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Lack of interaction between a new antihistamine, mizolastine, and lorazepam on psychomotor performance and memory in healthy volunteers

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1 The possible interaction between a new H_1 antihistamine, mizolastine, and lorazepam was assessed in a randomised, double-blind, cross-over, placebo-controlled study involving 16 healthy young male volunteers who received mizolastine 10 mg or placebo once daily for 8 days with a 1 week wash-out interval. The interaction of mizolastine, at steady-state, with a single oral dose of lorazepam or placebo was assessed on days 6 or 8 of each treatment period.

2 Psychomotor performance and cognitive function were evaluated using objective tests (critical flicker fusion threshold, choice reaction time, tapping, arithmetic calculation, body sway) and self-ratings (visual analogue scale, ARCI) before and at 2, 4, 6 and 8 h after dosing. Short-term memory (Sternberg memory scanning, immediate free recall of a word list) and long-term memory (delayed free recall and recognition of words and pictures) were assessed before and at 3 h after dosing. Pharmacodynamic interactions were evaluated by repeated measures ANOVA in a 2 × 2 factorial interaction model.

3 Mizolastine, 10 mg once daily, at steady-state, was devoid of sedation and detrimental effect on skilled performance and memory.

4 In contrast, a single 2 mg dose of lorazepam produced marked impairment of psychomotor performance, cognitive functions (significant reduction in flicker fusion threshold, tapping and arithmetic calculation and increase in reaction times and body sway) and subjective sedation from 2 to 8 h after dosing. In addition, lorazepam induced an anterograde amnesia, characterised by a decrease in delayed free recall and recognition, and a deficit in short term memory.

5 Mizolastine did not potentiate the detrimental effect of lorazepam. The time course and the intensity of the disruption induced by the combination of lorazepam and mizolastine closely paralleled the changes induced by lorazepam alone.

Keywords mizolastine lorazepam antihistamine benzodiazepine interaction psychomotor performance memory cognitive function psychopharmacology

Introduction

Mizolastine, a new benzimidazole derivative, is a selective, peripherally-acting, histamine H_1-receptor antagonist. It is more potent in several animal models of allergy and asthma than astemizole, loratadine, or terfenadine and seems devoid of sedative effects in animals [1, 2]. Mizolastine in single doses of 2 mg or more in healthy volunteers has antihistaminic activity (histamine challenge), being most effective at 10–20 mg [3–5]. The antihistaminic effects occur within 2 h and lasts for at least 24 h. Mizolastine, at doses of up to 40 mg, is devoid of anticholinergic effects [6]. At doses up to 20 mg, it causes no sedation or

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psychomotor or cognitive impairment [7–9]. In man, mizolastine is absorbed rapidly and has a terminal elimination half-life of about 14 h [10, 11]. There is no major active metabolite.

Combination of benzodiazepines with sedative drugs, such as first generation antihistamines, often leads to an interaction or at least additive detrimental effects. Therefore, this study was designed to detect a possible pharmacodynamic interaction between the therapeutic dose of mizolastine, 10 mg, at steady state, and a single dose of lorazepam 2 mg, the sedative and amnesic properties of which are well documented [12–17].

Methods

Subjects

Sixteen healthy, non-smoking males, aged 21–29 years (24 ± 2 s.d. years), weighing between 57 and 80 kg (69 ± 7 kg) and 169 and 188 cm (176 ± 5 cm) in height were studied. All underwent a full medical examination, an ECG and routine laboratory tests. Each subject gave written informed consent to the study which was approved by the Charente-Poitou Ethics Committee. All medication was prohibited from 2 weeks before and during the study.

Study design and medication

This was a randomised, double-blind, cross-over, placebo-controlled study with two treatment periods of 8 days separated by a wash-out interval of at least 1 week. During each treatment period, the volunteers received either placebo or mizolastine, 10 mg by mouth, for 8 days. The compounds were presented as indistinguishable tablets and administered once daily in the morning between 08.00 and 09.00 h. On days 6 and 8 of each treatment period, a single oral dose of either lorazepam 2 mg or placebo was coadministered with mizolastine or placebo. Lorazepam and placebo were presented as indistinguishable capsules. The treatment was allocated on the basis of a complete balanced block design with two blocks of eight sequences. Two test sessions lasting 10 h were held on days 6 and 8 of each treatment period.

Assessment criteria

Psychomotor performance: Critical flicker fusion (CFF) Subjects were required to discriminate flicker from fusion of a red-light emitting diode held at a viewing distance of 30 cm through a tunnel. Individual thresholds were determined by the psychophysical method of limits using the Biodata Multipsy 801 (Biodata GmbH, Sternbach, Germany). The score was the mean of four ascending and four descending measurements.

Choice reaction time (CRT) Sensory-motor performance was assessed from the CRT, which measures both Motor (MRT) and Recognition Reaction Time (RRT) as well as Total Reaction Time (CRT). The Leeds psychomotor tester was used. Subjects were required to extinguish one of six LED lights, illuminated at random, by touching the appropriate response button. The score recorded was the mean reaction time of 50 stimuli presentations.

Tapping test (TAP) The subject had to tap with the spike of a stylus as quickly as possible for 30 s. The score was the mean number of taps per second.

Arithmetic calculation test The subject was asked to add one-digit numbers as quickly and accurately as possible over a 3 min period. Performance was expressed as the number of correct answers.

Body sway Body sway was recorded using a force-platform. Marks corresponding to the subject's foot size were fixed to the centre of the platform so that the subject's feet could be repositioned accurately to obtain reliable measurements. Subjects were asked to stand erect and motionless, looking at a plumbline placed in front of them. Measurements of body sway (1 min with eyes open and 1 min with eyes closed) were recorded as recommended by the International Society of Posturography [18]. The length and area of the body sway oscillations were then calculated.

Memory: Sternberg memory scanning task The subjects were required to judge whether a test digit (probe) was contained within a short sequence of previously presented memorized digits (stimulus set) using a two-button yes/no choice response box. The stimulus set consisted of short sequences of 2, 4 or 6 digits and 120 probes were made. The mean response time was recorded.

Picture test Twelve images were presented to the subjects at the rate of one image every 10 s and they were then instructed to name the picture as soon as it was displayed and to devise a story involving the pictures. One hour later, the subjects were requested to recall as many of the pictures as they could remember within 2 min and then recognize them within 12 distractors of the same semantic category. The composition of the picture set was validated in terms of frequency and affective load, which was equivalent between sets. The correct answers in delayed free recall and recognition were analysed.

Buschke selective reminding test [19, 20] This test consists of the presentation of a list of 16 words. Equivalent lists were constructed using words selected according their degree of concreteness, imagery and meaning [21]. The entire list was read to the subject at a rate of one word every 2 s. Following the presentation of the 16-item list, the subject was asked to recall as many nouns as possible in any order during 1 min (immediate free recall). If the subject failed to recall some of the items, he was selectively reminded of only those items missed on the previous trial. This process was repeated until 10 trials had elapsed. The test was administered to the subject 3 h after dosing. Delayed free recall was then assessed 3 h after learning the list (i.e. 6 h after dosing). The measured scores were for immediate and delayed free recall.

Subjective assessment: Visual analogue scales (VAS) The subject's mood was self-rated on 16 bipolar

analogue scales with opposite mood related adjectives at each end. A principal component analysis of these scales provided three factors: alertness, contentedness and calmness [22].

ARCI This is a 49-item questionnaire, which is a shortened version of the original Addiction Research Center Inventory [23, 24]. It can be used to calculate three scores: the pentobarbitone-chlorpromazine-alcohol group (PCAG), assessing sedation; the morphine-benzedrine group (MBG), assessing euphoria and the LSD group (LSD), exploring somatic and dysphoric effects of drugs.

Study procedure

Psychometric tests, visual analogue scales and body sway were carried out before (baseline) and at 2, 3 (CFF only), 4, 6 and 8 h after dose. The Sternberg memory scanning test and the picture test were done before and at 3 h after dosing. The Buschke selective reminding test was performed 3 h after dosing. Finally, ARCI was done before and at 4 h after dosing.

Spontaneous adverse events were recorded throughout each treatment period. Blood samples were collected before dosage on days 1, 5, 6, 7 and 8 and 3 h after dosage on days 6 and 8 of each treatment period. Mizolastine was assayed using an h.p.l.c. method with u.v. detection with a limit of determination of 2.5 ng ml^{-1} [25] and lorazepam was assayed by GC with electron capture detection with a limit of determination of 1 ng ml^{-1} [26].

Subjects abstained from drinking xanthine-containing beverages or alcohol from 24 h before and throughout the period of the assessment.

All subjects were trained before entering the trial in order to familiarize them with the experimental tasks and to minimise any learning effects.

Statistical analysis

The possible pharmacodynamic interaction was evaluated by repeated measures analysis of variance in a 2 × 2 factorial interaction model [27]. The ANOVA model included subject, period, treatment and carry over. When the carry-over and period effects and their interactions with time were not significant, they were deleted from the model. Body sway was analysed after log transformation. The treatment effect was partitioned into four levels (placebo, mizolastine, lorazepam, mizolastine + lorazepam) and orthogonal contrasts were computed in order to test main drug effects and interactions with a fixed α level of 5%. For the mizolastine and lorazepam interaction, pairwise comparisons were tested using the Student Newman Keuls procedure.

Results

There were no significant differences between the baseline values before dosing for the four sessions (on days 6 or 8 of each treatment period), except for

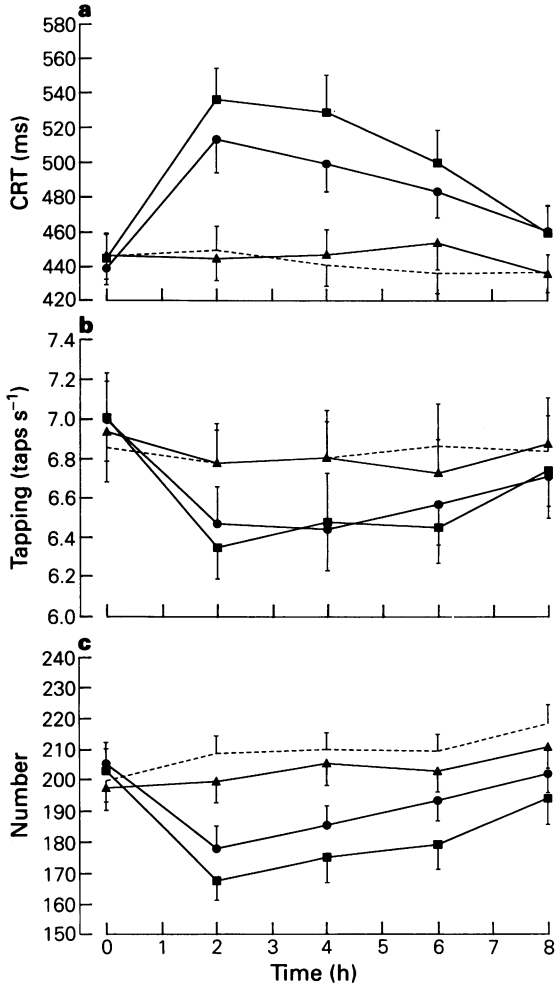

Figure 1 Effects of multiple doses of mizolastine, 10 mg, alone or combined with a single dose of lorazepam, 2 mg, on psychomotor performance assessed by a) choice reaction time (total reaction time), b) tapping and c) arithmetic calculation in 16 healthy young volunteers. Bars indicate s.e. mean. - - - placebo, ▲ mizolastine 10 mg, ● lorazepam 2 mg, ■ mizolastine 10 mg + lorazepam 2 mg.

arithmetic calculation, where performance was significantly lower before mizolastine alone than before placebo alone. In addition, there was no significant carry-over effect. Results from all three CRT measures (total, recognition and motor times) were similar and, therefore, only total reaction time is presented.

Psychomotor performance and information processing

At steady state, mizolastine did not significantly impair the CFF threshold ($P = 0.66$), CRT ($P = 0.20$), tapping ($P = 0.55$), body sway area with eyes open ($P = 0.36$) or eyes closed ($P = 0.80$) at any time in comparison with placebo (Figure 1). The only significant change was a slighly lower score in arithmetic calculation ($P = 0.01$). Pairwise comparisons indicated that performance after mizolastine was significantly lower than after placebo only at 8 h after dose, but was also significantly better than after lorazepam. In addition, this score never decreased from baseline.

In contrast, lorazepam had significant detrimental effects on psychomotor performance and cognitive functions : a decrease in CFF from 2 to 6 h ($P < 0.01$), increase in reaction times (total, recognition and motor) from 2 to 8 h ($P < 0.01$), reduction of tapping rate from 2 to 6 h ($P < 0.01$), augmentation of body sway areas both with eyes closed and with eyes open from 2 to 8 h ($P < 0.01$) and impaired arithmetic calculation from 2 to 8 h after dosing ($P < 0.01$) in comparison with placebo (Figure 1). Pairwise comparisons also showed that lorazepam differed significantly from mizolastine in impairing CFF at 2 and 6 h, CRT from 2 to 4 h, tapping from 2 to 4 h, body sway from 2 to 8 h and arithmetic calculation at 2, 4 and 8 h after dosing.

Finally, the combination of mizolastine and lorazepam caused a similar decrease in psychomotor performance to lorazepam alone. The magnitude of these effects and their time-course were similar in tests carried out after lorazepam alone or after mizolastine + lorazepam. Thus, no significant interaction, i.e. potentiation of the disruptive effects of lorazepam, was detected on CFF ($P = 0.70$), CRT ($P = 0.44$), tapping ($P = 0.90$), body sway ($P = 0.33$ eyes closed and $P = 0.34$ eyes open) or arithmetic calculation ($P = 0.48$) (Figure 1).

Memory

Mizolastine, at steady state, had no discernible effect on memory scanning ($P = 0.10$), immediate free recall of words ($P = 0.56$), delayed free recall of words ($P = 0.82$) or pictures ($P = 0.91$) and picture recognition ($P = 0.44$) (Table 1).

In contrast, lorazepam caused a profound disruption of short-term memory, as shown by a significant increase in memory scanning reaction time ($P < 0.01$) and reduction in immediate free recall of words ($P < 0.01$). Lorazepam also caused an anterograde amnesia characterised by a significant decrease in delayed free recall of words ($P < 0.01$) and pictures ($P < 0.01$) without effect on recognition ($P = 0.42$) (Table 1). Thus, lorazepam produced significant memory deficits on all parameters in comparison with placebo and mizolastine.

The combination of lorazepam and mizolastine produced similar effect to lorazepam alone. There was no significant interaction between lorazepam and mizolastine in memory scanning ($P = 0.57$), immediate free recall of words ($P = 0.56$), delayed free recall of words ($P = 0.08$) and pictures ($P = 0.57$) or recognition of pictures ($P = 0.61$) (Table 1).

Subjective assessment

Mizolastine did not significantly change the self-rating of alertness ($P = 0.06$), contentedness ($P = 0.11$) or calmness ($P = 0.94$) at any time during the test day. In addition, mizolastine did not significantly modify the PCAG ($P = 0.88$), MBG ($P = 0.75$) or the LSD ($P = 0.23$) scores of the ARCI at 4 h after dosing (Figure 2, Table 2).

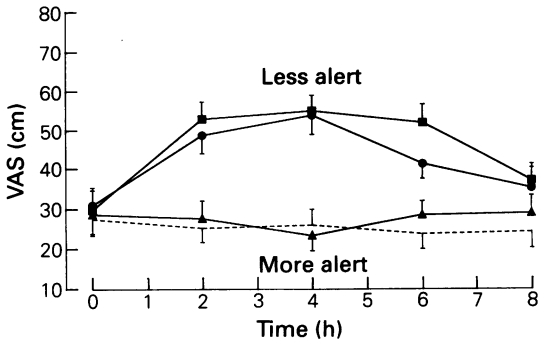

Figure 2 Effects of multiple doses of mizolastine, 10 mg, alone or combined with a single dose of lorazepam, 2 mg, on the alertness score of visual analogue scales in 16 healthy young volunteers. Bars indicate s.e. mean. - - - placebo, ▲ mizolastine 10 mg, ● lorazepam 2 mg, ■ mizolastine 10 mg + lorazepam 2 mg.

Table 1 Effects of multiple doses of mizolastine 10 mg alone and combined with a single dose of lorazepam 2 mg on memory tests in 16 healthy young subjects: the Sternberg memory scanning and the picture tests were performed before and 3 h after dose and the Buschke selective reminding test, only at 3 h after dose. The results are expressed as mean ± s.d.

Parameter	*Time of learning*	*Placebo*	*Mizolastine*	*Lorazepam*	*Mizolastine + lorazepam*
Picture test					
Delayed free recall (N*)	Baseline	10.4 ± 1.6	10.1 ± 1.8	10.1 ± 2.3	10.5 ± 1.4
	3 h post-dose	8.8 ± 2.6	9.2 ± 2.3	3.2 ± 3.7[1,2]	3.0 ± 3.1[1,2]
Recognition (N*)	Baseline	11.8 ± 0.4	11.8 ± 0.4	11.0 ± 0.3	11.8 ± 0.4
	3 h post-dose	11.7 ± 0.4	11.7 ± 0.6	11.1 ± 1.1	10.8 ± 1.7
Sternberg memory scanning					
Mean reaction time (ms)	Baseline	754.8 ± 152.3	781.1 ± 142.1	716.1 ± 172.7	808.7 ± 138.6
	3 h post-dose	740.2 ± 113.3	822.5 ± 145.5	1009.8 ± 276.7[1,2]	1136.2 ± 223.4[1,2]
Buschke selective reminding test					
Immediate free recall (first recall) (N*)		7.6 ± 2.7	7.1 ± 1.9	4.7 ± 1.6[1,2]	4.7 ± 2.0[1,2]
Immediate free recall (sum of the correct answers for the 10 trials)		135.6 ± 15.0	131.9 ± 17.4	103.7 ± 24.2[1,2]	99.6 ± 27.7[1,2]
Delayed free recall (N*)		12.7 ± 4.1	13.4 ± 3.2	9.5 ± 5.5[1,2]	8.4 ± 5.9[1,2]

N*: number of correct answers.
The confidence limits on differences between treatments can be supplied on request. [1] = Significant difference between drug treatment and placebo at $P < 0.01$. [2] = Significant difference between drug treatment and mizolastine at $P < 0.01$.

Table 2 Effects of multiple doses of mizolastine, 10 mg, alone and combined with a single dose of lorazepam, 2 mg, on the ARCI questionnaire in 16 healthy young volunteers. The results are expressed as mean ± s.d. The PCAG score explores sedation, MBG euphoria and LSD dysphoric effects. The results are expressed as mean ± s.d.

	Time	*Placebo*	*Mizolastine*	*Lorazepam*	*Mizolastine + lorazepam*
PCAG	baseline	−1.4 ± 1.3	−1.7 ± 1.8	−1.2 ± 1.8	−0.7 ± 2.4
score	4 h post-dose	−1.4 ± 1.7	−1.6 ± 1.4	5.5 ± 2.5[1,2]	5.9 ± 2.5[1,2]
MBG	baseline	2.3 ± 2.4	1.9 ± 2.6	1.5 ± 1.5	1.7 ± 1.9
score	4 h post-dose	2.3 ± 2.9	1.9 ± 2.9	0.9 ± 1.5	1.1 ± 1.6
LSD	baseline	−1.7 ± 0.8	−1.5 ± 0.6	−1.4 ± 0.6	−1.6 ± 1.4
score	4 h post-dose	−1.9 ± 1.0	−1.6 ± 0.8	−0.2 ± 1.6[1,2]	0.2 ± 2.0[1,2]

The confidence limits on differences between treatments can be supplied on request. [1] = Significant difference between drug treatment and placebo at $P < 0.01$. [2] = Significant difference between drug treatment and mizolastine at $P < 0.01$.

In contrast, lorazepam caused a significant decrease in subjective alertness from 2 to 8 h ($P < 0.01$), in contentedness at 4 h ($P < 0.01$) and significantly altered the PCAG and LSD scores at 4 h after dosing ($p < 0.01$) in comparison with placebo and mizolastine. It did not change the degree of calmness ($P = 0.23$) or the MBG score ($P = 0.05$) (Figure 2, Table 2).

The combination of lorazepam and mizolastine induced similar changes to lorazepam alone in alertness and contentedness and in the PCAG and LSD scores. However, 6 h after dose, mizolastine and lorazepam induced a more pronounced feeling of subjective sedation on the alertness score than lorazepam alone. No significant interaction occurred between lorazepam and mizolastine with respect to subjective alertness ($P = 0.55$), contentedness ($P = 0.61$) or calmness ($P = 0.79$), or in scores for PCAG ($P = 0.84$), MBG ($P = 0.53$) or LSD ($P = 0.55$) of the ARCI (Figure 2, Table 2).

Safety

No subject dropped out due to adverse events. The number of subjects complaining of at least one emergent adverse event was comparable after mizolastine ($n = 3$) and placebo ($n = 3$) and after lorazepam ($n = 16$) and mizolastine + lorazepam ($n = 15$). Three adverse events were reported after placebo (1 drowsiness) and four after mizolastine (1 drowsiness). In contrast, lorazepam caused 32 adverse events (17 drowsiness/asthenia and 4 dizziness/gait abnormal) and 27 adverse events were observed after mizolastine + lorazepam (16 drowsiness/asthenia and 5 dizziness/gait abnormal). These events were clearly related to the administration of lorazepam.

Plasma drug concentrations

Steady state plasma concentrations of mizolastine were reached on day 5. There was no significant change in the mean values before dosing between day 5 and day 8: 11.9 ± 7.0 s.d. ng ml^{-1} on day 5, 12.6 ± 7.2 on day 6, 14.5 ± 6.8 on day 7, and 13.7 ± 7.5 on day 8. Measurements of plasma mizolastine and lorazepam concentrations at 3 h after dosing on days 6 and 8 of each treatment period did not suggest any pharmacokinetic interaction. Mean plasma mizolastine concentrations ranged from 220 ± 56 s.d. ng ml^{-1} after mizolastine alone and 231 ± 45 ng ml^{-1} after mizo-lastine plus lorazepam. Plasma lorazepam concentrations were 17.8 ± 4.5 s.d. ng ml^{-1} after lorazepam alone and 18.7 ± 5.8 ng ml^{-1} after lorazepam plus mizolastine.

Discussion

A single 2 mg oral dose of lorazepam caused pronounced disruptive effects on psychomotor performance and cognitive functions: reduction in CNS arousal (CFF), decrease in motor activity (tapping) and lengthening of response times (total, recognition and motor reaction times, Sternberg memory scanning), disturbances of balance (increase in body sway area and length) and decrease in information processing (fewer correct mental arithmetic responses). Subjective sedation was also experienced by the volunteers throughout the test day, on the alertness score of the visual analogue scales and on the PCAG score of the ARCI. The deficit in psychomotor skills peaked 2 to 4 h after dosing and was persistent, being present at the last determination, 8 h post-dosing, for some of the tests used. Similar impairment had already been demonstrated up to 12 h post-dose [12, 13, 15–17, 28]. Lorazepam also impaired short-term memory, as demonstrated by the decrease in the number of words correctly remembered after the first immediate free recall or throughout the 10 learning trials and by the increase in the reaction time recorded in the Sternberg memory scanning test. This was partly related to the marked sedative properties of that drug. Finally, lorazepam greatly impaired ability to learn new information in episodic memory, resulting in profound anterograde amnesia, which was characterised by the reduction in delayed free recall and recognition of words or pictures learned 3 h following lorazepam administration. The present results are consistent with published data demonstrating a similar time-course of the psychomotor, cognitive and amnesic effects of lorazepam after oral administration [14–16, 29–31].

In contrast, in the present study, the recommended therapeutic dose (10 mg) of mizolastine was shown at steady state not to cause impairment of attention,

psychomotor performance, memory and subjective drowsiness in comparison with placebo. In arithmetic calculation, the number of correct answers was significantly lower 8 h post-dose after mizolastine (mean ± s.d. = 210.6 ± 27.6) than after placebo (218.3 ± 24.2). However, the mental arithmetic performance never declined during the test day, and even improved over time after mizolastine as after placebo indicating the absence of any clinically relevant detrimental effect (baseline value 199.9 ± 28.1 and 197.4 ± 29.3). This performance decreased significantly to a larger extent from 2 to 8 h after lorazepam and after the combination of mizolastine and lorazepam in comparison with placebo, but also to mizolastine.

The present results are consistent with earlier findings in healthy young and elderly volunteers indicating that single oral doses of mizolastine up to 15 mg do not impair skilled performance, cognitive functions and driving or produce subjective sedation [7–9, 32]. The lowest sedative dose was 20 mg as determined by changes occurring in saccadic eyes movements, critical flicker fusion threshold, choice reaction time, divided attention task and driving [8, 9]. The time of onset of the sedative effect at doses greater than 15 mg (20, 40 and 45 mg) was longer than that of the antihistamine effect determined by skin tests, suggesting that the drug crosses the blood-brain barrier slowly. This sedation occurred between 3 and 8 h after dosing (with a peak effect at approximately 4 to 5 h) and was not associated with memory loss [7, 9]. The lack of sedative activity observed under these experimental conditions at the effective therapeutic dose (10 mg), and the delayed CNS effect of mizolastine at higher doses may be explained by its relatively low lipophilicity, its higher affinity and specificity for histamine H_1-receptors than the earlier antihistamines and an absence of antiadrenergic, anticholinergic or antiserotoninergic activity. These results are also consistent with those observed with second generation histamine H_1-receptor antagonists. In single-dose studies the incidence of somnolence and impairment of CNS function associated with recommended daily doses of most of the second generation H_1-receptor antagonists was similar to that produced by placebo and was significantly lower than that produced by first generation antihistamines [33]. However, these newer antihistamines penetrate the brain slowly and may cause sedation and CNS dysfunction. This occurs frequently at doses just above the recommended ones, as shown for terfenadine 240 mg [34, 35], cetirizine 20 mg [36, 37] and loratidine 40 mg [35, 38, 39]. Some studies have reported slight impairment of some measurements at therapeutic dose [36, 39, 40–42]. However the therapeutic ratio for sedation of these new antihistamines is much greater than that of the older compounds [33].

The combination of mizolastine, 10 mg at steady state, and a single oral dose of 2 mg lorazepam did not potentiate significantly the detrimental sedative and amnesic effects of lorazepam. The decrements observed after lorazepam alone and after mizolastine combined with lorazepam were similar in extent and in duration. Plasma concentrations of both mizolastine and lorazepam (C_{min} and $C3$ h) were also similar whether the drugs were administered alone or combined.

There are few reports of antihistamine-benzodiazepine interactions. Moser *et al.* [43] studied the time-course of effects, up to 4 h after dosing, of a single oral dose of terfenadine 120 mg (twice the therapeutic dose) and diphenhydramine 100 mg combined with a single oral dose of diazepam 10 mg. Terfenadine did not modify the effects of diazepam. In contrast, diphenhydramine combined with diazepam showed additive impairment of performance. Mattila *et al.* [44] assessed the time-course of effects, up to 3 h after dosing, of telemastine (100 mg twice daily) and diphenhydramine (50 mg twice daily) administered orally for 5 days and combined, on day 5, with a single oral dose of 0.3 mg kg^{-1} of diazepam. No additive effect with diazepam was found for either antihistamine. One explanation for this lack of additive effect, in particular with the older antihistamine diphenhydramine, is the development of tolerance after multiple doses. Mattila *et al.* [45] also evaluated the effects, up to 6.5 h, of repeated doses of ebastine (20 mg for 7 days) and a single dose of diazepam 15 mg. Ebastine had no effect on plasma diazepam concentrations and did not increase diazepam-induced psychomotor impairment. In all of these studies, the benzodiazepine anxiolytic was diazepam. However, diazepam induces short-lasting detrimental effects, which peak between 30 min to 1 h and disappear within 3 h after dosing [29, 46–48]. The failure to detect additive effects or potentiation with diazepam could, therefore, be explained by a dissociation between the time-course of the CNS effects of diazepam and that of the new antihistamines, and by the short duration of the assessment session.

In the present study, assessment was continued up to 8 h after dosing, and lorazepam was used as the benzodiazepine because of its long-lasting disrupting effects on performance.

It can be concluded from the present study that treatment with a therapeutic dose of mizolastine (10 mg daily) for 8 days had minimal or no effect on human performance and memory, and did not interact to any great extent with a single oral dose of 2 mg lorazepam.

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