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PHARMACODYNAMICS

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Effects of mizolastine and clemastine on actual driving and psychomotor performance in healthy volunteers

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Abstract The acute effect of doses of mizolastine 5, 10, 20 and 40 mg, an active control (clemastine 2 mg) and placebo on actual car driving and psychomotor performance have been compared. Twenty four healthy volunteers were treated according to a double-blind, 6-way cross-over design. In the driving test, lasting about 1 h, lateral position control and speed were continuously measured; the psychomotor test battery, lasting 50 min, comprised critical flicker-fusion frequency, critical instability tracking, divided attention, memory search and choice reaction time, and vigilance studies; and mood changes and possible adverse-effects were rated on visual analogue scales.

The results showed a dose-response relationship: mizolastine 40 and 20 mg impaired driving and psychomotor performance. The effect of mizolastine 40 mg on driving was strongly correlated with that of clemastine ($r = 0.78$) and was comparable to the effect of a blood ethanol level of 0.8 mg · ml^{-1}. Mizolastine 5 mg and 10 mg did not have a significant effect on driving performance and psychomotor tests.

It was concluded that at a 10 mg dose of mizolastine, the therapeutic dose, it could be considered a safe antihistamine, although individual adverse reactions cannot be completely ruled out.

Key words Mizolastine, Psychomotor performance; clemastine, driving

Initial claims that second generation antihistamines are fundamentally "non-sedating" have been questioned in several studies [1]. It now appears that the newer antihistamines also have sedative properties, which begin to affect performance after single or multiple doses lying within or just above their therapeutic ranges [2]. Studies aimed at defining the performance impairing properties of newer antihistamines should focus on the dose-effect relationship rather than simply measuring the effects of a single dose.

Mizolastine is a new benzimidazole derative which has the clinical profile of an antihistamine drug (Fig. 1).

It is a potent and selective H_1-receptor antagonist. It shows rapid absorption, with a t_{max} of about 1 h and a elimination $t_{1/2}$ of about 14 h, independent of the administered dose [3]. The inhibition of the histamine-induced wheal and flare reaction was maximal within 2 h after doses of 10 mg or higher [3]; mean flare inhibition was 30 % at 24 h post- dosing. Like other second generation antihistamines, mizolastine is highly polar at a physiological pH and slowly penetrates the blood brain barrier as a consequence. It should, therefore, produce little sedative activity when taken in the therapeutic dose of 10 mg once daily.

In the present study the behavioural effects of four doses of mizolastine were evaluated and compared to those of a reference drug, clemastine 2 mg, and placebo, employing a driving test and standard psychometric laboratory tests. The former was developed by O'Hanlon and colleagues [4] and has proven to be a reliable and very sensitive test, which can reveal mild impairing effects of the usual dose of cetirizine (10 mg o. d.) and twice the usual doses of loratadine both (20 mg o. d.) and terfenadine (120 mg b. i. d.) [5].

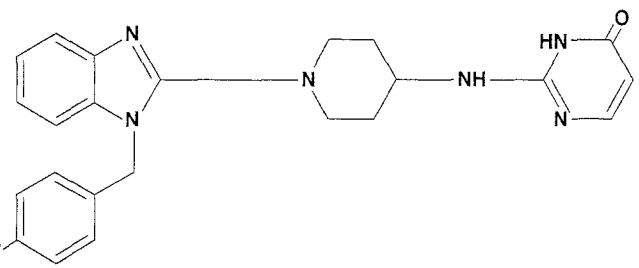

Fig. 1 Chemical structure of mizolastine

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Subjects and methods

Subjects

Twenty four healthy volunteers (12 men and 12 women) aged 21–39 (mean 26.1 (SD 4.4) y), of normal height range (mean 175.9 (SD 10.3) cm) and weight (mean 66.8 (SD 8.7) kg) participated in the study. They were recruited via advertisements in local newspapers and were paid for their participation. All held a driver's licence, and had driven their own vehicles for at least 8000 km per year during each of the preceding three years. Subjects underwent medical screening before entry in the trial, including blood chemistry and haematology tests, and 12-lead ECG recording. Approval was obtained from the Medical Ethics Committee of the University of Limburg. All subjects gave written informed consent.

Design

The study was conducted according to a 6-way, double-blind, placebo and active drug controlled cross-over design. Drugs and placebo were administered in single oral doses: mizolastine 5 mg (M5), 10 mg (M10), 20 mg (M20), 40 mg (M40), clemastine 2 mg (CLM) and placebo (PLA). Treatment order was balanced in a Latin Square design. Subjects were individually trained on the psychometric tests to be used until they reached a stable performance level, and they undertook a "dress rehearsal" of the standard driving test prior to the first treatment. Drugs and placebo were taken 8 h after the last meal, and always at the same time for each subject. An interval of at least one week separated successive treatments for each subject. Test sessions began between 08:30 and 10:00 am with administration of the psychometric test battery, including subjective scales and questionnaires to establish baseline values. Subjects then ingested drug or placebo in identical appearing capsules. This was followed by the first repetition of the test battery after 2.00–3.00 h, the driving test after 3.45–4.45 h and second repetition of the psychometric tests after 5.30–6.30 h post-dosing. The scheduling of the driving test was such that it occurred within the period when the effect of mizolastine 40 mg on performance had been maximal in a pilot study. The time of testing was kept constant for each subject over the study. On test days all subjects were served standardized meals and caffeine-free beverages. Smoking was allowed until 30 min before any of the tests.

Driving test

The standard driving test has been fully described in numerous publications [6, 7]. As usual, the subject's task was to operate a specially instrumented Volvo estate car over a 100 km primary highway circuit at a constant speed (95 km · h^{-1}) and keeping a steady lateral position between the delineated boundaries of the right (slower) traffic lane. A licensed driving instructor was seated in the front passenger seat and monitored the subject's performance. He had access to duplicate vehicle controls to intervene if necessary. Standard deviation of lateral position (SDLP), an index of "weaving" amplitude, was the primary measure of driving performance.

Psychometric tests

Subjects performed all psychometric tests at the Institute for Human Psychopharmacology in an isolation chamber specially constructed for this purpose. The following tests were administered in the order given:

Critical fusion frequency test (CFF, 6 min)

CFF [8] was tested employing a combination of the psychophysical Method of Limits and Successive Approximation in a computer controlled system. The subject was seated looking into a visual tunnel that displayed a bisected, circular, white light source in Maxwellian perspective. The pupillary diameter was not measured or controlled in this version of the test. To begin, the computer alternately increased and decreased the flicker frequency (1:1 light/dark ratio) in the left hemisphere of the source, keeping the right hemisphere constant as a standard reference. The subject responded by pressing separate buttons whenever his perception changed from one state to the other. Three complete cycles yielded an approximate value of the subject's CFF according to the Method of Limits. At this point, the program identified five frequencies 1 Hz apart, two below , two above and one at the suspected threshold frequency. Each stimulus was shown 5 times in separate, randomized presentations lasting 3 s apiece. The subject was instructed not to respond during the presentation period and then to give one of two responses indicating the perception of flicker or fusion. The proportions of each type of response were used to calculate intersecting linear functions in the frequency domain. The equal probability point where the functions intersected was defined the CFF, with an accuracy of 0.2 Hz.

Sustained attention or vigilance test (VIG, 11 min)

The vigilance test [9] involved rapid serial discriminations between visually degraded images of numerical signals ("0") and non-signals ("2",3",5",6",8",9"). Stimuli lasting 34 ms were shown at the rate of one every 2 s. A trial contained 160 signals and 488 non-signals in random order. The subjects depressed a button each time when they believed the stimulus had been a signal. Correct and false detections were transformed into A'_v,a measure of perceptual discriminability, according to the formula of Pollack and Norman [10].

Critical tracking test (CTT, 5 min)

This test [11] measured the subject's ability to control a displayed error signal, using a joystick in a first-order compensatory tracking task. Error was shown as horizontal deviation of a cursor from the midpoint of a linear scale. As the task progressed, the velocity of the cursor's deviation increased and the subject was required to make compensatory movements with a progressively higher frequency. Eventually the response frequency lagged the error signal by 180°. At that point the subject's response added to rather than subtracted from the error and control was lost. The frequency at which control loss occurred is defined as the "critical frequency" or λ_c. The subject performed this test in five trials on each occasion, and the median λ_c was recorded as the final score.

Divided attention test (DAT, 12 min)

This test [12] measured the ability of the subject to perform two tasks simultaneously. The first subtask was identical to the CTT except that the error signal velocity was fixed at a constant level, 50 % of that which was just controllable by the particular subject. The absolute mean tracking error over the entire test was taken as the first subtask score. The second subtest was that of monitoring 24 LED displays fixed in 2 × 3 clusters at every corner of the main display. The displays presented the numerals 0–9, which changed asynchronously every 5 s. The subject reacted with one foot on a pedal switch after detecting the presence of the target numeral "2". Inter-target times varied randomly between 5 and 25 s. Mean reaction time was recorded as the second subtask score.

Choice reaction time (CRT, 12 min)

This test was based on Sternberg's [13] memory search paradigm. Each trial was divided in three blocks. The subject was shown sets of 1, 2 or 4 letters at the beginning of each block and was told to memorize them.After the presentation of each set, he was shown a series of 90 letters, presented at intervals of 2 s. The subject responded as quickly as possible by pressing a push-button if the letter presented belonged to the memorized set. The presented letters comprised equal numbers of members and non-members of the memory set, in random order. Average reaction time for correct responses was recorded as the performance measure.

Subjective assessments

Mood (5 min)

Mood was assessed using the Bond and Laders [14] series of visual analogue scales. The authors recommended procedure was followed for deriving three independent mood scores: Alertness, Contentedness and Calmness.

Subjective feelings (VAS, 5 min)

Feelings related to possible drug adverse-effects were measured on 10 cm visual analogue scales indicating the presence and severity of drowsiness, weakness, headache, fatigue, nervousness, nausea, dizziness and memory disturbances. These were bounded by the descriptive terms "absent" and "intolerable".

Statistical analysis

Analysis of each dependant variable was done in the same way. First, the effects of placebo and the active control, clemastine 2 mg, were compared to establish the sensitivity of the particular test for impairment caused by antihistamine drugs. This was done by repeated-measures analysis of variance (ANOVA). Second, a multivariate analysis of variance (MANOVA) was applied to determine whether any overall significant ($P < 0.05$) difference existed between the effects of all doses of mizolastine and placebo. A final step involved separate mizolastine dose-placebo comparisons by successive applications of repeated-measures ANOVA, using a pooled error variance term as common denominator for all F-tests in the series. The criterion P-value for statistical significance was adjusted for multiple comparisons, according to the sequential Bonferoni (Bonferoni-Hölm) adjustment [15]. Adverse effects were analysed using non-parametric procedures, as the data were skewed. All initial tests involved gender as a between-group factor. If this factor was not significant, subsequent analyses treated the subjects as a homogenous group. All analysis were conducted with the SPSS/PC + statistical program series.

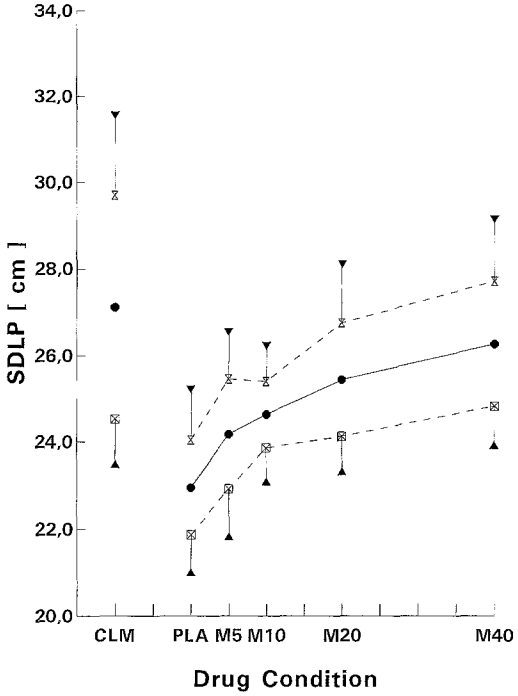

Fig. 2 Mean scores with SEM of Standard Deviation of Lateral Position (*SDLP*) after treatment with clemastine 2 mg (*CLM*), placebo (*PLA*), mizolastine 5 mg (*M5*), mizolastine 10 mg (*M10*), mizolastine 20 mg (*M20*) and mizolastine 40 mg (*M40*). Scores are given for females (⧖ $n = 12$) males (⊠ , $n = 12$), and both groups combined (● , $n = 24$)

Results

Driving performance

Mean SDLP for males and females and the group as a whole varied between conditions, as shown in Fig. 2. The average SDLP of the group was highest after clemastine 2 mg and lowest after placebo, indicating that the worst and best driving performances occurred in the appropriate circumstances. Average SDLP varied between these extremes as a monotonic function of mizolastine dose. The major findings were a significant difference in SDLP between CLM and PLA ($F_{1,22} = 19.2$; $P < 0.001$), and an overall difference between mizolastine and PLA ($F_{4,19} = 7.80$; $P = 0.001$). Separate mizolastine dose – placebo comparisons revealed that the latter was due to the 40 mg and 20 mg doses ($F_{1,88} = 16.7$ and 9.65; $P < 0.001$ and $P = 0.003$ respectively). The lower doses of mizolastine 10 mg and 5 mg had no significant effects on SDLP relative to placebo when judged in relation to the adjusted P_α criteria ($F_{1,88} = 4.43$; $P = 0.038$; $P_\alpha = 0.025$ and $F_{1,88} = 2.63$; $P = 0.108$; $P_\alpha = 0.05$ respectively). Gender was significant in the CLM-PLA comparison ($F_{1,22} = 5.00$; $P = 0.036$) and was almost significant in the overall mizolastine – placebo comparison ($F_{1,22} = 4.07$; $P = 0.056$). However, no significant interactions of Gender with Clemastine ($F_{1,22} = 3.07$; $P = 0.094$) or Mizolastine ($F_{4,19} = 0.63$; $P = 0.648$) was found.

Psychometric tests

There was no significant mean difference between the performance of men and women on any psychometric test. All data were analysed as changes from pre-drug baseline score. The baseline scores were equal for all conditions in each of the tests employed.

CFF

Mean CFF in all conditions is shown in Fig. 3. A significant effect of clemastine was found in the first test ($F_{1,23} = 4.67$; $P = 0.041$) and separate dose-placebo comparisons showed that mizolastine 40 mg and 20 mg caused a drop in CFF relative to placebo in the first test. ($F_{1,92} = 8.43$; $P = 0.005$ and $F_{1,92} = 6.53$; $P = 0.012$).

CTT

Changes in mean CTT performance are summarized in Fig. 4. Changes in λ_c were significant in both the first and second test, after clemastine ($F_{1,23} = 17.21$ and 6.99; $P < 0.001$ and $P = 0.014$ respectively). Separate dose-placebo comparisons showed that M40 had a significant effect relative to PLA in the first test ($F_{1,92} = 35.05$; $P < 001$).

DAT

The performance measures from the two subtasks were analyzed separately. Figure 5 a shows mean changes in tracking error. Clemastine impaired tracking performance in both the first and second test ($F_{1,23} = 9.35$ and 4.37 ; $P = 0.006$ and $P = 0.047$, respectively), and separate dose-placebo comparisons showed a highly significant effect of mizolastine 40 mg in both tests ($F_{1,92} = 22.79$ and 8.60; $P < 0.001$ and $P = 0.004$ respectively), as well as of mizolastine 20 mg ($F_{1,92} = 13.46$ and 10.10; $P < 0.001$ and $P = 0.002$).

Mean changes in reaction time are shown in Fig. 5 b. Clemastine significantly lengthened reaction time in both the first and second test ($F_{1,23} = 7.17$ and 7.19; $P = 0.013$ and $P = 0.013$). Effects of mizolastine were found in the first test after 40 and 20 mg ($F_{1,92} = 7.20$ and 6.05; $P = 0.009$ and $P = 0.016$).

VIG

No significant mizolastine dose-placebo or clemastine-placebo differences were found.

CRT

The change in mean choice reaction time (RT) over all three memory sets are shown in Fig. 6. Clemastine significantly lengthened mean RT in the first ($F_{1,23} = 5.58$; $P = 0.027$) but not in the second test. A significant effect of mizolastine versus placebo on mean RT was found after 40 and 20 mg in the first test ($F_{1,92} = 10.93$ and 6.58; $P = 0.001$ and $P = 0.011$), and none in the second test.

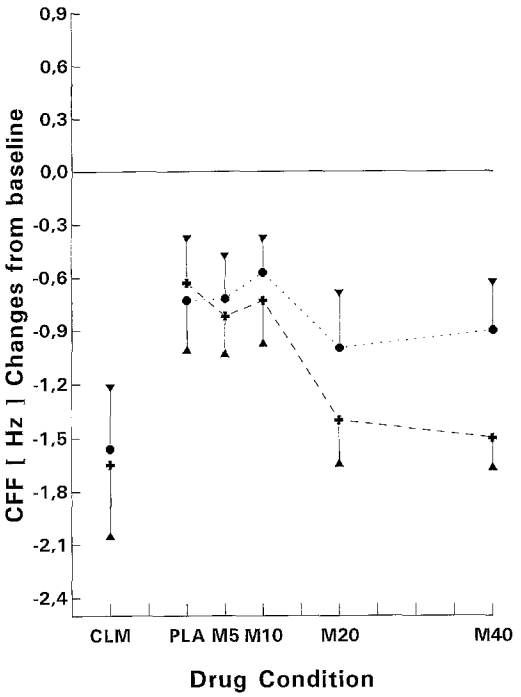

Fig. 3 Average change in Critical Flicker Fusion (*CFF*) threshold relative to morning baseline and as a function of drug treatment in the first and second tests. ✚ 2:00 h post dosing; ● 5:30 h post dosing

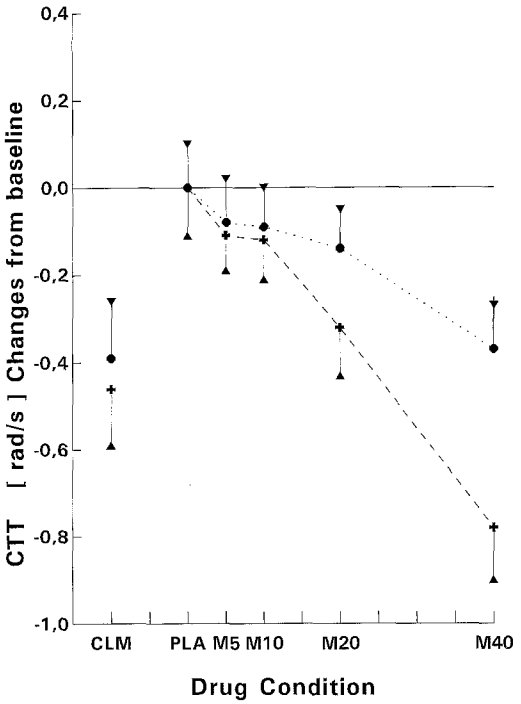

Fig. 4 Average change in λ-c relative to morning baseline and as a function of drug treatment in the first and second tests. ✚ 2:00 h post dosing; ● 5:30 h post dosing

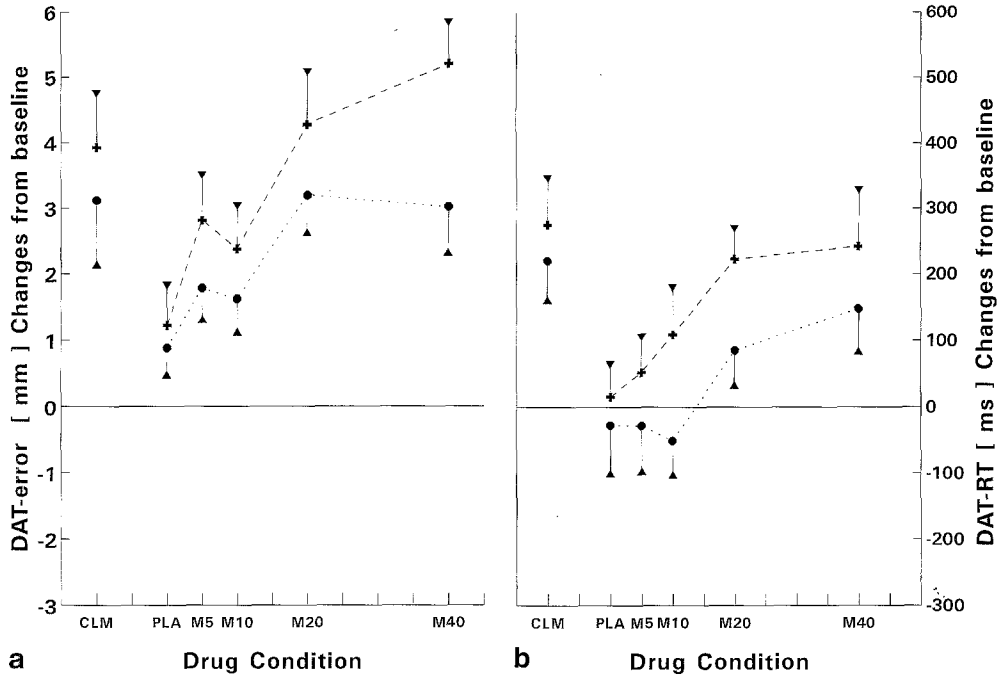

Fig. 5a,b Average change in Divided Attention tracking error (DAT-error, **a**) and reaction time (DAT-RT, **b**) relative to morning baseline and as a function of drug treatment in the first and second tests. ✚ 2:00 h post dosing; ● 5:30 h post dosing

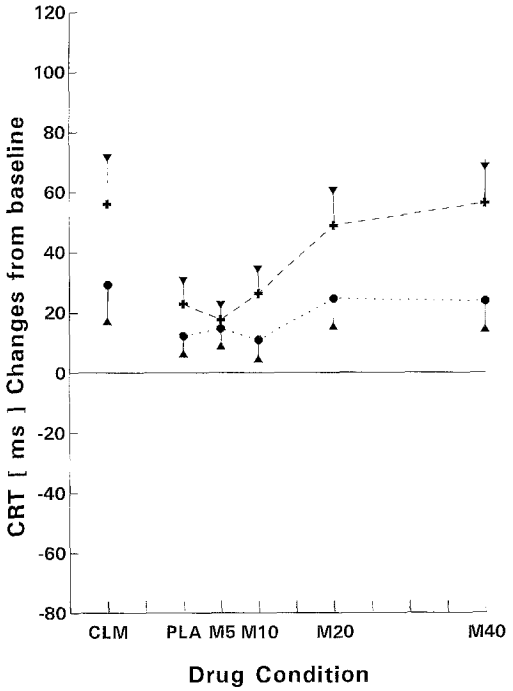

Fig. 6 Average change in choice reaction time (CRT) relative to morning baseline and as a function of drug treatment. The data are combined for all three memory sets and are shown in the first and second tests. ✚ 2:00 h post dosing; ● 5:30 h post dosing

Mood

Clemastine significantly depressed the mean Alertness score ($F_{1,23} = 5.09$; $P = 0.034$). There were significant overall mizolastine effects on the mean Contentedness and Calmness scores ($F_{4,20} = 4.95$ and 2.96; $P = 0.006$ and $P = 0.045$), indicating adverse effects on mood. Separate dose-placebo comparisons showed only a significant effect of the highest dose on contentedness ($F_{1,92} = 9.88$; $P = 0.002$).

Subjective feelings

Among the eight side effects rated by the subjects, two showed significant treatment effects. Clemastine significantly increased ratings of "drowsiness" and "lack of concentration" (Wilcoxon, $Z = -3.78$ and -3.25; $P < 0.001$ and 0.001). "Drowsiness" was significantly increased as an overall effect of mizolastine (Friedman, $X^2 = 14.87$; $P < 0.05$), and dose-placebo comparisons showed significant effects of the 40 and 20 mg doses (Wilcoxon, $Z = -3.00$ and -2.84; $P < 0.001$ and 0.01).

Five rides were stopped prematurely by the driving instructor when he judged that the subjects were becoming too drowsy to continue safely. This occurred twice after mizolastine 10 mg, twice after mizolastine 20 mg, and once after clemastine 2 mg. In all cases, this happened after the ride was more than 75 % complete.

Discussion

The results of this study show that mizolastine, like any other H_1 antagonist, becomes sedating and impairing when present above some threshold concentration in the brain. A single 40 mg dose of mizolastine (four-times the therapeutic dose) produced sufficient sedation to cause general behavioural impairment. The mean effects of the 5 and 10 mg doses were not signifi-

cant, while that of mizolastine 20 mg was intermediate. The findings confirm the results of previous studies [17, 18, 19]. Although the mean effect on most performance variables varied as a monotonic function of the mizolastine dose, this was not always true in individual cases.

Clemastine 2 mg had a large effect on SDLP, which was comparable to that seen at a blood ethanol levels of 0.8 mg · ml^{-1} [20]. The effect of mizolastine 40 mg closely resembled that of clemastine, both with respect to mean change and individual reactions. The high and significant correlation between changes in SDLP from placebo levels ($r = 0.78$; $P < 0.001$) in these conditions suggests there is a common mechanism underlying the harmful effects of the two drugs'. The mean effects of 5, 10 and 20 mg doses were low to moderate (1.20 cm, 1.56 cm and 2.30 cm, respectively) and were more difficult to interpret. Judged by the statistical tests, only mizolastine 20 mg caused significant impairment. However, after both the 10 and 20 mg conditions two subjects were unable to complete the driving test for safety reasons. After the 10 mg this occurred after achieving moderate and high SDLP scores, and after 20 mg there was a high score in both tests. Yet, the same two subjects whose driving was stopped after treatment with mizolastine 10 mg showed very little impairment after receiving mizolastine 40 mg. It is not possible definitely to attribute the inability of any particular subject to complete a trial solely to the treatment administered beforehand and in some instances the reaction may have been caused by another, unknown factor. The correlations between the effects on SDLP of the 40 mg dose and each of the three lower doses were low ($r < 0.30$), supporting the idea of a sedative "threshold" that varies both between and within subjects. Mizolastine seems to merely increase sedative activity towards this threshold in a dose dependant manner. Whether the activity of drug actually crosses the threshold may depend on the additional effect of other factors, such as sleep loss, fatigue or emotional stress. Restrictions imposed on the activities of the subjects' in the present study should have reduced the possible influence of extraneous factors, but it is doubtful that they were entirely eliminated.

The difference in mean driving performance between males and females was an interesting finding. Females reacted more adversely to clemastine 2 mg than males. Although no significant sex by drug interaction was found, the results indicate that females reached the sedative threshold after lower doses of mizolastine. This also appears to be the case with at least two other second generation antihistamines, acrivastine and cetirizine. Robbe and O'Hanlon [21] found no mean effect on SDLP after acute or subchronic treatment with acrivastine 8 mg in a group of 15 male subjects. Employing the same test, Ramaekers et al [22] did find a significant mean increase in SDLP after a single dose of acrivastine 8 mg in a group of 18 female subjects. Volkerts et al. [23] employed male subjects and found no significant effects of cetirizine 10 mg on SDLP, but Ramaekers et al. [3] demonstrated a significant rise in SDLP in a mixed-gender group. Regardless of the underlying cause of these differences, there is a strong suggestion that females generally have a smaller safety margin while taking antihistamine drugs.

The results of the psychomotor test battery generally supported the findings in the driving test, although no mean differences in test performance were seen between males and females. The strongest effects of both mizolastine and clemastine were found in the first repetition of each test. Impairment by clemastine usually outlasted that produced by mizolastine, which conforms with the observation that the sedative activity of clemastine persists for at least 6.5 h after a single dose [24]. The failure to find a statistically significant effect in the vigilance test was probably due to the relative low power of the test.

The primary practical goal of this investigation was to determine whether the therapeutic dose of mizolastine, 10 mg, was free of sedative effects that might pose a safety problem for patients. A decision based solely upon the results of statistical tests would conclude that this dose was not sedating. But to do so would ignore certain disconcerting indications that sedation occurred in some individuals, especially during the driving test. Similar effects have been found in studies conducted with other "nonsedating" antihistamines; e.g. in previous studies of terfenadine and loratadine given in twice their usual doses [5], and acrivastine and cetirizine given in their usual doses [3], there have been recorded instances of subjects who were unable to complete the driving test for safety reasons. Moreover the adverse effect of mizolastine 10 mg on mean SDLP in the present study was comparable to that of terfenadine 120 mg, loratadine 20 mg and cetirizine 10 mg as previously measured. The latter were all statistically significant, as would have been the case in the present study for mizolastine 10 mg without the adjustment of P_α for multiple testing.

We conclude that it is unlikely that patients treated for the first time with mizolastine 10 mg will experience sedation that causes practically relevant impairment of performance. The likelihood that the drug given in this dose would cause important impairment in any individual is low, probably comparable to that after cetirizine 10 mg or terfenadine 120 mg. Relative to its alternatives, mizolastine 10 mg should be considered as a very safe antihistamine. As with any antihistamine, an individual adverse reaction can never be entirely ruled out.

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