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The Influence of Antihistamines on Human Performance

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Summary. We have studied the effects of three antihistamines on task performance in two separate experiments. Healthy subjects were tested at weekly intervals in a double-blind, Latin square design. In Experiment I the subjects were treated orally with loratadine 10 mg, clemastine 1 mg, terfenadine 60 mg, or placebo. In Experiment II 5 mg diazepam was given orally with each of the four treatments used in Experiment I. In both experiments subjects' performance was evaluated in reaction time and tracking tasks after treatment. In both experiments, the tracking task initially was performed alone and then simultaneously with a continuous memory task; the subject also graded their mental status on visual analogue rating scales.

In both experiments task performance was not generally impaired after treatment with loratadine or terfenadine. The concomitant administration of diazepam in Experiment II appeared not to affect subjects' performance. However, clemastine caused a decay in subjects' performance in both Experiments I and II, but only on the tracking task.

At the conclusion of both experiments, sleepiness was reported by more subjects when treated with clemastine than when treated with loratadine, terfenadine, or placebo.

Key words: loratadine, terfenadine, clemastine; psychomotor performance, subjective feeling, diazepam

Antihistamines may impair central nervous system function, and may therefore cause drowsiness and decreased task performance. There are now antihistamines available which selectively inhibit H_1-histamine receptors without significant effects on the central and autonomic nervous systems. The present study was undertaken to compare the effects on human performance of three antihistamines, loratadine and terfenadine, which were expected to depress the central nervous system only minimally, and clemastine, which has a documented sedative effect (Carter et al. 1985; Clarke and Nicholson 1978, Nicholson 1984; Sorkin and Heel 1985). The effects of the three antihistamines were compared with placebo. The study involved two separate experiments: each of the four treatments was given alone in Experiment I and together with 5 mg diazepam in Experiment II. It was expected that the addition of diazepam would facilitate the eventual effects of the antihistamines on the central nervous system.

The healthy volunteers were tested in a pursuit tracking task and in a reaction task. The tracking task was carried out alone or simultaneously with a continuous memory task. The pursuit tracking task requires both perceptual and motor processing and is sensitive to lapses of attention, while the continuous memory task places heavy demands on subjects' working memory (Boer et al. 1987).

With prolonged exposure to the task, performance tends to deteriorate as subjects become more fatigued. It has been shown that this deterioration is larger after sleep deprivation or after a barbiturate, in particular with degraded stimuli (Frowein et al. 1981; Sanders et al. 1982). When antihistamines are sedative they may cause a similar deterioration in performance.

Methods

Experiment I

Subjects. The subjects were 12 male students from the University of Utrecht, who were paid for their participation. Their average age was 21.9 years

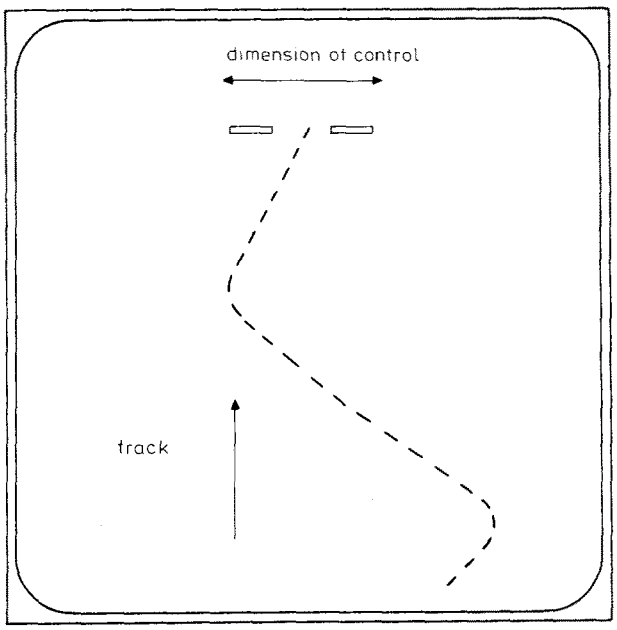

Fig. 1. The stimulus configuration in the tracking task

(SD 2) and their average weight 74.8 kg (SD 8). The subjects came to the Institute on five days at weekly intervals. The first day was dedicated to a medical examination and training in the tasks. Subjects were excluded if they had been ill recently or were using drugs. On the four test days subjects were not allowed to smoke, to drive a car, or to drink any beverages containing stimulants. They were told to have a normal amount of sleep before each test day. All the subjects signed a letter of consent containing all essential information on the study.

Treatments. The following four treatments were administered double-blind: loratadine (10 mg), clemastine (1 mg), terfenadine (60 mg), and placebo. The treatments were supplied by code in capsules that looked identical. There were four sequences of treatment administration, according to a Latin square design, three subjects being assigned to each sequence. The treatments were taken on an empty stomach after arriving at the Institute, followed 15 min later by breakfast.

Reaction Task. The subjects were seated in a sound-attenuating cubicle and responded as quickly as possible to series of stimuli. Each session lasted 24 min. The stimuli were the digits 2, 3, 4, and 5 formed by a dot pattern and surrounded by a frame of dots. The digits could also be "degraded" by taking 10 dots from the frame and by placing them pseudo-randomly around the digit. Each of the digits was degraded in four different ways, to prevent subjects from learning to respond to the degradation pattern instead of the digit.

Tracking Task. The stimulus in this pursuit tracking task consisted of random combinations of sawtooth patterns of dotted lines of which the edges were rounded. Tracks and cursor appeared on a monochrome Taxan monitor, located approximately 1 m in front of the subject. The cursor consisted of a horizontal 22-mm line segment with a 6.5-mm gap in the middle and could be moved horizontally with the aid of a joystick (see also Fig. 1). The cursor had to be manipulated so that the track went through the middle of the gap. The track moved upwards and the preview time was one second.

The tracking task was administered in two blocks, each of which lasted 7 min. During the first block the tracking task was performed alone, and during the second block a continuous memory task was added 1 min after the start of the tracking task. The continuous memory task lasted 5 min, during which series of letters of the alphabet (only the consonants) were presented by earphones. The subject had to detect 4 target letters and to count them in separate tallies. At the end of the block the subjects reported the count for each of the 4 target letters. Before the task started four letters were assigned as targets, different in each test session. Of the 144 letters presented approximately 25% were targets. Interstimulus intervals (onset-onset) were varied randomly between 2.0, 2.5, 3.0, 3.5, 4.0, and 4.5 s.

In the tracking task the distance (i.e. error) between the track and the middle of the gap was computed every 200 ms. The root mean square (RMS) was computed for each of the ten 30-s periods of each block, omitting the first and last minute of the 7-min block. In the continuous memory task differences between presented and reported number of target letters were computed separately for each of the target letters, with the limitation that differences larger than three were counted as three. Thus, the minimum error score was zero and the maximum twelve.

Subjective Measures. The subjects completed a form with ten visual analogue scales. Each scale represented a particular dimension, indicated by the extremes of that dimension (e.g. calm-excited, alert-drowsy, etc). The scales consisted of horizontal lines (10 cm), on which the subjects marked the point which represented their current state for a dimension, as compared with their state for the same dimension before treatment.

At the end of each test day the subjects were asked whether they thought they had received an antihis-

tamine or a placebo on that day, how certain they were about this, and whether they had experienced any psychosomatic complaints. At the end of the fourth test day the subjects were asked which treatment they thought they had received on each test day and the extent to which each treatment had made them feel sleepy. Response scales ranged from 100% to 0%: from absolute certainty of having received an antihistamine to absolute certainty of having received a placebo, and from extremely sleepy to absolutely not sleepy.

Procedures. The subjects received their treatment at between 09.00 h and 10.30 h at weekly intervals. After the treatment all the subjects received the same experimental programme according to the following time schedule:

Time	Activity
0:00	Treatment
0:45-1:15	Tracking task I
1:15	Rating scales I
1:45-2.15	Reaction task I
2:15	Rating scales II
2:45-3:15	Tracking task II
3:15	Rating scales III
3:45-4:15	Reaction task II
4:15	Rating scales IV
4:45-5:15	Tracking task III
5:15	Rating scales V
5:45-6:15	Reaction task III
6:15	Rating scales VI
	End of test day questionnaire

Each subject was tested in 6 sessions, three with the tracking and three with the visual field task: the tracking task was done 1, 3, and 5 h after treatment and the reaction task 2, 4, and 6 h after treatment. Rating scales were filled out after the completion of each task. At the end of the test day a questionnaire was completed.

Experiment II

Subjects. the subjects were 16 male students from the University of Utrecht, who were paid for their participation. Their average age was 21.4 years (SD 2) and their average weight was 79.2 kg (SD 7). The criteria for the selection of the subjects were the same as in Experiment I.

Design. The experimental design was the same as in Experiment I. The same treatments were given but now a capsule containing 5 mg diazepam was given with each of the four treatments.

Procedure. Subjects followed the same programme as in Experiment I.

Results

Reaction Task

Analyses of variance (ANOVAs) were carried out on the mean reaction time and the percentage of errors. In Experiment I the effects of treatments, groups, and weeks were not significant. The only significant interaction ($p<0.04$) involving treatments was with stimulus quality, which was caused by a larger degradation effect after clemastine than after loratadine, terfenadine, or placebo.

Because of a technical failure in Experiment II the data of 1 subject had to be omitted from the analysis. In order to have the same number of subjects in each of the 4 sequences, the data of three randomly chosen subjects were omitted. Consequently the data analyses were performed on 4 sequence groups, comprising three subjects each.

ANOVAs were carried out on the mean reaction time and the percentage of errors. The main effects of treatments and groups were not significant. Reaction time increased over the 24-min task session for all of the 4 treatments ($p<0.01$).

The interaction between treatments and time on task was also significant ($p<0.02$). Post-hoc comparisons showed that the increase during the session was larger after loratadine and clemastine (88 ms for both agents, $p<0.01$), and to a lesser degree after terfenadine (71 ms, $p<0.05$) than after placebo (50 ms).

Tracking Task

The results obtained in the tracking task are shown in Fig. 2 (Experiment I) and Fig. 3 (Experiment II) as a function of treatments and sessions for single (i.e. tracking alone) and dual (i.e. tracking and continuous memory task) conditions. A main effect of treatments was found in both Experiment I ($p<0.01$) and Experiment II ($p<0.02$). Planned comparisons revealed that this was caused by the larger error scores in the second and third session with clemastine than with the other treatments, which did not differ significantly from each other. The interaction between treatments and sessions approached significance in Experiment I ($p<0.06$), but was highly significant in Experiment II ($p<0.005$). This interaction demonstrates that the

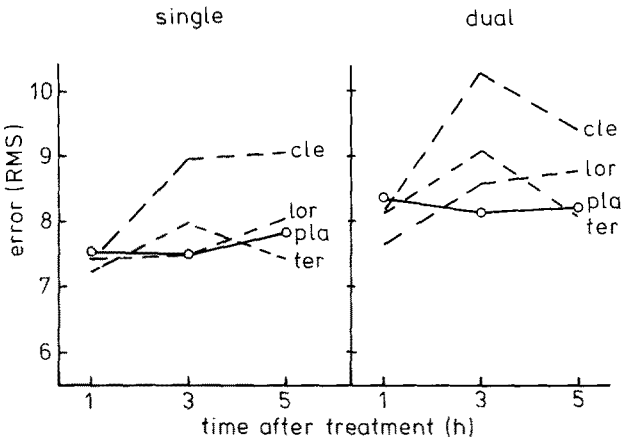

Fig. 2. Tracking error in Experiment I as a function of treatment and hours after treatment, for single and dual conditions

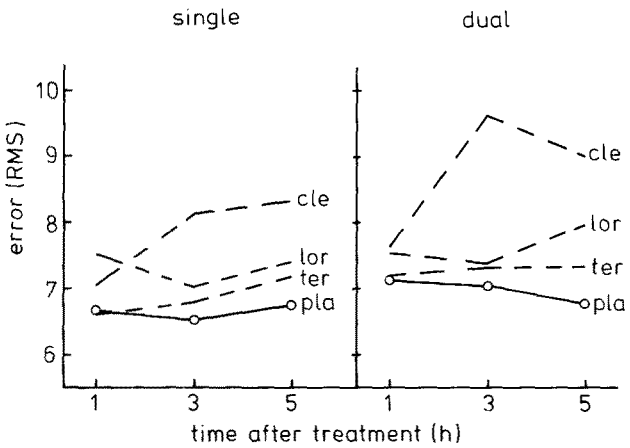

Fig. 3. Tracking error in Experiment II as a function of treatment and hours after treatment, for single and dual conditions

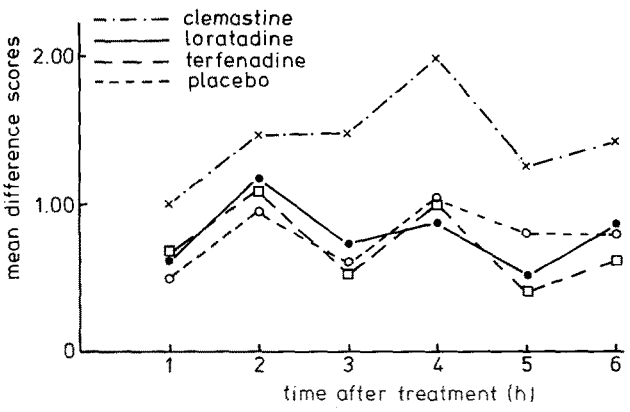

Fig. 4. Mean difference scores on the visual analogue rating scales, as a function of treatments and hours after treatment. The tracking task was done 1, 3, and 5 h after treatment and the reaction time task 2, 4, and 6 h after treatment

effect of clemastine were not evident at 1 h after treatment, but clearly were present at 3 h and 5 h after treatment. As can be seen in Figs. 2 and 3 this is the case both under single and dual task conditions and in Experiments I and II.

A significant treatment effect ($p<0.03$) on the error scores of the continuous memory task was found in Experiment I; error scores were higher for both loratadine and for terfenadine. However, no such effects were observed in Experiment II.

Subjective Measures

The effects of treatment on the visual analogue rating scale scores were about the same for the ten dimensions. Therefore, the individual scores were averaged across the ten dimensions. The mean scores were compared with the baseline (i.e. pre-treatment) score. A positive score indicated that the subjects rated themselves as being more "drowsy", "passive", etc after treatment then in the morning before treatment. ANOVAs were carried out on the mean difference scores. As can be seen in Fig. 4, subjects felt more "drowsy" on the even hours than on the odd hours. This suggests that they had more problems in remaining alert after the reaction task than after the tracking task ($p<0.001$ in Experiment I and $p<0.02$ in Experiment II). The figure suggests an effect of clemastine, although this was not statistically significant.

In both experiments the percentage of subjects who thought they had received an antihistamine was larger when they actually had taken clemastine than for the other treatments. Averaged across the two experiments the percentages were: clemastine 87%, loratadine 60%, terfenadine 53.5%, placebo 63.5%. Similar results were obtained when the same question was asked at the end of the experiment: clemastine 73.5%, loratadine 54%, terfenadine 52.5%, placebo 48.5%.

Discussion

Except for the effects discussed below these results suggest that neither loratadine nor terfenadine affects the performance or subjective feelings of healthy volunteers; for several measures the two antihistamines did not differ significantly from each other or from placebo in either Experiment I or II. Only in the continuous memory task of Experiment I were error scores for both loratadine and terfenadine significantly higher than for placebo. However, this result was not replicated in Experi-

ment II. In Experiment II a significant difference was found in the reaction task between the three active agents and placebo; with placebo reaction time increased over the 24-min working period by 50 ms, whereas this increase was larger after the intake of an antihistamine. This result suggests that subjects had greater difficulty in maintaining concentration on the task after an antihistamine than after placebo. However, observed effects were rather small.

Treatment with clemastine resulted in a decay of subjects' performance on the tracking task, whether performed alone or simultaneously with the continuous memory task. This effect was of the same magnitude in both Experiment I and II, despite the fact that diazepam was also given during Experiment II. Perhaps the 5-mg dose of diazepam was too small or its action too short to interact with clemastine 3 h after administration. Peak concentrations of diazepam occur at between 1 h and 2 h after administration (Bittencourt et al. 1983; Nicholson 1984). Clemastine caused no significant decay in the continuous memory test, suggesting that central processing and memory are not affected by this antihistamine. Since clemastine had no important effect in the reaction task, which requires perceptual processing, it seems likely that this antihistamine affects subjects' motor processes, or at least those processes involved in fast and continuous perceptual-motor co-ordination, as was measured by the tracking task.

With clemastine the subjects felt more drowsy than with the other treatments. This was particularly evident in Experiment II (see also Fig. 4), although this difference was not significant. After the administration of clemastine more subjects reported that they throught had been treated with an antihistamine, both at the end of a test day and at the end of the whole experiment. These findings were evident in both experiments.

The present results are similar to those obtained by Nicholson and coworkers (Nicholson and Stone 1982; Nicholson et al. 1982, 1984), who showed that terfenadine had no effect on either performance or subjective assessments. The visuo-motor co-ordination task they used was similar to the tracking task in the present study. In an earlier study Clarke and Nicholson (1978) also showed decreased visuo-motor co-ordination after clemastine given in the same dose.

The present results suggests that both loratadine and terfenadine have minimal effects on task performance and do not evoke drowsiness.

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