computed according to Boxenbaum et al. [13].

Blood ethanol concentrations were measured indirectly in the breath with a digital Alcolmeter after each testing run before the blood sampling. For parallel control, direct assay of ethanol in the blood was carried out with the head-space modification of the Alcolmeter [14] at 2.5 and 4.5 h.

Statistics

Mean (SEM) values were computed for absolute test performances and for the Δ-values (changes from respective baselines) at each post-drug testing time. These changes, if significant, represented the responses to the last dose of ebastine or placebo. The significance of these Δ-values vs. zero was evaluated by paired two-tailed Student's t-tests. The contribution by the trial period to those responses was evaluated by comparing the Δ-values of the two periods, irrespective of the drugs given (paired t-test). Since alcoholic and placebo drinks were not randomized between the testing days, the effects of ethanol were primarily 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 × drug), computed to compare the Δ-values for Day 6 and Day 7 during maintenance with placebo. In order to compare placebo with ebastine on Day 6 (drug effects) and on Day 7 (drug-alcohol interactions), repeated measures three-way ANOVA (subject × period × drug) was computed (SAS general linear models) at each post-drug testing time (2, 4, and 6 h). These analyses were used for the objective and subjective data. Data from the questionnaire were analyzed with Fisher's fourfold table test.

Results

The study was carraied out without drop-outs. The clinical chemistry tests were in the reference ranges, except for some borderline values which were interpreted as being normal. The subjects did not report important unwanted

Table 1. Performances in some objective tests during maintenance treatment with ebastine or placebo, on Day 6 (placebo drink) and Day 7 (alcoholic drink). Symbols: a ($P < 0.05$), b ($P < 0.01$), and c ($P < 0.001$) refer to significant differences from baseline; F_D refers to drug effects in three-way ANOVA on Day 6 (placebo vs. ebastine) and on Day 7 (alcohol vs. ebastine + alcohol). F_S and F_P refer to a significant contribution by subject or period to the overall variation in ANOVA. TESI refers to the tracking error severity index. * = $P < 0.05$ in ANOVA. For further details see the text

Test / Treatment	Mean values of performance ($n = 12$)			
	Baseline	2 h	4 h	6 h
Digits substituted/3 min				
Placebo	148	147	144	147
(+ alcohol)	149	131[c]	131[b]	148
Ebastine	152	148	143[a]	150
(+ alcohol)	152	131[c]	133[c]	150
F_D Day 6		0.29	1.26	0.06
F_D Day 7		2.02	0.17	0.26
TESI				
Placebo	22	22	23	21
(+ alcohol)	18	28[a]	29[a]	26
Ebastine	27	27	23	22
(+ alcohol)	22	32[a]	29[a]	28
F_D Day 6		0.35	1.65	1.05
F_D Day 7		0.00 (F_S, F_P)	1.65	0.10
Reaction time (s)				
Placebo	49.3	49.5	49.3	50.4
(+ alcohol)	45.5	51.1[c]	51.0[c]	53.1[a]
Ebastine	49.7	50.5	50.6	49.4
(+ alcohol)	46.8	50.7[a]	50.2[a]	49.4
F_D Day 6		0.46	0.58	0.85
F_D Day 7		10.01 * (F_S, F_P)	2.83	3.47 (F_S)

Table 2. Performances in some objective tests during maintenance treatment with ebastine or placebo, on Day 6 (placebo drink) and Day 7 (alcoholic drink). Body balance refers to the sum of lateral and sagittal sway. For symbols and further details see Table 1 and the text

Test / Treatment	Mean values of performance ($n = 12$)			
	Baseline	2 h	4 h	6 h
Body balance, eyes open				
Placebo	57	60	62	61
(+ alcohol)	72	95[c]	81	69
Ebastine	63	55[a]	61	61
(+ alcohol)	72	91[c]	85[a]	68
F_D Day 6		3.81	7.75* (F_S)	2.02
F_D Day 7		1.10	1.53 (F_S)	0.00
Angle of nystagmus (°)				
Placebo	70	70	70	70
(+ alcohol)	70	52[c]	64[a]	70
Ebastine	70	70	70	70
(+ alcohol)	70	51[c]	64[b]	70
F_D Day 6				
F_D Day 7		0.88 (F_S)	0.04 (F_P)	
Maddox wing (d)				
Placebo	6.1	6.4	5.9	6.3
(+ alcohol)	6.3	6.2	7.5[a]	7.6[a]
Ebastine	6.4	6.2	6.3	6.3
(+ alcohol)	6.4	6.6	6.9	6.5
F_D Day 6		3.33	0.04	0.22
F_D Day 7		0.98 (F_S)	1.65	0.22

effects, except one case of vertigo; vestibular disturbances of viral origin were not uncommon in Helsinki that winter.

Despite ample pretraining, some objective test functions which require skill and motivation improved during the study. The use of Δ-values for analysis reduced but did not abolish the contribution of the treatment sequence to the overall variation. Thus, there were significant ($P < 0.05$) period effects associated with the responses to ethanol on Day 7: errors of complex tracking at 2, 4, and 6 h ($P < 0.01$), reaction times at 2 h ($P < 0.01$), body sway with the eyes closed at 2 h, and nystagmus at 4 h ($P < 0.05$). There were no major improvements in performance within the session when the subjects took placebo.

Ebastine versus placebo

Tables 1 and 2 show some variation in the baseline performances of various objective tests. There were no significant differences between placebo and ebastine, suggesting that ebastine did not impair performance at trough concentrations of carebastine during maintenance. Responses to an additional daily dose were similar with ebastine and placebo in reaction times, tracking (TESI), and cognitive performance (digit substitution), although slightly lower digit substitutions were found after ebastine than after placebo. Ebastine tended to reduce body sway with the eyes open (Table 2), particularly lateral sway, but not when the eyes were closed. Ebastine did not prolong reaction times (Table 1) and it even reduced ($F_D = 7.13$; $P < 0.05$ at 4.5 h) the error severity of simple tracking during the first half of simulated driving. Similar improvement was not seen during the complex second half, the overall error severity index (TESI) remaining unaltered (Table 1).

The only visual analogue scale for which ebastine perhaps differed from placebo was muzziness, which was reduced by ebastine (Table 3). This unexpected difference could have resulted from different baselines, and there was a significant subject effect at each testing time after administration. There was a period effect on the alert/drowsy scale, and particularly clear ($P < 0.01$) subject and period effects on the scale mentally slow/quick-witted.

Effects of ethanol

The first post-treatment test (at 2 h) actually began 1.5 h after having started drinking. The mean concentrations ($g \cdot l^{-1}$) of ethanol in blood estimated indirectly from the breath were 0.76 (17 $mmol \cdot l^{-1}$) at 2 h, 0.50 (11 $mmol \cdot l^{-1}$) at 4 h, and 0.26 (6 $mmol \cdot l^{-1}$) at 6 h. The respective concentrations measured directly in the blood were 0.76 (17 $mmol \cdot l^{-1}$) at 2 h and 0.60 (13 $mmol \cdot l^{-1}$) at 4 h.

Ethanol alone impaired performance in most but not all objective tests at 2 h and 4 h, but only exceptionally (Maddox wing) at 6 h. The changes from the baselines shown in Tables 1 and 2 were confirmed by ANOVA (subject × drug) computed between Day 6 and Day 7 during the placebo period. There were significant effects of etha-

Table 3. Self-assessments on some visual analogue scales during maintenance treatment with ebastine or placebo, on Day 6 (placebo drink) and Day 7 (alcoholic drink). For symbols and more details see Table 1 and the text

Test / Treatment	Mean values of performance ($n = 12$) Baseline	2 h	4 h	6 h
Alert/Drowsy (mm)				
Placebo	59	50	61	62
(+ alcohol)	61	70	79[b]	59
Ebastine	65	56[a]	62	63
(+ alcohol)	60	67	76[b]	63
F_D Day 6		0.00	0.89 (F_P)	1.35
F_D Day 7		0.04	0.18	0.52
Muzzy/Clear-headed (mm)				
Placebo	68	63	56	56
(+ alcohol)	68	26[c]	32[c]	58
Ebastine	62	62	58	55
(+ alcohol)	57	32[b]	37	47[a]
F_D Day 6		3.57 (F_S)	5.79 (F_S)	3.11 (F_S)
F_D Day 7		6.89*	6.69	0.01
Skilful/Clumsy (mm)				
Placebo	43	40	45	47
(+ alcohol)	45	71[b]	70[b]	55[a]
Ebastine	48	46	49[b]	55[a]
(+ alcohol)	50	72[c]	65	47
F_D Day 6		0.02	0.32	0.41
F_D Day 7		0.40	3.90	0.00

nol for TESI ($P < 0.05$) at 2 h and 4 h, reaction times ($P < 0.001$) at 2 h and 4 h, digit substitution ($P < 0.01$) at 2 h, body sway with the eyes open and closed ($P < 0.01$) at 2 h, nystagmus ($P < 0.001$) at 2 and 4 h, and Maddox wing ($P < 0.05$) at 4 h and 6 h. Ethanol did not alter the flicker fusion threshold significantly. Ethanol shifted the ratings on some but not all of the visual analogue scales at 2 h and 4 h but not at 6 h. The effects shown in Table 3 were confirmed by ANOVA, which showed significant ethanol-induced muzziness and clumsiness ($P < 0.01$) at 2 h and 4 h, mental slowness ($P < 0.01$) and poor performance ($P < 0.05$) at 2 h, and drowsiness and weakness ($P < 0.05$) at 4 h.

Ebastine and alcohol

Mean blood concentrations ($g \cdot l^{-1}$) of ethanol measured indirectly from the breath after ebastine + ethanol were 0.87 (19 $mmol \cdot l^{-1}$) at 2 h, 0.55 (12 $mmol \cdot l^{-1}$) at 4 h, and 0.25 (5 $mmol \cdot l^{-1}$) at 6 h. The respective concentrations measured in blood were 0.82 (19 $mmol \cdot l^{-1}$) at 2 h and 0.62 (13 $mmol \cdot l^{-1}$) 4 h. Thus, ebastine did not alter blood ethanol concentrations.

As seen in Tables 1 and 2, ebastine did not enhance the effects of ethanol. The only objective test in which ebastine prolonged the effect of ethanol was the lateral component of body sway with the eyes open, the difference from ethanol alone being significant (F_D 11.09; $P < 0.01$) at 4 h. Ebastine tended to counteract ethanol-induced prolongation of reaction times (Table 1), although the baseline values were different and the individual effects significant. Ebastine did not enhance the subjective effects of ethanol (Table 3). Increased muzziness after ebastine + ethanol was relatively less than after ethanol alone.

Pharmacokinetics of ebastine

Ebastine 20 mg daily resulted in steady-state carebastine trough concentrations ($\mu g \cdot l^{-1}$) from the third day on: 103 (SD 19) on Day 3, 98 (18) on Day 4, 98 (16) on Day 5, 92 (19) on Day 6, and 104 (27) on Day 7. The plasma concentrations of carebastine on the testing days are given in Table 5, and were not significantly different between Days 6 and 7. The values of C_{max}, t_{max}, and AUC of carebastine after the additional dose of ebastine are given in Table 5. The t_{max} values differed significantly ($P < 0.05$; Wilcoxon rank sign test) from each other, while the values of C_{max} and $AUC_{6.5\,h}$ did not.

Adverse effects

Baseline and post-dose sedative complaints were commoner than expected on Day 6 on placebo. This could have happened by chance or could have resulted from the fact that the tests began in the morning after minimum coffee or tea. The baseline values of drowsiness on the analogue scale were slightly higher than those we usually record, this being in line with the questionnaire data.

Symptoms of sedation after placebo were similar to those after ebastine and ethanol. The feeling of unsteadiness after ethanol differed from that recorded after placebo, and the same symptom after ebastine + alcohol differed from that reported after ebastine alone. One subject reported vertigo lasting over several days when on ebastine, but he considered that the symptom had not resulted from drug effect but rather from fasting after the test session.

One subject had slightly increased activities of serum transaminases at the post-trial test with normal values a week later.

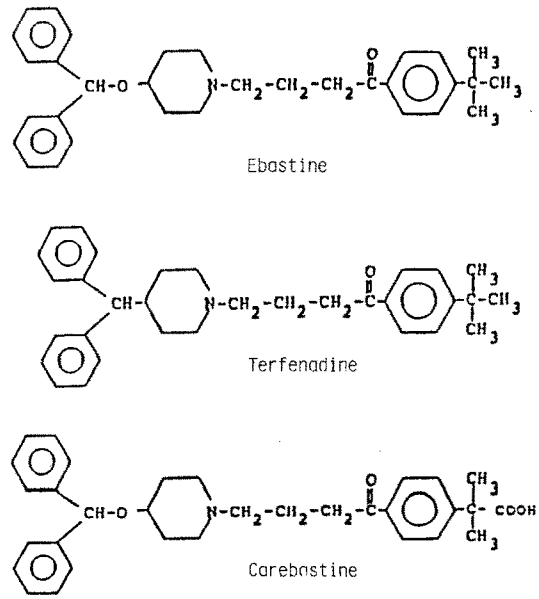

Fig. 1. Structural formulae of ebastine and carebastine, with terfenadine for comparison

Table 4. Bodily symptoms reported by 12 subjects on questionnaire after oral ebastine 20 mg, ethanol 0.8 g·kg^{-1}, and their combination. The numbers of subjects complaining and their total scores (scoring 0–3) are given. Significant differences: [a] $P < 0.01$ vs. placebo and [b] $P < 0.01$ vs. ebastine (Fisher's fourfold table test)

Treatment / Time	Number of subjects reporting various symptoms				
	A	B	C	D	E
Placebo					
0 h	2 (4)	7 (14)	9 (17)	1 (1)	3 (5)
2 h	2 (4)	8 (12)	10 (16)		3 (3)
4 h	5 (10)	5 (9)	8 (14)	1 (1)	5 (6)
6 h	6 (12)	7 (12)	8 (14)	1 (1)	2 (2)
Ebastine					
0 h	1 (1)	10 (18)	10 (17)		3 (4)
2 h	3 (3)	9 (13)	8 (13)		5 (6)
4 h	4 (7)	6 (10)	5 (11)	1 (1)	4 (5)
6 h	6 (11)	6 (10)	7 (13)	1 (1)	3 (4)
Ethanol					
0 h	2 (3)	8 (12)	8 (11)		3 (3)
2 h	2 (3)	10 (17)	10 (17)	9 (20)[a]	3 (7)
4 h	4 (9)	11 (22)	12 (24)	9 (11)[a]	5 (12)
6 h	8 (14)	9 (15)	9 (17)	3 (4)	3 (3)
Ebastine + ethanol					
0 h	1 (3)	7 (13)	6 (13)		4 (6)
2 h	4 (4)	9 (17)	9 (18)	11 (17)[b]	6 (8)
4 h	5 (9)	9 (15)	9 (18)	5 (6)	6 (9)
6 h	7 (13)	6 (10)	8 (15)	2 (2)	4 (5)

A = headaches, heavy-headness B = drowsiness C = tiredness
D = unsteadiness E = thirst, dry mouth

Table 5. Plasma concentrations of carebastine at consecutive testing times on days 6 and 7 of one week of maintenance treatment with ebastine 20 mg daily. Mean (SEM) values ($n = 12$) are given

Time (h)	Plasma carebastine (μg·l^{-1})	
	Day 6	Day 7
Baseline	92 (5.5)	104 (7.7)
1.5	157 (10.2)	154 (9.4)
2.5	216 (14.4)	218 (15.7)
4.5	235 (12.7)	252 (15.8)
6.5	244 (15.6)	223 (16.0)
C_{max}	249.3	249.4

The median t_{max} values were 6.5 (range 4.5–6.5) h on Day 6 and 4.5 (range 2.5–6.5) h on Day 7. The mean $AUC_{6.5\,h}$ values were 1318 h·μg·l^{-1} and 1324 h·μg·l^{-1} respectively

Discussion

This was a randomized double-blind for placebo and ebastine capsules but open and non-randomized for placebo (Day 6) and ethanol (Day 7) drinks. Attempts to blind this dose of ethanol (0.8 g·l^{-1}) are useless because it is easily detected. Randomization of the treatments on Days 6 and 7 was omitted because a residual effect from Day 6 could not have been excluded on Day 7. The design allowed an adequate comparison of ebastine versus placebo, and of ebastine + ethanol versus ethanol alone, and showed that ebastine neither impaired performance nor interacted significantly with ethanol. In fact, ebastine tended to reduce body sway, which could have been due to a mild suppressant effect on the labyrinth.

The design for a comparison of ethanol with placebo was less robust but still feasible. In these circumstances, ethanol proved detrimental in most of the objective tests, without lowering the flicker fusion threshold, and with only a moderate effect on tracking. The lack of significant effect on flicker fusion agress well with the selective lack of drowsiness at the time of peak ethanol concentrations associated with strong effects of ethanol on several other variables.

The central sedative actions of various psychotropic drugs are attributable to their H_1-antihistamine activity, and the presence or absence of sedation after various H_1-antihistamines depends on several factors [15]. Low lipid solubility of the drug reduces and/or slows its penetration into the central nervous system, thus allowing time for tachyphylaxis to develop to the sedative action. This assumption is based on the development of tolerance to sedative antihistamines within a few days [16]. A relatively low affinity for central histamine receptors may be responsible for the non-sedative character of mequitazine, a phenothiazine H_1-antihistamine [17], which none the less has other types of central effects. Individual sensitivity to the central sedative but not the peripheral effects of H_1-antihistamines, unrelated to their plasma concentrations, has been reported, and sedation has been attributed, at least in part, to 5-HT-linked mechanisms [18, 19]. Diphenhydramine impairs performance after the first dose but hardly at all on the fourth day of maintenance, and even its subjective sedative effect is mild [16]. Such acquired tolerance may also work during maintenance administration of long-acting non-sedative antihistamines.

Ebastine resembles terfenadine not only structurally, but also in its lack of objective and subjective impairment after treatment with therapeutic doses for 1 week and in its lack of interaction with alcohol [20]. These compounds have active metabolites which are largely responsible for their H_1-antihistamine effects in peripheral tissues. The lack of central sedation is not an absolute characteristic, and at least subjective sedation may occur after larger than usual doses [3, 21].

Ebastine tended to prolong the effects of ethanol on body sway although it tended to counteract ethanol-induced prolongation of reaction times and muzziness. These effects could be coincidences only, resulting from different baselines and from the light breakfast served when drinking ethanol, which might have contributed to intersubject and interperiod differences.

We conclude that ebastine in the recommended therapeutic doses is a non-sedative H_1-antihistamine which does not enhance the decremental effects of moderate single doses of ethanol.

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