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Antihistamines: Impaired Performance and the Tendency to Sleep

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Summary. The central effects of various antihistamines were studied using a variety of tests of performance, including visuo-motor co-ordination and dynamic visual acuity, as well as paper and pencil tests and critical flicker fusion.

The possible relationship between performance and sedation was also studied using digit symbol substitution and latencies to drowsy sleep.

There was high degree of correlation between drowsiness, as indicated by the relative ease with which individuals fell asleep over the day, and impaired performance, but it was not possible to establish the relationship for each time of the day.

These findings lend some support to the suggestion that impaired performance with antihistamines may be a non-specific effect of sedation.

Key words: histamine antagonists; sedation, performance, multiple sleep latencies

Antihistamines often cause drowsiness and impaired performance [10, 14] and these effects are usually assumed to be related. Indeed, reduced performance may be the consequence of sedation, although the existence of such a relationship is uncertain and may, in any case, depend on the nature of the tests used to detect it and on their sensitivity to drugs. In previous studies we have used a variety of tasks to investigate the effects of antihistamines on performance [11, 12, 13], but we have not used any objective techniques to assess drowsiness or tendency to sleep. However, the measurement of latencies to Stage 1 sleep may be a useful approach [16], and in the present experiment we have adopted this technique, together with performance tests, to assess the central activity of various antihistamines.

We studied three antihistamines: triprolidine, which has well established sedative effects and clearly impairs performance [9]; terfenadine, which does not appear to influence performance and may even lead to the subjective impression of increased alertness in some individuals [4]; and tazifylline, which, clinically at least, has limited sedative activity, although little is known about its possible adverse effects on performance. To investigate these drugs we have used tests of visuo-motor co-ordination and dynamic visual acuity, as well as paper and pencil tests [17] and assessment of critical flicker fusion, and we have attempted to correlate impairment of performance on the digit symbol substitution test with the possible sedative effects of the drugs as indicated by the multiple sleep latency test [3].

Methods

The subjects were six healthy women aged between 19 and 29 years (mean 23 years) and weighing between 45 and 72 kg (mean 59 kg). They were required to drink no alcohol on the night before an experiment and during the experimental day. They drank no coffee or other beverages containing caffeine on experimental days. In the two studies ingestions were separated by at least 4 days, and the design was based on a Latin square. All treatments were identical in appearance, and each study was double-blind.

Studies on Performance

Each subject took 5, 10, and 15 mg tazifylline, 60 and 120 mg terfenadine, 10 mg triprolidine (Pro-Actidil), and two placebos. The drug was taken at 08.30 h, and performance was measured at 09.00, 10.00, 12.00, 14.00 and 16.00 h. The subjects were trained until

they achieved a steady level of performance on all tasks.

Visuo-Motor Coordination. The subjects were required to position a spot inside a randomly moving circle displayed on an oscilloscope using a hand-held stick [1]. An error signal proportional to the distance between the spot and the centre of the circle controlled the difficulty of the task by modulating the mean amplitude of the movement of the circle. The position of the circle and spot, and so the radial error, were recorded. Each run lasted 10 min. The subjects reached plateau performance within 100 s, after which scoring began. After each run subjects completed assessments of performance related to a 100 mm line. The extremes of the analogue scale of performance were: How well did you perform? Useless (00) - Perfect (100). Other assessments using analogue scales included questions on sleepiness, lethargy and the ability to concentrate.

Digit Symbol Substitution (DSS). This was tested using a series of 50 sheets with 200 randomized digits (0-9) arranged in 10 rows on each side. Subjects were presented with one sheet and in the space below each digit they were required to insert the appropriate symbol, indicated by a code at the top of each page. Subjects were given 2 min per side to complete as many substitutions as possible, and the total number of substitutions was recorded.

Symbol Copying. Subjects were presented with one of a series of 50 sheets with 200 randomized symbols (those used in the digit symbol substitution test) arranged in 10 rows on each side. They were allowed 1 min per side to copy as many symbols as possible, and the total number of symbols copied was recorded.

Critical Flicker Fusion. The subjects were adapted to the lighting intensity of the room for 5 min, and the flicker fusion threshold was assessed using a central flickering field superimposed on a concentric background. Presentations were in Maxwellian view at optical infinity and were viewed monocularly through an artificial pupil. Cross-wires were used for fixation and this kept the retinal location of the stimulus constant. The flickering light was presented for 2 s at 16 Hz (lower than the possible fusion point) and the frequency was altered stepwise according to the pattern of response. The threshold was defined as the lowest frequency at which 50% or more of the last 25 responses were considered to be fused [13].

Dynamic Visual Acuity. This was measured using Landolt ring targets with critical detail ranging from 1-10 min of arc projected on to a curved screen by a rotating mirror galvanometer placed at its centre of curvature. The images swept from right to left at a constant velocity of 43 or 68° s^{-1}. A buzzer warned of each presentation and the subject had to indicate the position of the gap in the ring within 1 s after completion of the target sweep [13].

Studies on Daytime Sleepiness

Each subject took 5, 10, and 15 mg tazifylline, 2.5 and 5.0 mg triprolidine, 5 mg diazepam, and 2 placebos. After drug ingestion at 08.30 h, performance and sleep latency tests were carried out at 09.00, 10.00, 12.00, 14.00 and 16.00 h. Digit symbol substitution performance was measured and subjects assessed their mood and well-being on visual analogue scales related to a 100 mm line. The assessments and extremes of the scale were: I am Very wide awake - Extremely sleepy; I am Very tense - Very relaxed; I am Very calm - Extremely anxious; I am Very energetic - Very lethargic; I am Very dull - Very alert; I have No ability to concentrate - Complete ability to concentrate; I am Highly efficient - Completely useless. For all assessments the subjects were instructed to mark the line at a point which corresponded to their present state.

Multiple Sleep Latency Test (MSLT). Electrical activity from the C4-A1 and OzPz-03 positions together with the submental electromyogram and bilateral electroculograms were recorded on a Grass 8-10 EEG machine sited in a room adjoining the individual bedrooms. The paper was run at 10 mms^{-1} throughout each recording. Subjects were allowed to remain in bed for 20 min unless Stage 2 sleep was observed, when they were woken immediately. Latencies to Stage 1 (drowsy) sleep were measured. Subjects were monitored between testing sessions to ensure that no additional napping occurred.

Statistical Analysis

The data were analysed by analysis of variance (ANOVA). The proportions of correct scores in the dynamic visual acuity task were transformed before analysis using the arc sine square root transformation, which is a variance stabilizing transformation for a binomially distributed variable. The twelve subjective assessments of well-being were investigated using principal component analysis. Subsequent analysis was confined to the two largest components, which were rotated according to the varimax criteri-

Table 1. Effects of drugs on visuo-motor co-ordination (arbitrary units) (means for 6 subjects)

Time (h) after ingestion	Placebo	Triprolidine (mg)	Terfenadine (mg)		Tazifylline (mg)		
		10	60	120	5	10	15
0.5	5353	4866	5460	5343	5678	5290	5340
1.5	5770	4195[b]	5598	5332	5025	4918[a]	4853[b]
3.5	5777	4781[b]	6172	6181	5558	5263	5096
5.5	5681	4516[b]	5765	5774	5650	5289	5342
7.5	5674	4875[a]	6262	5291	5545	5425	5286
Mean	5651	4647[c]	5852	5584	5491	5237[a]	5183[a]

Significance levels: [a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$

Table 2. Effects of drugs on the numbers of substitutions on digit symbol substitution (means for 6 subjects)

Time (h) after ingestion	Placebo	Triprolidine (mg)	Terfenadine (mg)		Tazifylline (mg)		
		10	60	120	5	10	15
0.7	239.3	227.5	240.0	240.0	236.7	239.2	234.8
1.7	243.3	224.5[b]	239.7	235.3	234.7	231.5	234.7
3.7	243.8	228.8[a]	248.5	239.0	238.8	236.2	238.7
5.7	238.8	228.8	239.7	232.2	235.0	237.2	239.3
7.7	236.0	228.7	241.2	237.5	234.7	235.8	235.3
Mean	240.2	227.7[c]	241.8	236.8	236.0	236.0	236.6

Significance levels: [a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$

Table 3. Effect of drugs on the numbers of symbols copied on symbol copying (means for 6 subjects)

Time (h) after ingestion	Placebo	Triprolidine (mg)	Terfenadine (mg)		Tazifylline (mg)		
		10	60	120	5	10	15
0.8	206.2	192.8[a]	203.0	206.2	203.0	206.0	199.8
1.8	211.7	190.5[b]	206.7	208.0	201.2	203.2	199.8
3.8	209.2	196.7	205.8	205.8	203.7	202.3	204.0
5.8	207.4	194.5[a]	203.5	204.3	200.0	208.0	202.8
7.8	207.6	202.3	209.2	205.2	199.7	207.7	208.5
Mean	208.4	195.4[c]	205.6	205.9	201.5	205.5	203.0

Significance levels: [a] $p < 0.05$; [b] $p < 0.01$; [c] < 0.001

Table 4. Effect of drugs on critical flicker-fusion threshold (means for 6 subjects)

Time (h) after ingestion	Placebo	Triprolidine (mg)	Terfenadine (mg)		Tazifylline (mg)		
		10	60	120	5	10	15
0.9	23.5	21.8[a]	23.8	23.0	23.3	23.6	23.4
1.9	23.1	21.2[a]	22.8	22.4	23.0	22.5	22.2
3.9	23.3	22.0	23.0	22.8	22.8	22.5	23.3
5.9	23.3	21.5[a]	23.0	22.8	22.9	23.0	23.4
7.9	23.2	22.5	23.3	22.2	23.2	23.0	23.7
Mean	23.3	21.8[b]	23.2	22.7	23.0	22.9	23.2

Significance levels: [a] $p < 0.05$; [b] $p < 0.01$

on [8]. Both measures were re-scaled before analysis of variance using a logarithmic transformation after investigation with the maximum likelihood method [2]. Analysis of variance of the multiple sleep latencies was performed on log transformed data, using a modified ANOVA algorithm, assuming that the sample was normally distributed, censored at the logarithm of 21.0 min.

The possibility of an order effect from week to week, perhaps representing a learning or adaptation effect, was examined by covariance analysis. If this indicated a significant main effect due to order, or a significant linear trend, this was retained in the analysis and the means adjusted, their standard errors being modified by Finney's correction factor [7]. A similar method was used for a subject by linear order

Table 5. Effect of drugs on the percentage of correct responses on dynamic visual acuity at 2 target velocities (means for 6 subjects)

Time (h) after ingestion	Placebo	Triprolidine (mg)	Terfenadine (mg)		Tazifylline (mg)		
		10	60	120	5	10	15
Target velocity 43 deg/s							
1.0	90.5	80.2[a]	91.7	91.0	88.5	89.5	89.6
2.0	90.5	82.5	92.6	91.5	89.1	90.3	86.7
4.0	92.5	87.0	92.3	92.4	91.2	89.6	91.4
6.0	94.1	86.5	94.4	91.3	93.4	91.9	93.3
8.0	91.0	93.1	91.8	93.0	91.5	93.7	92.8
Mean	91.8	86.2[a]	92.6	91.8	90.8	91.1	90.9
Target velocity 68 deg/s							
1.0	69.9	51.5[b]	66.9	66.5	68.5	66.0	63.1
2.0	70.9	56.3[b]	74.0	70.6	66.0	70.7	58.8
4.0	74.1	63.0[b]	73.4	70.5	68.7	75.4	68.4
6.0	70.8	61.9[a]	71.9	69.7	69.3	74.1	69.6
8.0	74.0	67.5	72.0	71.6	69.7	74.4	75.8
Mean	72.0	60.1[c]	71.7	69.8	68.5	72.2	67.3

Significance levels: [a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$

Table 6. Effect of drugs on latency (min) to Stage 1 sleep (means for 5 subjects)

Time (h) after ingestion	Placebo	Diazepam (mg)	Triprolidine (mg)		Tazifylline (mg)		
		5	2.5	5	5	10	15
0.5	21.9	9.0[b]	12.1	10.8	18.3	22.7	12.6
1.5	20.1	15.9	7.4[a]	5.2[b]	12.6	17.8	7.0[b]
3.5	12.7	12.3	8.7	7.7	10.0	8.7	9.1
5.5	10.8	10.2	11.0	8.6	10.6	14.1	10.3
7.5	15.8	13.5	14.1	12.4	12.6	14.2	12.3
Mean	16.2	12.2	10.7	9.0[a]	12.8	15.5	10.3[a]

Data are back-transformed and corrected for bias - this has resulted in values in excess of 20 min.
Significance levels: [a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$

Table 7. Effect of drugs on the numbers of substitutions on digit symbol substitution (means for 5 subjects)

Time (h) after ingestion	Placebo	Diasepam (mg)	Triprolidine (mg)		Tazifylline (mg)		
		5	2.5	5	5	10	15
0.5	246.4	221.1[a]	241.3	236.1	241.2	241.3	242.7
1.5	244.4	228.3[a]	238.5	235.9	242.2	237.1	242.5
3.5	242.6	242.1	242.7	241.9	244.6	242.9	247.3
5.5	242.5	246.9	245.9	244.3	241.6	243.9	246.5
7.5	242.1	239.1	245.7	248.7	247.2	242.3	244.7
Mean	243.6	235.5	242.9	241.4	243.3	241.5	244.8

Significance levels: [a] $p < 0.01$

interaction. When such an interaction was present, it was used to form a composite error term with the residual drug by subject interaction to obtain the necessary standard errors for the drug means.

In the performance study, after calculation of the ANOVA the planned comparisons were made between the two placebo ingestions, and also between the mean value of the placebo ingestions and triprolidine, the mean of the three doses of tazifylline and the mean of the two doses of terfenadine. The individual doses of tazifylline and terfenadine were compared with the mean of the two placebos using Dunnett's multiple comparison method [6], and the set of doses for each drug was treated as a distinct family. Differences from mean placebo at individual times were tested using Dunn's multiple comparison procedure [5].

In the multiple sleep latency study similar comparisons were made between drugs and placebo, with diazepam as control drug. It was possible to an-

alyse the results in only five out of the six subjects, as one subject fell asleep on only four out of forty possible occasions. Relationships between DSST, the measures of well-being, and MSLT were sought using a multivariate analysis of covariance, taking sequence as the single covariate.

Results

Performance

These results are given in Tables 1–5. Triprolidine (10 mg) impaired visuo-motor co-ordination from 1.5 to 7.5 h after ingestion ($p < 0.05$). The number of substitutions on the digit symbol test was reduced at 1.7 and 3.7 h ($p < 0.01$ and $p < 0.05$) and the number of symbols copied was reduced from 0.8 to 5.8 h ($p < 0.05$). The flicker fusion threshold was reduced from 0.9 to 5.9 h ($p < 0.05$). Triprolidine also reduced the percentage of correct detections at the low target velocity of dynamic visual acuity at 1.0 h ($p < 0.05$) and at the high velocity from 1.0 to 6.0 h ($p < 0.05$). The subjects also considered that their performance was impaired ($p < 0.001$). There were no changes in the first rotated component of mood. The second rotated component showed higher scores with triprolidine (10 mg) 0.5 and 1.5 h after ingestion ($p < 0.05$); this represented increased sleepiness.

Tazifylline (10 mg and 15 mg) impaired visuo-motor co-ordination at 1.5 h ($p < 0.05$ and $p < 0.01$ respectively). With dynamic visual acuity there was a decrease in the proportion of correct response at the higher speed with 15 mg tazifylline at 2.0 h ($p < 0.01$). It was not possible to establish any other effects of individual doses of the drug. No subjective effects of tazifylline on performance or well-being were reported.

With terfenadine (60 and 120 mg) there were no performance decrements or changes in mood or well-being.

Latencies to Sleep

These results are given in Tables 6 and 7. With 5.0 mg diazepam the latency to Stage 1 sleep and the number of substitutions on the DSST were reduced at around 0.5 h after ingestion ($p < 0.01$) and the effects on DSST persisted to 1.5 h ($p < 0.01$). Sleep onset was also faster with 2.5 mg and 5.0 mg triprolidine (1.5 h – $p < 0.05$, $p < 0.01$ respectively), but substitutions on the DSST were unchanged. With tazifylline (5 mg and 10 mg) sleep latencies and the number of substitutions on DSST were not altered, although 15 mg shortened sleep latencies at 1.5 h ($p < 0.01$) but did not diminish the number of symbols substituted. There were no changes in the two principal components of mood with any treatment.

The correlation matrices between DSST, MSLT, and subjective assessments are given in Table 8. There was no relationship between DSST and MSLT at individual times, but with antihistamines the daily change in the number of substitutions from placebo and in latency to Stage 1 from placebo were correlated ($p < 0.001$). There were no relationships between MSLT and any of the measures of subjective sleepiness at individual times, although, again, there were daily correlations.

Discussion

The present observations have confirmed the results of previous studies with triprolidine and terfenadine [4, 9, 11, 13]. Triprolidine (10 mg in a sustained-release preparation) subjectively impairs performance and increases sleepiness, and visuo-motor co-ordination, dynamic visual acuity, and other skills are impaired for several hours. In contrast, terfenadine, even in doses twice that currently recommended as the maximum of the therapeutic dose range, has no effect on performance or on subjective assessments. The lowest dose of tazifylline (5 mg) did not alter performance, but with both 10 mg and 15 mg visuo-motor co-ordination was impaired, and with the highest dose (15 mg) there was also a decrease in the proportion of correct responses on dynamic visual acuity.

Daytime sleep latencies were reduced after ingestion of 2.5 mg and 5.0 mg triprolidine and 15 mg tazifylline, but the number of substitutions on the digit symbol test was not altered, although with diazepam (5 mg) there were reductions both in the number of substitutions and daytime sleep latencies. It would, therefore, appear that even with a relatively small dose of diazepam the latencies to Stage 1 sleep were altered, and that with the antihistamines the daytime sleep latencies were more sensitive than the digit symbol substitution test.

Correlation analyses between sleep latencies and digit symbol substitution were of interest. The mean sleep latency calculated over each day correlated with subjective assessments of sleepiness and with performance on digit symbol substitution, although such relationships could not be established at individual times of the day. It seems that sedative effects of centrally-acting drugs may, in general, be associated with impaired performance, but that sedation and impaired performance during the day may not coincide. Performance tends to follow a sinusoidal curve

of circadian rhythmicity, and a steady improvement in performance is often seen during the day, whereas sleep latencies, although following a similar curve, appear to be lengthened immediately after sleep [15]. Performance and latencies to drowsy sleep may not correlate at individual times, at least during the day, but centrally-acting drugs may lower both, although each retains its distinct time-related pattern.

These studies suggest that it is likely that a high degree of correlation exists between drowsiness, as indicated by the relative ease with which individuals fall asleep during the day, and impaired performance, but that the failure to establish such relationships related to individual times of the day may rest with the sensitivity of sleep latency to a previous period of sleep. These findings lend some support to the suggestion that impaired performance with antihistamines may be a non-specific effect of sedation, rather than arising from an effect of the drugs on a particular skill essential to carrying out the task.

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