ANTI-HISTAMINES AND VISUAL FUNCTION: STUDIES ON DYNAMIC ACUITY AND THE PUPILLARY RESPONSE TO LIGHT

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- 1 Effects of three antihistamines, triprolidine (10 mg) in a sustained release form, astemizole (10 mg) and terfenadine (60 mg), have been studied on dynamic visual acuity and on the response of the pupil to light, together with critical flicker fusion, digit symbol substitution and cancellation, and subjective assessment of mood. The study was double-blind and effects were observed from 0.5–4.0 h after ingestion.
- 2 Triprolidine impaired dynamic acuity and reduced the threshold for subjective fusion of a flickering light, but there were no changes with astemizole or terfenadine. The diameter of the pupil and its response to light were not changed by the drugs.
- 3 Performance on digit symbol substitution and cancellation was not altered by the drugs.
- 4 Astemizole and terfenadine are promising antihistamines for those involved in skilled activity.

Introduction

Impaired central nervous function as indicated by drowsiness and by altered psychomotor performance is often a sequel to the use of antihistamines. Various mechanisms have been proposed, but a common property of many H_1 -antihistamines is the ease with which they cross the blood–brain barrier. However, some compounds cross with difficulty, and, as in the case of astemizole (Nicholson & Stone, 1982; Chapman & Rawlins, 1982) and terfenadine (Moser *et al.*, 1978; Kulshrestha *et al.*, 1978; Clarke & Nicholson, 1978; Nicholson & Stone, 1982), they would appear to have little, if any, depressant effect on the central nervous system.

The nature of impaired performance with antihistamines and the possibility of antihistamines without adverse effects on performance are important issues, and so we have extended our previous studies on visuo-motor coordination to examine the possible ocular mechanisms involved. In these studies we have used triprolidine, an antihistamine with marked effects on performance, as well as astemizole and terfenadine. We have studied dynamic visual acuity and the pupillary response to light, and have included observations on critical flicker fusion as well as psychological tests and subjective assessments of mood.

Methods

Dynamic visual acuity

Dynamic visual acuity (DVA) 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 (Figure 1). The screen had a radius of curvature of 1.5 m, and it subtended an angle of $\pm 30^\circ$ in the horizontal and $\pm 10^\circ$ in the vertical planes to the subject's eye. The screen was painted matt white and was illuminated by a single lamp (luminance: 2.76×10^{-2} cd m $^{-2}$) placed on the centre line of its cylinder of arc.

The targets (luminance: 5.92×10^1 cd m $^{-2}$) were brighter than the screen (negative contrast 94.2%), and the gap in each ring was orientated to an oblique meridian. The image sweep was limited to the central 30° of the screen by shutters external to the subject's field of view and the images swept from right to left at a constant velocity of 21, 43, 68 or 83°/s. The order of the presentations and speed of each sweep were controlled by a fixed balanced random table of numbers programmed into the trials generator. An experimental run consisted of eight trials of 10 target sizes at each of the four angular velocities (320 in all), and each run started at a random point within the table.

Figure 1 Measurement of dynamic visual acuity. The target images were four Landolt C rings with gaps at the oblique meridians, which were projected on to a curved screen by a rotating mirror. A fixation light was provided, and the subject was required to determine the orientation of the gap.

Five minutes were allowed to adapt to the lighting intensities of the room. The targets were viewed monocularly with the right eye, and the left eye was covered. The position of the head was steady using a chin-rest and browmount, and the subject was provided with a fixation light on the right hand side of the screen. A buzzer warned of each presentation. The subject had to indicate within 1 s after completion of the target sweep the position of the gap in the ring by pressing one of four buttons arranged to correspond with the oblique meridians. They were instructed to respond only if certain of the orientation. Subjects were trained on the task until they reached steady day-to-day performance, though in the subsequent experiments there was additional learning when the subjects were tested several times within a few hours.

The threshold of detection for each target velocity and for each subject was determined by fitting the cumulative integral of the normal distribution to the frequencies of correct responses at the different target sizes. These frequencies were assumed to be samples from binomial distributions with means $f(x_i)$, and accordingly were given weights proportional to

$$[f(x_i)(1 - f(x_i))]^{-1/2}$$

Fitting was performed by a Non-Linear Least Squares Program with weights recalculated at each iteration. The percentage correct of the total number of

presentations at each angular velocity was also calculated for each subject.

Pupillary diameter

Pupillary diameter was measured using a television pupillometer with an infra-red sensitive camera based on the design of Green & Masseidevag (1967). The pupil was illuminated by infra-red light reflected from the retina, and a Maxwellian view light stimulator permitted measurements of the pupillary response (Figure 2). Subjects were dark adapted for 5 min. Pupillary size was recorded for 2 min, and this involved a 40 s control period, responses to three flashes of light each of 0.5 s duration and separated by 10 s, and a 1 min recovery period. The resting diameter of the pupil and change in response to each flash of light were measured.

Critical flicker fusion

Critical flicker fusion (CFF) was measured using two visual fields. A central flickering field with a mark-to-space ratio of 1:1 (mean luminance: 3.4 cd m^{-2} with a 2° visual angle subtense) was superimposed on a concentric background (luminance: 0.34 cd m^{-2} with a 10° visual angle subtense). Both fields were generated by green light-emitting diodes (Hewlett-Packard

Figure 2 Measurement of pupillary diameter and the response to light. Light from a source was split by an infra-red transmitting mirror into visible and infra-red beams. The visible beam stimulated the retina, and the change in pupil size was detected by the infra-red sensitive camera.

5082-4950 series, dominant wavelength 572 nm). They were in Maxwellian view and appeared at optical infinity, and were viewed through an artificial pupil (2.5 mm diameter) which ensured a constant retinal illumination. Cross-wires were used for fixation and this kept the retinal location of the stimulus constant.

the fields monocularly with the preferred eye. The flickering light was presented for 2 s, and the subject was required to respond during the inter-trial delay of 3 s by pressing a 'Yes' button if flicker was detected and a 'No' button if the light appeared fused. The same stimulus was re-presented if the subject failed to respond. Initially the flickering light was presented at 16 Hz (lower than the possible fusion point) and the frequency was altered stepwise according to the pattern of response. The frequency step started at +4 Hz, and each time the direction of the subject's response changed (No to Yes: Yes to No) it was reduced by half and the direction reversed, i.e. -2 Hz, +1 Hz, -0.5 Hz and finally ± 0.25 Hz. A further 25 responses were recorded, and fusion was defined as the lowest frequency at which 50% or more of the last 25 responses was considered to be fused (No responses). A typical response pattern is given in Figure 3.

Psychological tests

Digital symbol substitution This was measured using one of 100 different sheets, each with 200 randomized

digits (0-9) arranged in ten rows. Under each digit there was a space and the subjects were required to write in the space the appropriate symbol indicated by a code at the top of each page. The code was different for each of the 100 sheets. At each assessment the subjects were given two sheets, and 2 min to complete as many spaces as possible for each sheet. Errors were very rare, and so the number of substitutions completed within the period of time was used as the performance measure (Nicholson & Stone, 1982).

Cancellation task The subjects were presented with one of 75 different sheets each with 1200 randomized symbols consisting of 24 different Greek letters arranged in 40 columns. Five key letters were given at the top of each page, and these letters were different for each of the 75 sheets. The subjects were required to work down each column cancelling out the letters given in the key, and if all five key letters appeared at least once to indicate this at the foot of the column. The subjects were instructed to work quickly and accurately covering as many letters as possible in 5 min, and to indicate how far they had reached. The number of letters covered and the number of correct responses were recorded.

Mood

Mood was assessed at each performance run by visual analogue scales. The subjects were asked to consider the mid-point of a 100 mm scale as their normal state.

Figure 3 Measurement of critical flicker fusion. Initially, the subject indicated that a light flickering at 16 Hz was not fused. In response the frequency was altered stepwise. Fusion was defined as the frequency at which 50% or more of the last 25 responses was considered to be fused.

The statements 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.

Experimental procedure

Six healthy female volunteers aged between 21 and 34 (mean 26) years and weighing between 49 and 72 (mean 57) kg were used. Some of the subjects had

taken antihistamines in previous experiments though none used these drugs for clinical reasons. They were instructed to avoid alcohol within 24 h of the experiment, and they were not involved with any other drug therapy except, possibly, the use of oral contraceptives. Beverages containing stimulants were avoided from 17.00 h on the evening before the experiment, and the subjects refrained from smoking from 0.5 h before each performance measurement. Subjects retired to bed at their normal times the night before, and on the day of the experiment had a light breakfast 1 h after ingestion of the tablets. Transport was provided to and from the laboratory.

Figure 4 Structural formulae of: (a) triprolidine (E)-2-[1-(4-methylphenyl)-3-(1-pyrrolidinyl)-1-propenyl]pyridine. (b) terfenadine α -(4-tert-butylphenyl)-4-(α -hydroxy- α -phenylbenzyl)-1-piperidine-butanol and (c) astemizole 1-(4-fluorophenylmethyl)-N-1-[2-(4-methoxyphenyl-ethyl)]-4-piperidinyl-1H-benzimidazole-2-amine.

Three drugs (Figure 4) were studied—triprolidine hydrochloride in a sustained release form (10 mg), terfenadine (60 mg) and astemizole (10 mg). These are the presently recommended or anticipated single doses of each drug, though it must be noted that the doses may not be given at equal intervals of time, and that the doses may not be equivalent in histamine antagonising ability. Each subject received, on three separate occasions, an active tablet and a placebo for each of the other two drugs, and on two further occasions matching placebos for each drug. A random order was used and the trial was double-blind. At least 2 weeks separated ingestion of active compounds, and performance studies within 2 days of the onset of menstruation were avoided or repeated. Placebo or drug was ingested at 08.00 and 08.30 h. Performance on DVA was measured exactly 1.0, 2.5 and 4.0 h after ingestion and the remaining tests were carried out around 0.5, 2.0 and 3.5 h after ingestion.

Drug effects on performance were tested by analysis of variance. Mean levels for each drug were compared with the mean of the two placebos at the same time after ingestion. To allow for three comparisons to be made simultaneously for the three different drugs, Fisher's modification to the test for least significant differences was used.

Results

Dynamic visual acuity

All subjects occasionally made an 'impossible' error,

i.e. they made an incorrect response to an image which was well above their threshold. The probability of such an error $p(e)$ was estimated for each subject, and $f(x)$ was scaled by the factor $(1-p(e))$. In three out of the 90 experimental runs at the highest target velocity there were no responses, and this suggested that the threshold sizes were outside the range used in the experiment. In several other runs the number of correct responses at the highest target velocity was very low and in others the numbers of correct responses at the lowest velocity was very high. This led to imprecise estimates of 50% threshold points at the extreme target velocities, and so a different threshold on the frequency-of-seeing curve was chosen for each velocity such that the corresponding target sizes were within the range used in the experiment. The threshold points were at the 91, 61, 33 and 15% levels for target speeds 21, 43, 68 and 83°/s respectively.

An analysis of variance was performed on the threshold points with separate analyses for each target velocity using a square root transform for variance stabilization. Those cases where the threshold had not been reached were treated as missing values in the analysis. A similar analysis of variance was also performed on the DVA% scores applying an arc sin square root transform to achieve variance stabilization. With placebo there was an improvement ($P < 0.001$) of acuity at the fastest target velocity over the three times of testing. Compared with placebo triprolidine (10 mg) impaired performance 1.0 and 2.5 h after ingestion at target velocities of 21 and 43°/s, and at 1.0, 2.5 and 4.0 h

Table 1 Effects of antihistamines on the dynamic visual acuity thresholds (minutes of arc) at four target velocities

Drug	Target velocity (deg/s)	Threshold point (%)	Time (h) after ingestion		
			1.0	2.5	4.0
Placebo	21	91	1.86	2.11	2.03
Terfenadine (60 mg)			1.69	2.00	1.75
Triprolidine (10 mg)			2.97**	3.24**	2.60
Astemizole (10 mg)			2.35	1.94	1.95
Placebo	43	61	2.17	2.18	2.10
Terfenadine (60 mg)			2.14	2.03	1.94
Triprolidine (10 mg)			3.01**	3.58***	2.51
Astemizole (10 mg)			2.12	2.44	2.18
Placebo	68	33	3.25	3.14	2.91
Terfenadine (60 mg)			3.37	3.12	3.00
Triprolidine (10 mg)			4.29*	4.40**	3.68*
Astemizole (10 mg)			3.77	3.17	3.37
Placebo	83	16	4.01	3.93	3.31
Terfenadine (60 mg)			4.26	4.56	3.24
Triprolidine (10 mg)			4.17	5.25	5.26**
Astemizole (10 mg)			4.43	4.25	4.08

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Table 2 Effects of antihistamines on the percentage of correct responses on dynamic visual acuity at four target velocities

Drug	Target velocity (deg/s)	Time (h) after ingestion		
		1.0	2.5	4.0
Placebo	21	93.7	93.1	93.1
Terfenadine (60 mg)		94.4	92.4	92.7
Triprolidine (10 mg)		87.4*	80.7***	88.7
Astemizole (10 mg)		90.7	92.4	92.0
Placebo	43	80.6	80.7	82.0
Terfenadine (60 mg)		81.1	81.5	82.8
Triprolidine (10 mg)		65.8**	61.2***	74.2
Astemizole (10 mg)		82.4	74.7	79.5
Placebo	68	42.5	45.6	51.1
Terfenadine (60 mg)		40.3	48.2	48.7
Triprolidine (10 mg)		31.7	28.2**	36.8*
Astemizole (10 mg)		38.9	44.3	44.2
Placebo	83	13.8	17.4	21.7
Terfenadine (60 mg)		13.8	14.6	22.1
Triprolidine (10 mg)		11.7	10.0	10.7**
Astemizole (10 mg)		10.0	16.1	16.4

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

after ingestion at the target velocity of 68°/s. At 83°/s dynamic acuity was impaired only at 4.0 h (Tables 1 and 2). No changes in acuity were observed after terfenadine or astemizole.

Pupillary diameter

There were no changes in the diameter of the resting pupil or in the response to light with the three antihistamines (Table 3).

Critical flicker fusion

Performance on critical flicker fusion was analysed by analysis of variance. Triprolidine (10 mg) reduced the threshold for fusion at 0.75 h ($P < 0.01$), and at 2.25 h ($P < 0.001$) with recovery at 3.75 h. There were no changes with terfenadine or with astemizole (Table 4).

Psychological tests and moods

Performance on the digit symbol substitution and the cancellation tasks were not altered. Subjective assessments of mood showed a tendency towards increased sleepiness, less ability to concentrate and less effectiveness 2.0 h after ingestion of triprolidine, although none of these changes was significant.

Discussion

Dynamic visual acuity was the term used by Ludvigh & Miller (1958) to describe the ability of an individual to perceive detail in moving targets during ocular pursuit. It is not a fundamental visual attribute, but it depends on the sensory and motor components of the ocular response, together with the feedback systems which link them. Position and velocity errors lead to

Table 3 Effects of antihistamines on the pupillary size and response to light

	Drug	Time (h) after ingestion		
		0.5	2.0	3.5
Resting pupil diameter (mm)	Placebo	7.70	7.35	7.26
	Terfenadine (60 mg)	7.73	7.24	7.15
	Triprolidine (10 mg)	7.37	7.44	7.35
	Astemizole (10 mg)	7.88	7.53	7.58
Change in diameter in response to light (mm, mean of three measurements)	Placebo	1.57	1.69	1.99
	Terfenadine (60 mg)	1.30	1.71	1.81
	Triprolidine (10 mg)	1.34	1.91	1.74
	Astemizole (10 mg)	1.73	1.61	2.07

Table 4 Effects of antihistamines on critical flicker fusion frequency (Hz)

Drug	Time (h) after ingestion		
	0.75	2.25	3.75
Placebo	26.02	25.19	25.58
Terfenadine (60 mg)	25.54	25.58	25.46
Tripolidine (10 mg)	24.58**	23.46***	25.54
Astemizole (10 mg)	26.17	25.21	25.33

Least significant differences for three simultaneous comparisons between drug and placebo for means of six are:

* $P < 0.05 = 0.974$, ** $P < 0.01 = 1.215$,

*** $P < 0.001 = 1.530$

displacement of the image from the fovea with increasing deterioration in acuity as target velocity increases (Brown, 1972b).

Dynamic visual acuity unlike simpler measures of visual performance is related to a variety of variables such as age and gender (Burg, 1966; Reading, 1972a,b), fatigue (Behar *et al.*, 1972) and drugs (Brown *et al.*, 1976). With drugs changes may be due to a number of factors (Brown *et al.*, 1976). An increase in reaction time will lead to a greater displacement of the target image before any corrective movement is made, while displacement of the image from the fovea will persist even after ocular movement if a decrease in the size of corrective saccades or in saccadic velocity occurs. Further, a decrease in the velocity of the smooth pursuit phase may lead to a continued displacement, and even to movement of the image on the retina.

In the present experiment the exposure times of the target on the screen were 1.40, 0.70, 0.44 and 0.36 s for velocities of 21, 43, 68 and 83°/s respectively. Essentially one saccadic eye movement with a latency about 0.2 s would have been necessary to attain smooth pursuit with velocities up to 50°/s, while with velocities between 50 and 90°/s two saccades would have been necessary, and the latency of the commencement of the second saccade would have been around 0.3 s (Barmack, 1970; Brown, 1972b). At the two slowest speeds there was at least 0.5 s of smooth pursuit for the resolution of detail, but at the faster speeds there was much less time—probably less than 0.15 s.

Impairment of dynamic visual activity by tripolidine varied with target velocity. At low velocities there was a reduction in acuity 1.0 and 2.5 h after ingestion followed by recovery. This pattern of impairment and recovery was similar to that observed with visuo-motor coordination (Clarke & Nicholson, 1978; Nicholson & Stone, 1982) in which the stimulus had an average velocity of 15°/s. Slowed smooth pursuit may be involved both in the impairments of dynamic acuity at these velocities as well as in visuo-motor coordination.

With the highest velocity (83°/s) an improvement in

acuity after placebo was observed over the three times of testing within the same day, and this may have been due to learning or to an improvement in performance related to circadian rhythmicity. During the first run, 1.0 h after ingestion, tripolidine did not impair acuity any further than that due to the high velocity of the target, but an effect appeared as the level of skill improved over the times of testing. This would suggest that, initially at least, performance was so low that an additional effect could not be brought about by the drug. The subsequent decrement associated with improved baseline performance is more likely to be related to slowing of saccadic eye movements than to slowing of smooth pursuit, which occupies very little time at this target velocity.

The present studies on tripolidine suggest that antihistamines may slow both saccadic eye movements and smooth pursuit, and this conclusion is similar to that drawn from studies with barbiturates (Rashbass, 1961; Tedeschi *et al.*, 1982) and with benzodiazepines (Bittencourt & Richens, 1982; Bittencourt *et al.*, 1981). Peak saccadic velocity and smooth pursuit are impaired after ingestion of amylobarbitone and after diazepam and temazepam, and so with barbiturates, benzodiazepines and antihistamines impaired performance of complex tasks could involve ocular mechanisms.

It is unlikely that any peripheral anticholinergic activity contributed to the effects of tripolidine, at least as indicated by the absence of any change in pupillary diameter or in the pupillary response to light. On the other hand the studies on critical flicker fusion and on mood, together with those of Peck *et al.* (1975) on vigilance, indicate reduced levels of alertness, and, as pointed out by Bittencourt *et al.* (1981), there is much evidence to suggest an association between the control of eye movement and some aspects of sleep as both involve pontine mechanisms (Keller, 1974, 1977).

Although tripolidine leads to obvious deficits in behaviour, both terfenadine and astemizole are without these effects and so central depression and impaired performance may not be essential properties of an antihistamine. Indeed, it would appear that with astemizole and terfenadine H₁-antihistaminic activity and central effects are largely dissociated. Absence of adverse effects on performance with terfenadine (Kulshrestha *et al.*, 1978; Clarke & Nicholson, 1978; Moser *et al.*, 1978; Fink & Irwin, 1979; Nicholson & Stone, 1982) and with astemizole (Nicholson & Stone, 1982) together with the present studies on visual function, suggest that both drugs are likely to be useful for those involved with skilled work.

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